THE EFFECTS OF ANTI-HYPERTENSIVE DRUGS IN DIFFERENT CLINICAL SETTINGS; LESSONS LEARNED FROM TWO SYSTEMATIC REVIEWS AND A CLINICAL TRIAL

by

MARCO ANTONIO I. PEREZ GARCIA

M.D. University of Guadalajara Mexico, 1991

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ABSTRACT

**Context:** The ultimate goal when using anti-hypertensive drugs is to reduce adverse health outcomes. In acute clinical settings, total all-cause mortality is the best measure of net health effect (benefit minus harm).

**Objectives:** a) To determine the effects of anti-hypertensive drugs on all-cause mortality compared to a control in hypertensive emergencies and acute cardiovascular events b) To learn randomized controlled trial (RCT) methodology.

**Methods:** Two systematic reviews were conducted of published RCTs evaluating blood pressure (BP) lowering drugs. The first review was limited to patients with a hypertensive emergency. The second was limited to patients treated within 24 hours of an acute cardiovascular event. A parallel RCT was conducted in hypertensive outpatients comparing the blood pressure lowering effect of hydrochlorothiazide with two psychological interventions.

**Results:** In hypertensive emergency patients, 15 RCTs (N=869) studying nitrates, ACE inhibitors, calcium channel blockers (CCBs), alpha-1 adrenergic antagonists, diuretics, and direct vasodilators were analyzed. There was no evidence for an effect on mortality with any of these drug classes. In the acute cardiovascular event review, sixty-five RCTs (N=166,206) were analyzed, involving four classes of anti-hypertensive drugs. Acute stroke was studied in 6 RCTs and acute myocardial infarction (AMI) in 59 RCTs. Immediate treatment with nitrates in patients with AMI significantly reduced all-cause mortality at 2 days (RR 0.81, 95%CI [0.74, 0.89], p<0.0001, ARR 0.4 %). Immediate treatment with ACE-inhibitors significantly reduced mortality only when continued for
10 days (RR 0.93, 95%CI [0.87, 0.98] p=0.01, ARR 0.4%). The other classes did not reduce all-cause mortality. Conducting the RCT assisted with and improved the critical appraisal of RCTs analyzed in the systematic reviews and prepared me to design and conduct a large high-quality RCT.

**Conclusion:** In patients with suspected or definite acute myocardial infarction nitrates administered immediately and continued for 2 days reduce all-cause mortality at 2 days. In the same clinical setting ACE inhibitors started within 24 hours and continued for 10 days reduce mortality at 10 days. There is no RCT evidence that anti-hypertensive drugs reduce mortality in hypertensive emergencies.
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GLOSSARY

ACC: American College of Cardiology

ACE-i (ACEi): Angiotensin converting enzyme inhibitors

ACUTE MYOCARDIAL INFARCTION (ICD-9 410): Commonly called a “heart attack”, an acute myocardial infarction is a manifestation of ischemic heart disease, describing a severe sudden onset of myocardial necrosis due to the formation of a thrombus in the coronary arterial system obstructing arterial blood flow to that section of cardiac muscle.

AHA: American Heart Association

AMI: Acute myocardial infarction

ARBs (ARB’s): Angiotensin II receptor blockers

ARR: Absolute risk reduction

ASA: American Stroke Association

AT1: Angiotensin II type 1 receptor

BB: Beta-adrenergic receptor blockers

BHS: British Hypertension Society

BP: Blood pressure

BPM: Beats per minute

CARDIOVASCULAR DISEASES (ICD-9 390-459): All diseases of the circulatory system, including acute myocardial infarction, ischemic heart disease, valvular heart disease, peripheral vascular disease, arrhythmias, high blood pressure and stroke.
CCB: Calcium channel blockers

CVD: Cerebrovascular disease (ICD-9 430-438): Disease of one or more blood vessels of the brain.

CHF: Congestive heart failure

CK: Creatine kinase

CPK: Phosphocreatine kinase

CVE: Cardiovascular event

DBP: Diastolic blood pressure

EOF: End of follow-up

ESC: European Society of Cardiology

ESH: European Society of Hypertension

FDA: Federal Drug Administration

HR: Heart rate

ICD: International Classification of Diseases is a disease classification system created by the World Health Organization (WHO). Version 9 of the ICD is currently used in Canada; this was revised in 1977. There is also a "Clinical Modification" version (ICD9-CM) being used in Canada, which has extended coding for more precise disease classification. Version 10 of the ICD has been released and will be introduced in Canada in the next few years.

ICH: International Conference of Harmonization

IHD: Ischemic Heart Disease (ICD-9 410-414): Any condition in which heart muscle is damaged or works inefficiently because of an absence or relative deficiency of its blood supply; most often causes by atherosclerosis, it includes angina pectoris, acute myocardial infarction, chronic ischemic heart disease and sudden death. It is also called coronary heart disease (CHD).
ISH: International Society of Hypertension

IU: International units

IV: Intravenous

JNC: Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

LVFP: Left ventricular filling pressure

MAP: Mean arterial pressure

MESH: Medical subject headings

Mo: Month

N/A: Not applicable

NA: Not available

NNH: Number needed to harm

NNT: Number needed to treat

NO: Nitric oxide

NR: Not reported

NS: Not significant

NSTEMI: Non-ST elevation myocardial infarction

NTG: Nitroglycerin

RAAS: Renin angiotensin aldosterone system
RCT: Randomized controlled trial

RR: Relative risk

RRR: Relative risk reduction

SAE: Serious adverse events

SBP: Systolic blood pressure

SD: Standard deviation

SE: Standard error

SNP: Sodium nitroprusside

STROKE: A condition which results in a reduction of blood flow to a region of the brain resulting in the "death" of brain tissue; specifically, infarction from hemorrhage (ICD-9 430-432), thrombotic/embolic stroke (ICD-9 433-434) or rupturing aneurysm. Thrombolytic strokes are due to cerebral thrombosis and are often superimposed on a plaque of atherosclerosis; symptom onset ranges from minutes to days. Embolic strokes are due to cerebral embolism; they usually have a sudden onset of symptoms reflecting abrupt loss of blood flow to the brain region of the occluded artery.

THROMBUS (THROMBOSIS): An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causes vascular obstruction at the point of its formation.

UA: Unstable angina

WHO: World Health Organization
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me mine, even though they had raised 10 children before me. They sacrificed their entire lives in order to give each of us a superior education.
DEDICATION

To my wonderful wife and kids,

Elizabeth, you are the most precious gift that God has given to me. It is a great honor to be your spouse. You are incredibly amazing and charming. I love you in a way that I could never have imagined. With your unconditional giving and your unlimited power of love, you have given me my beautiful and intelligent daughter, Liz, and my handsome and charming son, Paco. Thanks to you and to my kids, I am the most fortunate man in the world. This work is dedicated to all of you,

With all of my Love and Soul,

Marco A.
CO-AUTHORSHIP STATEMENT

Chapter 2: Pharmacological Interventions for Hypertensive Emergencies

Marco Perez and James Wright formulated the idea for the review and developed the basis for the protocol. Marco Perez took the lead roles in searching for, identifying and assessing studies, in data extraction methodology, analysis and in writing up the review. Vijaya Musini independently checked the trials for inclusion and exclusion and independently checked the data extraction as well as helped with the methodology of the review. James Wright assisted with the methodology of the review and with the interpretation and writing of the review.

Chapter 3: Effects of Early Treatment with Anti-hypertensive Drugs on Short and Long-term Mortality in Patients with an Acute Cardiovascular Event

Marco Perez formulated the idea for the review and developed the basis for the protocol. Marco Perez took the lead roles in searching for, identifying and assessing studies and in data extraction, methodology, analysis, interpretation and in writing up the review. Vijaya Musini independently checked the trials for inclusion and exclusion and independently checked the data extraction. James Wright helped with the methodology of the review, interpretation and writing of the review.

Chapter 4: Failure of Psychological Interventions to Lower Blood Pressure: a Randomized Controlled Trial

Marco Perez participated in the design of the trial, did the majority of the recruiting, clinical assessments, clinic blood pressure measurements, analysis, interpretation, and writing of the manuscript. Wolfgang Linden, Lorri Puil and James
Wright participated in the conception of the study as well as the design, conduct and revisions of the manuscript. Lorri Puil, Thomas Perry, Jr., and James Wright assisted in the conduct of the trial.
1 INTRODUCTION

1.1 Conception of the research question

My interest in this research project began in the intensive care unit of a teaching hospital in Mexico in the year 2000 when I questioned whether or not to use blood pressure lowering medications in my acutely ill cardiovascular patients. At the time, I knew almost nothing about evidence-based medicine, nor had I had any experience in conducting or evaluating clinical research. For the most part, I uncritically accepted the opinions of local experts and rigorously followed clinical practice guidelines; both recommended prescribing blood pressure-lowering drugs to these patients.

I questioned this approach recognizing that blood pressure changes in acute cardiovascular injuries could be appropriate physiological adjustments to injury and perhaps necessary to achieve homeostasis. Lowering blood pressure, in these instances, could increase rather than decrease harm. However, while I could raise these questions, I recognized that I had no capacity to answer them.

I gradually realized that no one in my institution or country (that I could find) had the capacity to answer these questions either. I tried to build my research skills by becoming a co-investigator in a local clinical trial. Unfortunately, although the trial was conducted in a leading university teaching hospital, the methodological standards were too low to achieve scientifically valid results. I also tried and failed to get scientific justification from local experts as to why they recommended blood pressure lowering therapy. This led me to go elsewhere both to learn high quality clinical trial methodology and to
attempt to establish the scientific basis of blood pressure treatment during acute cardiovascular events.

From the beginning my thesis committee strongly supported my interest in both learning clinical trial and systematic review methodology, recognizing the obvious synergy between these two dimensions of clinical research.

1.1.1 Hypertension in acute cardiovascular emergencies: pathological or physiological response

The acute phase of cardiovascular event is the period when organs are most vulnerable to local and systemic changes. This high vulnerability is substantiated by the high mortality rate during this critical period, e.g., during acute myocardial infarction the highest mortality rates occur within the first 24 hours\(^1\). Finding interventions to halt this increased mortality has been the goal of many investigations.

An acute cardiovascular event is a sudden manifestation of a cardiovascular disease (e.g., myocardial infarction or stroke). Cardiovascular diseases are the leading cause of death in the world\(^2\) and the leading cause of hospitalization in Canada\(^3\).

The hypothesis behind this research work is that the timing for initiation of blood pressure lowering drugs determines their effects (benefit or harm). The primary objective of this thesis is to study the effects of these drugs in the \textbf{acute phase} (<24 hr after the event) of different cardiovascular clinical settings.

1.1.2 Other drugs in the acute phase of cardiovascular events

The most successful drugs at reducing mortality during the acute phase of a cardiovascular event have been anti-platelets and thrombolytics for patients with acute
myocardial infarction or stroke. These drugs have been shown to be most effective when administered as early as possible after the event and within the first 24 hours.

For example, in a meta-analysis of randomized controlled trials, published in 1994, for thrombolytics in acute myocardial infarction it was demonstrated that there were 30 lives saved per 1000 treated within 6 hours of the onset, 20 lives saved per 1000 treated between 7-12 hours, and uncertain benefit for those treated between 13-18 hours\textsuperscript{4}. This meta-analysis was conducted based on pathophysiological mechanisms thought to be the cause of acute myocardial infarction (thrombotic occlusion at the site of atherosclerotic plaques). These results established that the timing of initiation of this type of pharmacological intervention was critical in obtaining the benefits in clinical outcomes.

In other words, in the initial hours and days after the insult has occurred there is a dynamic and changing sequence of events and effective treatments in the initial hours after the event may not be effective when started 2 days after the event and vice versa.

1.2 Research outline

I began by researching the most accepted acute clinical setting where blood pressure-lowering drugs could logically be used: “Hypertensive Emergencies”. This clinical entity is defined, by The JNC 7- as “marked blood pressure elevation associated with acute end organ damage”\textsuperscript{5}. Examples of acute end organ damage include acute cardiovascular events (myocardial infarction, unstable angina, acute cardiogenic pulmonary edema, acute aortic dissection, hypertensive encephalopathy and stroke). This interest led me to embark on my first systematic review (Chapter 2 of this thesis).

The hypertensive emergencies project was limited to patients with a marked elevation in BP and as such restricted the number of RCTs that would fit the inclusion criteria. It thus,
did not allow a study of the benefits and harms of antihypertensive therapy in a broader spectrum of patients. Therefore, I developed a second research project, which includes the same acute cardiovascular events mentioned in the hypertensive emergency definition but without being limited by any specific BP criterion. This second, broader research project represents chapter 3 of this thesis. Since patients with these acute clinical settings could have “normal” blood pressure they are simply referred as “acute cardiovascular events”. However, in this second research project RCTs were only included if the treatment was initiated within the first 24 hours of the onset in order to measure the effect of the drugs during this early vulnerable period of the clinical setting.

The importance of this second research project is exemplified by the fact that blood pressure lowering drugs are recommended during this time-frame independent of the BP by most current clinical guidelines\textsuperscript{6-8}, despite the fact that elevated blood pressure is not present in most cases in these clinical settings.

At the present time there has not been a systematic review study to assess whether blood pressure-lowering drugs administrated to patients in an \textbf{acute} clinical setting provide mortality and morbidity benefits. Others have attempted to study this, but with the wrong approach or with different objectives. In each of my two systematic reviews, I discuss in detail the weakness of these other systematic reviews. Basically, all of the reviews accept patients in these “acute” clinical settings but also accept patients who are identified and treated more than 24 hours after the onset of the condition. For example, these systematic reviews include trials where the treatment started days after the onset of the acute cardiovascular event\textsuperscript{9-13}, when the patients are not in the high-risk most vulnerable phase. Another difference and disadvantage of those reviews is that they are out of date. By
conducting Cochrane collaboration systematic reviews I am committing to update these
two reviews every two years so that they continue to represent current information.

1.3 What is a systematic review?

Systematic review is a scientific technique that summarizes and appraises large quantities
of information from randomized controlled trials in order to clarify controversial research
findings and to inform therapeutic recommendations that can improve population health.
In this modern time, publications about health care interventions have increased so much
that researchers, health care providers and policy makers can no longer keep up with the
large and often contradictory literature. A systematic review answers a specific research
question following a standard methodology. First, a pre-specified plan or protocol
(outlining the objectives, search strategy, criteria for inclusion and exclusion of trials, risk
of bias check points, etc.) is developed; then the critical appraisal is performed
(identification of the strengths and weaknesses of the primary trials as well as contacting
the authors for missing information). Next comes the phase of summarizing the overall
benefits and harms of the intervention in question. However, since all of these steps are
documented, the chances for introducing bias in the results are minimized. Furthermore
the rigorous transparent methods allow replication and validation of the work. A
systematic review can be qualitative or quantitative (if it has a meta-analysis component).
A meta-analysis involves combining the quantitative data from individual studies,
thereby increasing the statistical power and precision of the estimate of the effect size.
A systematic review is subject to difficulties and limitations. It is a retrospective study
and therefore is subject to bias. Possible sources of bias are those inherent in the primary
literature, such as publication bias (which describes the tendency of positive-result
studies to be more likely to be published, sometimes multiple times, than negative-result studies). In a quantitative systematic review with meta-analysis this can lead to an overestimate of the true treatment effect. Fortunately, there are some statistical methods to correct for this type of bias. Another source of bias is selection and observer bias: these can be minimized by having at least two independent reviewers selecting studies and extracting the relevant data. Despite these potential limitations, systematic reviews have become the gold standard of evidence-based medicine.

1.4 What is the Cochrane collaboration?

The Cochrane Collaboration is a national and international, not-for-profit, independent organization dedicated to improve healthcare decision-making by promoting, preparing, maintaining and disseminating up-to-date systematic reviews of randomized controlled trial (RCT) evidence. The major product of this organization is the Cochrane Database of Systematic Reviews, an electronic publication that is updated quarterly. Cochrane systematic reviews are prepared and published using special software, Review Manager, which facilitates the update of reviews by easily incorporating missed or newly published trials. This user-friendly format continues to be developed through an ongoing process of consultation with its users. A study that compared Cochrane reviews with articles published in paper-based journals concluded that Cochrane reviews were conducted with greater methodological rigor and were more likely to be updated.

1.5 What is the overall objective of this thesis?

To find and quantify, using Cochrane systematic review methodology, the randomized controlled trial evidence for the use of anti-hypertensive drugs in acute clinical settings, specifically acute cardiovascular events.
1.6 Additional tools used for performing Cochrane systematic reviews

In addition to completing two Cochrane systematic reviews, requiring meticulous analysis, and critical appraisal of randomized controlled trials (RCTs), I decided that I needed to also participate in an RCT. This was decided with two main purposes: to gain a deeper appreciation of the difficulties, strengths and potential biases, which occur while conducting an RCT (something I was analyzing and criticizing on the regular basis while performing my systematic reviews); and to become proficient in the steps involve in conducting a clinical trial in order to get the necessary skills and experience so that after I graduate, I would be in a position to design, get funding for and run a high quality randomized controlled trial. The trial I was fortunate to be able to participate in represents Chapter 4 of this thesis. This RCT involved patients with hypertension and included an antihypertensive drug as one of the arms of the trial.

1.7 Clinical background: acute cardiovascular events

Although different acute cardiovascular events could be considered different clinical entities, they have two things in common: they are life threatening and have a high rate of initial mortality; and, therefore, they require prompt management with the goal of reducing that mortality. The following is a description of the incidence, prevalence, pathophysiology, diagnosis and current recommended management of various acute cardiovascular events.

1.7.1 Acute myocardial infarction

**Incidence and prevalence:** According to the 2008 update of Heart Disease and Stroke Statistics, acute myocardial infarction is highly prevalent. It comprises half (~ 8 million) of all coronary heart disease in the United States\textsuperscript{15}. The estimated annual incidence of
acute myocardial infarction is 600,000 new attacks and 320,000 recurrent attacks. The average age at first myocardial infarction (MI) is 64.5 years for men and 70.4 years for women. In Canada, unfortunately, the existing surveillance system relies on administrative physician billing and hospitalization rates. Thus, the incidence of the disease has not been routinely determined\(^3\). However, the annual hospitalization rates for acute myocardial infarction have increased steadily since 1980 and are projected to increase further, especially for men, beginning at age 40 and for women at age 50\(^3\). In 2000/01 the MI hospitalization rates for men and women, age 40-79, were reported as 1/35 and 1/80, respectively\(^3\).

**Diagnosis:** The following three components are used: clinical, electrocardiogram and serum cardiac biomarkers. The first two are sufficient to initiate a therapeutic intervention and the third one is usually used to confirm the diagnosis and also for prognosis purposes. The clinical component consists of signs and symptoms (typical chest discomfort, diaphoresis, pale complexion, fatigue, lightheadedness, syncope, paraesthesias, nausea, vomiting, etc.). The electrocardiogram: a more accurate diagnosis of the acute myocardial infarction has evolved thanks to the better understanding of the correlation between the findings in the electrocardiogram and the pathology, therapeutic interventions and prognosis. In fact, acute myocardial infarction now is referred conventionally as ST-segment elevation myocardial infarction (STEMI)\(^6\) to distinguish it from non-STEMI myocardial infarction (see below). Although, there are still some diagnostic controversial issues, such as whether 0.2 mV ST elevation in leads V1 through V4 is a preferable threshold for diagnosis of STEMI rather than 0.1 mV elevation, a 12-lead electrocardiogram (ECG) remains the most important diagnostic tool for therapeutic
decisions. The diagnosis of MI by detecting proteins (biomarkers) released into the circulation due to damage of myocytes has also changed over the years. In the past (60-70's), non-specific biomarkers such as glutamic-oxaloacetic transaminase (SGOT), lactate dehydrogenase (LDH) and total creatine kinase (CK) were used. Now, highly specific cardiac biomarkers (MB fraction of creatine kinase [CK-MB], cardiac troponin I [cTnI], cardiac troponin T [cTnT]) are used to confirm the diagnosis. The latter biomarkers have higher sensitivity to detect very small infarcts that would not have been considered MI in an earlier era. Thus, by accepting that any amount of myocardial necrosis caused by ischemia is evidence of infarct, individuals who formerly would not have been diagnosed as having an MI are diagnosed today as having an MI. The American College of Cardiology and the European Society of Cardiology declared cardiac troponins the preferred biomarker for diagnosis of MI. An abnormal value that exceeds that of 99% of a reference control detected at least once within 24 hours of the clinical event is diagnostic.

**Pathophysiology:** Acute myocardial infarction occurs due to an inadequate supply of oxygen caused by an occlusion of one or more coronary arteries. This occlusion is usually caused by rupture of an atherosclerotic coronary artery plaque with subsequent acute thrombosis. The pathophysiological processes that occur following acute myocardial infarction are very complex. They are influenced by many factors, particularly the site and magnitude of the infarction. However, in general, as soon as the coronary blood flow is decreased the myocardial mechanics are altered (even before the actual myocardial cell death) due the acute oxygen deprivation, resulting in systolic and diastolic dysfunction. This activates a cascade of events with an increase of left-
ventricular filling pressure and decrease of cardiac output, decrease of blood pressure and activation of the sympathetic system. The sympathetic release of catecholamines increases the heart rate and vascular tone resulting in an increase of oxygen consumption and workload of the heart potentially worsening the ischemia and leading to a vicious circle with further dysfunction. There are, however, many clinical presentations specific for different pathophysiological processes\textsuperscript{16}.

**Management:** Restoration of blood flow to the myocardium is the cornerstone and ultimate goal of the treatment. Pharmacological treatments have been used to attempt to accomplish this blood flow restoration with some success. For example, randomized controlled trial (RCT) evidence has demonstrated a reduction in mortality with the use of thrombolytic drugs\textsuperscript{4:17} and anti-platelet drugs\textsuperscript{18}.

Although, both of these pharmacological interventions by themselves have been able to reduce mortality, the effect of their interaction seems to be additive. In the ISIS-2 trial\textsuperscript{19}, treatment with aspirin caused an absolute risk reduction (ARR) in mortality of 2.4\% at 35 days. When both treatments (aspirin and streptokinase) were given concomitantly the ARR was 5.2\% at 35 days.

The use of a non-pharmacological intervention, PCI (angioplasty with or without stent), has also been proven to reduce mortality and has been compared with the effectiveness of thrombolysis. There is still some controversy whether these non-pharmacological interventions are superior to the pharmacological ones for all types of AMI. However, these controversies have not been entirely resolved by meta-analysis mainly because of the use of different sub-modalities of these interventions in different randomized controlled trials (RCT) or because these interventions have been combined with other
pharmacological interventions across RCTs making it difficult to pool them all. Indications for blood pressure lowering drugs for this setting and the other acute cardiovascular settings are discussed under the individual blood pressure lowering classes below.

### 1.7.2 Unstable angina

**Incidence and prevalence:** The recent prevalence and incidence of unstable angina (UA) is difficult to estimate accurately as this entity has been included within a broader term the “acute coronary syndrome”, which comprises three main sub-settings: unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). Few epidemiological studies have reported unstable angina separately. A national U.S report of first-listed inpatient hospital discharges from hospitals in 2005 estimated that unstable angina was the diagnosis at discharge in 89,000 (11.5 %) out of 772,000 patients with acute coronary syndrome. But, when including secondary discharge diagnoses 558,000 (39%) were reported with unstable angina out of 1,430,000 patients with ACS\textsuperscript{15}.

**Diagnosis and Pathophysiology:** Unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI) are two acute settings that form a similar clinical syndrome\textsuperscript{7}. The most common cause of this syndrome is a reduction in myocardial perfusion that results from coronary artery narrowing caused by thrombus that developed on a disrupted atherosclerotic plaque that is usually non-occlusive\textsuperscript{7}. It has been defined as having typical signs and symptoms (chest pain-usually for more than 20 minutes- or anginal equivalent, shortness of breath, diaphoresis, dyspnea, fatigue) as well as changes in the electrocardiogram such as ST-segment depression or prominent T-wave inversion.
and/or absence of ST-segment elevation. The main distinction between these two entities is whether or not the ischemia was severe enough to cause sufficient myocardial damage to release detectable quantities of markers of myocardial injury (troponin or CK-MB). Since the detection of these biomarkers can be delayed for some hours after the onset, patients with either of these two are indistinguishable clinically at the time of presentation. However, as these biomarkers become available they allow the differentiation between UA (i.e., no release of biomarkers) and NSTEMI (i.e., elevated biomarkers). There are 3 principal presentations of UA: 1) rest angina, 2) new onset and, 3) increasing angina (increasing in intensity, duration and/or frequency).

**Management:** The management generally consists of two different approaches: an invasive or conservative approach. In the former, in addition to pharmacological treatment, coronary angiography and revascularization is usually performed within the first 4-24 hours after admission. In the conservative approach, the pharmacological treatments (nitrates, beta-blockers, calcium channel blockers, ACE-inhibitors, anti-platelets and anti-coagulants) are administered during the first 24-72 hours and depending on the clinical course an invasive procedure is performed later. Thus, the main difference between the two approaches is the treatment received during the first 24 hours. This emphasizes the importance that clinicians give to the acute or immediate period following the onset of this event.

There is still controversy as to which of these two approaches is superior. Some not so contemporary RCTs had shown no differences in hard outcomes. A more recent meta-analysis reported an 18% relative reduction in death or MI in favor of the invasive intervention approach. However, a recent large trial compared invasive versus
conservative approach in patients receiving currently recommended concomitant pharmacological therapies in both groups and found no difference in mortality or in the primary composite outcome. 

1.7.3 Stroke

Incidence and prevalence: According a nation-wide U.S survey it is reported that 2.7% of men and 2.5% of women 18 years or older have a history of stroke. Thus, in 2005 the estimated number of U.S residents with a history of stroke was 5,839,000. Also in the U.S. the estimated annual incidence of acute stroke has been reported as 600,000 new attacks and 180,000 recurrent attacks; and this incidence was greater for men than women except for those aged ≥ 85 where the incidence for women was reported to be higher than that for men. In Canada, the annual hospitalization rates for acute stroke for men and women, age 40-79, were reported as 1/67 and 1/95, respectively, whereas, those rates for those aged 90+ were 1/45 and 1/53, respectively.

Diagnosis: Stroke is caused by a reduction in cerebral blood flow to a region of the brain. It has been broadly classified as ischemic (most cases) or hemorrhagic. The former could ensue after a large vessel occlusion (usually the middle cerebral artery) or after small vessel occlusions. Hemorrhagic strokes have been described as those occurring in the parenchyma; intraventricular, subarachnoid and subdural. Chronic hypertension is the main risk factor.

The diagnosis of the stroke is usually made using two components: clinical and brain imaging (CT scan or MRI). There are some validated clinical tools currently used. The World Health Organization had defined stroke as “a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of
cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin”. A transient ischemic attack (TIA) is defined as stroke symptoms and signs that resolve within 24 hours.

**Pathophysiology:**

The pathophysiological processes that occur following a stroke are very complex and vary depending on type, localization and size of the stroke. For example, a hemorrhage of 60 ml in the basal ganglia is usually fatal within hours, whereas the same size bleed in the frontal or occipital lobe could have a good long-term outcome. Under normal circumstances the cerebral blood flow (CBF) is maintained constantly at 50 ml/ 100 g brain tissue per minute. CBF is a function of cerebral perfusion pressure (CPP), and cerebrovascular resistance (CVR), where CBF= CPP/ CVR; while CPP is equal to mean arterial pressure (MAP) minus intracranial pressure (ICP). In a normal individual ICP is negligible, therefore CPP is determined almost entirely by MAP; thus, CBF is held constant by adjusting CVR (autoregulation). In an acute stroke, the ability to adjust CVR is decreased and the autoregulation within and around the stroke area is impaired (global impairment may also be present). Furthermore, the ICP might be increased due to cerebral edema. As a result, small changes in MAP may cause dramatic changes in CBF, putting the brain at higher risk of further damage (further ischemia if MAP falls or hemorrhage if MAP increases).

**Management:** There is randomized controlled trial (RCT) evidence that early use of thrombolysis (especially within six hours) of an ischemic stroke significantly reduced the proportion of patients who were dead or dependent at three to six months. The initial
management for hemorrhagic stroke is to decrease the intracranial pressure in order to reduce the risk of further bleeding and neuronal deficit. Neurosurgery is sometimes required to evacuate a hematoma, though, the benefits of this are still in doubt. In a recent large multicenter randomized controlled trial involving 1,033 patients, the evacuation of the hematoma failed to show a benefit on survival or neurologic functioning at 6 months\textsuperscript{29}. On the other hand, no mortality or dependency benefit has been documented for any pharmacological agents to reduce intracranial pressure such as mannitol or barbiturate-inducing coma.

1.7.4 Cardiogenic pulmonary edema

Incidence and prevalence: There are two classes of pulmonary edema: cardiogenic and non-cardiogenic. The latter is referred to that resulting from an alteration in the permeability of the pulmonary capillary membrane such as in acute respiratory distress syndrome (ARDS). Non-cardiogenic pulmonary edema is not considered an acute cardiovascular event and is not within the scope of this thesis.

Cardiogenic pulmonary edema arises when there is a sufficient increase in left ventricular end-diastolic pressure to provoke backward elevation in pulmonary capillary hydrostatic pressure resulting in leakage of fluid from capillaries and venules into the alveolar space\textsuperscript{30}. Acute cardiogenic pulmonary edema most commonly occurs as a consequence of an anterior myocardial infarction, left-sided valvular disorders, acute dysrhythmias, myocardiopathies, drug-induced, and acute exacerbation of chronic left ventricular failure (most commonly due to a sudden increase in plasma volume)\textsuperscript{30}.

The exact incidence and prevalence of this clinical setting is not known. In a recent epidemiological study of 1,477 patients admitted to a tertiary hospital with diagnosis of
heart failure, 176 (12%) had acute pulmonary edema at admission in the emergency department. Of those, 106 (60%) patients suffered from an acute coronary event. The other 70 (40%) patients suffered from a non-ischemic event.

**Diagnosis:** Clinically patients with acute pulmonary edema are characterized by severe dyspnea, orthopnea, tachypnea, rales and “pink” sputum. They may also present with a gallop rhythm, third heart sound or murmurs (suggesting valvular dysfunction). Other tests that can help to make the diagnosis are the chest X-ray (to confirm pulmonary congestion), electrocardiogram (ischemia, dysrhythmia) and echocardiography (size of chambers, valvular structure and function, dyskinesis etc.). As it was pointed out above, the development of pulmonary edema secondary to an acute myocardial infarction is quite common. In fact, there is a clinical classification of severity of heart failure in the context of an AMI, the Killip classification, which is described in four stages: I – No heart failure; II – Heart failure with S3 gallop, wet rales in the lower half of lung fields; III- frank pulmonary edema with rales throughout the lung fields; IV- cardiogenic shock (SBP <90 mm Hg), oliguria, cyanosis, sweating.

**Pathophysiology:** Whatever the initial insult causing the left ventricular dysfunction and increase of left ventricular end-diastolic pressure, it eventually turns on a cascade of events leading to death if no intervention is given. When the pulmonary capillary hydrostatic pressure exceeds pulmonary interstitial pressure, the fluids start to build up in the pulmonary interstitium and alveolar space resulting in impaired gas exchange and hypoxia. This leads to increased catecholamine production and activation of the renin-angiotensin-aldosterone system (RAAS), which in turn increases the systemic vascular resistance (afterload), causing greater myocardial wall tension and oxygen demand,
resulting in myocardial ischemia (if not already present), and more systolic and/or
diastolic dysfunction. Ultimately, cardiac output decreases, which compromises kidney
perfusion and activates the sympathetic system and RAAS. The kidney tries to
compensate by increasing the reabsorption of salt and water to increase intravascular
volume\textsuperscript{32}.

**Management:** The specific management depends on the underlying cause. However,
some general measures include oxygen and the use of pharmacological interventions
(such as morphine) to reduce preload or afterload of the heart; and non-pharmacological
interventions (such as ventilatory support) to improve the alveolar patency.

### 1.7.5 Acute aortic dissection

**Incidence and prevalence:** The incidence has been estimated in some epidemiological
studies. In the 1950’s and 1960’s, Sorenson et al., reported an incidence of 5 to 10 cases
per 100,000 per year\textsuperscript{33}. In a more recent study published in 2004, Clouse et al., reported
an incidence of 3.5 per 100,000 per year between 1980 and 1994\textsuperscript{34}.

**Diagnosis:** Most patients with acute aortic dissection present with sudden, severe, chest
pain. They usually described it as “ripping” or “tearing” chest pain. Back pain could be
present with distal or descending dissection. The chest pain must be differentiated from
that of an acute coronary syndrome. The latter has been more often described as a
“crescendo” form. In contrast, in aortic dissection the pain has an abrupt onset. Patients
may also present with a neurologic complication such as acute stroke, ischemic
peripheral neuropathy (where the limb ischemia would be evident) or paraplegia due to
occlusion of an artery to the spinal cord. The diagnosis is made with the use of ECG (to
rule out acute coronary syndrome), chest X-ray, transesophageal echocardiogram, helical CT scan and MRI.

**Pathophysiology:** Acute aortic dissection is a tear in the aortic intima through which blood flows into the aortic media, separating the intima from the adventitia. Generally the tear and disruption of these layers is caused by degeneration or chronic insult. Chronic hypertension, congenital bicuspid aortic valve and connective tissue disease (e.g., Marfan syndrome) are among the list of associations with this condition. The two main serious consequences are: propagation of the dissection with occlusion of branching arteries or aortic wall rupture. The speed with which the maximal systolic pressure is attained (referred as dP/dTmax) in the aorta has been shown to be one of the most important factors in the propagation of dissection. When this occurs it could cause occlusion of aortic branch arteries, or prolapse of aortic valve cusps, resulting in aortic insufficiency. If the aortic wall is ruptured it can cause cardiac tamponade or hemorrhage into the pleural space. Rupture of the aorta is the most common cause of death.

**Management:** In addition to control of pain, reduction of systolic blood pressure and pulse wave (dP/dT) is important. Anti-hypertensive drugs have been used include:
- Labetalol (alpha and beta1 and 2 adrenergic blocker) - decreases peripheral resistance, heart rate and myocardial contractility (dP/dTmax);
- Esmolol decreases heart rate and myocardial contractility (dP/dTmax);
- Sodium nitroprusside decreases peripheral resistance and preload;
- Trimethaphan camsylate – autonomic ganglion blocker - decrease peripheral resistance. The latter two are usually used in combination with beta-blocker. Definitive management usually involves surgical repair, especially in dissections involving the ascending aorta. Those patients in whom only the descending aorta is
involved are initially managed medically unless there is a definite indication for surgery. Overall, untreated aortic dissection has been reported to have a mortality rate of 21% within the first 24 hours and 60% within 2 weeks. Dissection of the ascending aorta has been reported to have a mortality rate of 60% within 24 hours and 80% within two weeks. In a recent epidemiological study of 547 patients with dissection of the ascending aorta the in-hospital mortality rate was 26.6% for those treated with surgery and 55.9% for those treated medically. Although there have been improvements in technologies and surgical techniques, recent epidemiological studies have not shown improvement in mortality in this setting over the last 2 decades.

1.8 Pharmacological background: anti-hypertensive drugs

Blood-pressure lowering drugs or anti-hypertensives are defined here as those pharmacological agents indicated and used to treat elevated blood pressure or hypertension. According to the World Health Organization / International Society of Hypertension and other international committees (such as JNC-7), these include the following classes of drugs: angiotensin converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARBs), beta-adrenergic receptor blockers (BB), calcium channel blockers (CCB), diuretics, nitrates (including nitroprusside), alpha-adrenergic antagonists, direct vasodilators (diazoxide, hydralazine) and others (such as reserpine). However, it is important to emphasize that many anti-hypertensive drugs have pharmacological actions other than lowering BP (for example, reducing heart rate), which makes them usable for indications other than the management of hypertension. In contrast, there are drugs that have the potential to reduce blood pressure (for example:
morphine in certain doses and setting) but are not classified as anti-hypertensive drugs. The latter classes of drugs are not covered in this thesis.

In the next section a description of the mechanism of action, pharmacokinetics, indications and dosage of the major anti-hypertensive drug classes is covered. Indication and dosing information is limited to those drugs with an indication listed in the Compendium of Pharmaceutical and Specialties (CPS) of Canada\(^2\) or approved by the U.S. Food & Drug Administration (FDA) for the treatment of any acute cardiovascular event.

1.8.1 Angiotensin converting enzyme inhibitors (ACE-I)

Mechanism of action:

ACE-I competitively block the conversion of angiotensin I, a relatively inactive peptide, to angiotensin II, a potent vasoconstrictor and stimulator of the release of aldosterone, from the adrenal cortex. ACE-I probably lower blood pressure by reducing the blood pressure increasing effects of Angiotensin II. There are numerous drugs under this class such as captopril, enalapril (a complete list can be found in the following 2 chapters), but all of these drugs are thought to act in a similar manner.

Pharmacokinetics:

Except for enalaprilat, ACE inhibitors are administered orally. Most ACE inhibitors are pro-drug esters that must be converted in the liver and/or GI mucosa to active metabolites. The pharmacokinetic properties vary depending on the specific drug. (See Table 1-1)
Table 1-1. Pharmacokinetics of ACE-inhibitors

<table>
<thead>
<tr>
<th>Parent Drug</th>
<th>Bioavailability (%)</th>
<th>Protein Bound (%)</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>Elimination (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Metabolite</td>
<td>Hepatic</td>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benazepril</td>
<td>37</td>
<td>97</td>
<td>0.5-1</td>
<td>10-11</td>
<td>12 88</td>
</tr>
<tr>
<td>Captopril</td>
<td>65</td>
<td>30</td>
<td>1-1.5</td>
<td>4</td>
<td>60 40^</td>
</tr>
<tr>
<td>Enalapril</td>
<td>40-60</td>
<td>&lt;50</td>
<td>3-4</td>
<td>1.3 11</td>
<td>94</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>25</td>
<td>7</td>
<td>12</td>
<td>&lt;1</td>
<td>98^</td>
</tr>
<tr>
<td>Perindopril</td>
<td>30-35</td>
<td>10-20</td>
<td>0.5-1</td>
<td>1.2</td>
<td>&gt;90 4-12^</td>
</tr>
<tr>
<td>Quinapril</td>
<td>60</td>
<td>97</td>
<td>1</td>
<td>2</td>
<td>40 60</td>
</tr>
<tr>
<td>Ramipril</td>
<td>28-44</td>
<td>73</td>
<td>1</td>
<td>2-4</td>
<td>40 60</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>4-14</td>
<td>94</td>
<td>1-6</td>
<td></td>
<td>&gt;90 &lt;0.5^</td>
</tr>
</tbody>
</table>

^ Eliminated (%) unchanged
- t<sub>max</sub> = time to maximum plasma concentration
- t<sub>1/2</sub> = half-life

Other pharmacokinetic properties may differentiate ACE inhibitors including lipophilicity, tissue binding, peak-trough ratio, etc. However, it is not known whether these differences have any clinical significance.

**Indications and dosing for acute cardiovascular events:**

**Captopril:**

Post MI: initial dose 6.25 or 12.5 mg 3 times a day. Dose can be gradually increased up to 450 mg per day.

**Lisinopril**

Post MI: 5 mg within 24 hours of acute myocardial infarction follow by 5 mg after 24 hours and 10 mg per day after 48 hours and thereafter.
1.8.2 Angiotensin II receptor blockers (ARBs)

**Mechanism of action:**

ARBs inhibit the binding and action of Angiotensin II at the angiotensin II type 1 (AT1) receptor, which is the site of action to cause vasoconstriction and release of aldosterone. They, thus, similar to ACE-I probably reduce BP by blocking the BP increasing effects of Angiotensin II. The drugs under this category or class are candesartan, irbesartan, losartan, telmisartan, valsartan.

**Pharmacokinetics:**

There are differences in pharmacokinetic properties of drugs within the class that result in differences in the magnitude and duration of their blood pressure lowering effect (Table 1-2).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability (%)</th>
<th>Protein Bound (%)</th>
<th>( t_{\text{max}} ) (h)</th>
<th>( t_{1/2} ) (h)</th>
<th>Elimination (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hepatic Renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>unchanged</td>
</tr>
<tr>
<td>Candesartan</td>
<td>15</td>
<td>99.5</td>
<td>2-5</td>
<td>6-13</td>
<td>67</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>13</td>
<td>98.0</td>
<td>1-3</td>
<td>5-9</td>
<td>90</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>60-80</td>
<td>90.0</td>
<td>1.3-3</td>
<td>11-18</td>
<td>80</td>
</tr>
<tr>
<td>Losartan</td>
<td>29-43</td>
<td>98.7</td>
<td>1-1.5</td>
<td>1-3</td>
<td>65</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>30-60</td>
<td>99.5</td>
<td>0.5-1</td>
<td>21-38</td>
<td>98</td>
</tr>
<tr>
<td>Valsartan</td>
<td>10-35</td>
<td>95.0</td>
<td>2-4</td>
<td>6-10</td>
<td>80</td>
</tr>
</tbody>
</table>

- \( t_{\text{max}} \) = time to maximum plasma concentration
- \( t_{1/2} \) = half-life
**Indications and dosing for acute cardiovascular events:**

**Valsartan**

Post MI: start as early as 12 hours after myocardial infarction in clinically stable patients at 20 mg two times a day. Increase at 7 days to 40 mg twice daily, and then progressively, over weeks, up to 160 mg twice daily.

**1.8.3 Beta-adrenergic receptor blockers (BB)**

**Mechanism of action:**

In general, beta-adrenergic receptor blocking drugs, or beta-blockers (BB), are drugs that competitively inhibit the effect of the catecholamines, noradrenaline and adrenaline, on beta-adrenergic receptors. There are subtypes of beta-blockers depending on their relative affinity for B1 and B2 receptors, partial agonist activity, and ability to also block alpha-adrenergic receptors. Catecholamines have a positive chronotropic and inotropic actions on the heart, can cause vasoconstriction or vasodilatation of blood vessels and stimulate renin release from the kidney. Thus, BB drugs could lower BP by a number of these differing effects. The exact mechanism by which beta-blockers lower BP in humans is not known.

**Pharmacokinetics:**

The pharmacokinetics of beta-adrenergic blocking agents differs widely. This is mainly due to the variation in the aromatic ring structure. Pharmacokinetically, these drugs can be sub-divided into two general categories: those that are lipid soluble and primarily metabolized by the liver, and those that are water soluble and predominantly excreted unchanged by the kidney. See Table 1-3 for more details.
### Table 1-3. Pharmacokinetics of Beta-adrenergic blockers (BB)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability (%)</th>
<th>Protein Bound (%)</th>
<th>$t_{max}$ (h)</th>
<th>$t_{1/2}$ (h)</th>
<th>Elimination (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hepatic</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>40</td>
<td>25</td>
<td>2.5</td>
<td>3-4</td>
<td>60</td>
</tr>
<tr>
<td>Atenolol</td>
<td>5.0</td>
<td>&lt;5</td>
<td>2-4</td>
<td>5-8</td>
<td>40</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>30</td>
<td>98</td>
<td>1</td>
<td>6-10</td>
<td>98</td>
</tr>
<tr>
<td>Esmolol</td>
<td>NA</td>
<td>55</td>
<td>9 min</td>
<td>Ery</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Labetalol</td>
<td>20</td>
<td>50</td>
<td>1-2</td>
<td>4-6</td>
<td>95</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>40</td>
<td>12</td>
<td>3-4</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>Nadolol</td>
<td>30</td>
<td>20</td>
<td>10-20</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>25</td>
<td>93</td>
<td>1-4</td>
<td>3-6</td>
<td>99</td>
</tr>
<tr>
<td>Timolol</td>
<td>50</td>
<td>60</td>
<td>4-5</td>
<td>80</td>
<td>20</td>
</tr>
</tbody>
</table>

- $t_{max} = \text{time to maximum plasma concentration}$
- $t_{1/2} = \text{half-life}$
- Ery = mainly erythrocytes elimination

**Indications and dosing for acute cardiovascular events:**

**Labetalol**

Hypertensive emergencies: start with 20 mg IV, max: 300 mg IV bolus; or IV infusion 2 mg/min. convert to PO 200-400 mg q6-12 hours.

**Metoprolol**

Acute myocardial infarction: start with 5 mg IV, every 2 min (3 times); after 15 min, give 50 mg PO q6h x 48 h. Then gradually increase over the weeks to a maximum dose of 400 mg/day.

Post myocardial infarction: start as soon as possible with 50 mg PO bid. Then, gradually increase over the weeks to a maximum dose of 400 mg/day.
1.8.4 Calcium channel blockers (CCB)

Mechanism of action:
Calcium channel blockers reduce the cytosolic free-calcium concentrations by blocking transmembrane calcium influx through L-type calcium channels. Dihydropyridines (such as nifedipine), benzothiazepines (diltiazem) and phenylalkylamines (verapamil) bind to the pore-containing the α1-subunit of the L-type calcium channel. In general, calcium channel blockers relax arteriolar smooth muscle, resulting in vasodilatation and decreased peripheral resistance. The decreased systemic resistance is thought to cause the blood pressure reduction. Agents that slow the rate of recovery of L-type calcium channels (verapamil, diltiazem) have negative chronotropic and dromotropic (AV node conduction) effects on the heart's conducting system. The CCBs also have a natriuretic effect on the kidney that may contribute to their ability to lower blood pressure.

Pharmacokinetics:
In general CCBs drugs are well absorbed from the gastrointestinal tract but undergo first-pass hepatic metabolism resulting in low bioavailability. Early calcium antagonists were short acting, with time to maximum concentration occurring within about 2 hours. The rapid decreases in blood pressure gave rise to many side effects, especially tachycardia from reflex sympathetic nervous system activation, flushing, headache and dizziness. Newer CCBs such as amlodipine and slow-release formulations of older CCBs were developed to produce a more gradual decrease in blood pressure with a longer duration of BP control and less side effects.
The metabolism of CCBs occurs via oxidative enzymes in the liver, primarily the 3A4 isoenzyme of the cytochrome P450 family. See Table 1-4 for more details

**Table 1-4. Pharmacokinetics of Calcium Channel Blockers (CCBs)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability (%)</th>
<th>Protein Bound (%)</th>
<th>t(_{\text{max}}) (h)</th>
<th>t(_{1/2}) (h)</th>
<th>Elimination (%)</th>
<th>Hepatic metabolism</th>
<th>Renal unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydropyridines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>63</td>
<td>97.5</td>
<td>6-12</td>
<td>35-50</td>
<td>60</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Felodipine</td>
<td>15</td>
<td>99</td>
<td>2.5-5</td>
<td>11-16</td>
<td>70</td>
<td>&lt;0.5</td>
<td></td>
</tr>
<tr>
<td>Isradipine</td>
<td>15-24</td>
<td>95</td>
<td>2-4</td>
<td>8</td>
<td>65</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Nimodipine</td>
<td>10-17</td>
<td>98</td>
<td>0.5-1</td>
<td>2</td>
<td>60</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>45-75</td>
<td>95</td>
<td>0.5-2</td>
<td>2-5</td>
<td>75</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>45-75</td>
<td>95</td>
<td>0.5-2</td>
<td>2-5</td>
<td>75</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>40-67</td>
<td>70-80</td>
<td>2-4</td>
<td>3-6</td>
<td>2-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>10-20</td>
<td>&gt;90</td>
<td>1-2</td>
<td>3-7</td>
<td>86</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

- t\(_{\text{max}}\) = time to maximum plasma concentration
- t\(_{1/2}\) = half-life

**Indications and dosing for acute cardiovascular events:**

**Nimodipine:**

Post-subarachnoid hemorrhage (SAH): Therapy should commence as soon as possible or within 4 days of the diagnosis. The recommended dosage is 60-90 mg every 4 hours for 21 consecutive days.
1.8.5 Diuretics

Mechanism of action:

Thiazide diuretics inhibit the Na⁺Cl⁻ co-transporter in the proximal part of the distal convoluted tubule of the kidney. This decreases tubular reabsorption of sodium and chloride, and increases urinary excretion of sodium and water.

Furosemide and other loop diuretics inhibit sodium reabsorption in the ascending limb of loop of Henle as well as in both proximal and distal tubules.

The mechanism by which diuretics lower blood pressure has not been established.

The drugs under this category are the thiazide and thiazide-like diuretics (hydrochlorothiazide, chlorthalidone, indapamide) and loop diuretics (furosemide, ethacrynic acid).

Pharmacokinetics:

The pharmacokinetic parameters are shown in Table 1-5.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability (%)</th>
<th>Protein Bound (%)</th>
<th>t_{max} (h)</th>
<th>t_{1/2} (h)</th>
<th>Elimination (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>60-70</td>
<td>75</td>
<td>2-6</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>HCTZ</td>
<td>65-75</td>
<td>58</td>
<td>4-6</td>
<td>3-15</td>
<td>0</td>
</tr>
<tr>
<td>Indapamide</td>
<td>93</td>
<td>76</td>
<td>2</td>
<td>4-22</td>
<td>90</td>
</tr>
<tr>
<td>Loop-diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>60</td>
<td>98</td>
<td>2</td>
<td>4-6</td>
<td>10-15</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td></td>
<td></td>
<td>2</td>
<td>6-8</td>
<td></td>
</tr>
</tbody>
</table>

- t_{max} = time to maximum plasma concentration
- t_{1/2} = half-life
- HCTZ = hydrochlorothiazide
Indications and dosing for acute cardiovascular events:

Furosemide and ethacrynic acid are indicated for acute pulmonary edema.

**Furosemide:** 40 - 80 mg IV as single dose or it can be repeated every 4-8 hours

**Ethacrynic acid:** oral 50 mg or IV 0.5 to 1 mg/kg one or two doses. Maximum dose is 100 mg.

1.8.6 Nitrates (including nitroprusside)

**Mechanism of action:** Organic nitrates and sodium nitroprusside (SNP) are nitric oxide (NO) donors. Organic nitrates, such as glyceryl trinitrate (nitroglycerin) require enzymatic metabolism to generate NO. In contrast, SNP spontaneously generates NO. There are a number of theories about how nitrates cause vasodilatation: 1) acting on specific nitrate receptor (containing a sulphydryl group-SH), 2) NO exerts a potassium channel activation (hyperpolarizing the cell membrane) and 3) NO activates the enzyme guanylate cyclase increasing cGMP levels, which in turn inhibits Ca++ entry into smooth muscle cells and increases Ca++ uptake by the smooth endoplasmic reticulum resulting in vascular smooth muscle relaxation.

Included in this category of drugs are organic nitrates (including isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin) and nitroprusside.

**Pharmacokinetics:**

The organic nitrates are well absorbed from the gastrointestinal track and nitroglycerin is also absorbed through intact skin. They undergo first pass denitration in the liver yielding active metabolites. Isosorbide dinitrate is metabolized to isosorbide 2 and 5-mononitrate, the latter being available commercially as isosorbide mononitrate (as
sustained –release tablets). The onset and duration of action varies depending on the formulation and route of administration (See Table 1-6).

Table 1-6. Pharmacokinetics of Nitrates (including nitroprusside)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bioavailability (%)</th>
<th>Protein Bound (%)</th>
<th>Onset (min)</th>
<th>Duration (min)</th>
<th>Elimination (%)</th>
<th>Hepatic metabolism</th>
<th>Renal unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(sub-lingual)</td>
<td>90</td>
<td>--</td>
<td>1-3</td>
<td>10-30</td>
<td>99</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(intravenous)</td>
<td>1-2</td>
<td>-</td>
<td>3-5</td>
<td>99</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosorbide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mono-nitrate</td>
<td>99</td>
<td>5</td>
<td>2-5</td>
<td>120-240</td>
<td>99</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>(oral IR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosorbide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dinitrate</td>
<td>90</td>
<td></td>
<td>2-5</td>
<td>60-180</td>
<td>99</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>(sub-lingual)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td></td>
<td>--</td>
<td>0.5</td>
<td>2-3</td>
<td>Wall Ery Hepatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(intravenous)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- min = minutes
- wall = vascular wall
- Ery = erythrocytes
- IR = immediate release

**Indications and dosing for acute cardiovascular events:**

**Nitroglycerine:**

Hypertension in acute coronary syndrome: Intravenous (IV) nitroglycerin can be used as an initial dosage of 5 µg/min with increments every 3-5 min until blood pressure is controlled or increments of 10 to 20 µg/min (but the interval of the increments should be lengthened) up to a maximum of 100 µg per minute.
Nitroprusside:

Hypertensive emergency: The usual dose regimen is 0.25 to 10 µg / kg/ min as an IV infusion

1.8.7 Direct vasodilators (hydralazine, diazoxide)

Hydralazine

Mechanism of action:

Hydralazine has a direct vasodilatory effect that leads to a reduction in peripheral vascular resistance. The exact mechanism of this vasodilatory effect has not been established.

Pharmacokinetics:

Hydralazine is rapidly absorbed. The peak plasma concentration could be achieved at 2 hours. There are large inter-individual differences in plasma concentration after oral administration. Acetylator phenotype is an important determinant of these differences. The half-life is about 2 to 4 hours but may range up to 8 hours. It is metabolized in the gastrointestinal mucosa and in the liver.

Indications and dosing for acute cardiovascular events:

Hypertensive emergencies: initial bolus of 5 to 10 mg IV, followed by 5 to 10 mg IV every 20 to 30 minutes as necessary. Or it may be infused at a rate of 0.5 to 10 mg per hour.

Diazoxide:

Although an oral formulation is still on the market as a glucose-control agent in patients with hyperinsulinism, IV diazoxide has been discontinued from the market as an antihypertensive drug. It was formerly used as a potent intravenous antihypertensive. Its
mechanism of action is related to ATP-sensitive K channel activation, causing arteriolar relaxation.

**Indications and dosing for acute cardiovascular events:**

Hypertensive emergencies: 50 to 150 mg IV bolus or 15 to 30 mg/min in IV infusion.

### 1.9 Summary

This thesis consists of four chapters in addition to this introductory chapter. Chapter 2 is the published Cochrane systematic review, documenting all of the available RCT evidence supporting the use of blood pressure-lowering drugs in hypertensive emergencies. Chapter 3 is the published Cochrane systematic review assessing the effect of the early use of blood pressure-lowering drugs in acute cardiovascular events. Chapter 4 is the published randomized controlled trial, comparing the blood pressure-lowering effects of the antihypertensive drug hydrochlorothiazide with two psychological interventions. Chapter 5 interprets and discusses the relationships and conclusions coming from chapters 1 to 4.
1.10 References


(9) AMICG. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group.[see comment]. Circulation 1998; 97(22):2202-2212.


2 PHARMACOLOGICAL INTERVENTIONS FOR HYPERTENSIVE EMERGENCIES

2.1 Background

A hypertensive emergency is the clinical setting in which a marked elevation of blood pressure is associated with acute end organ damage; for example, hypertensive encephalopathy or aortic dissection. As such, a hypertensive emergency is a life-threatening condition. The goal of treatment is to reverse the end organ damage, prevent adverse outcomes and prolong life. This review focuses on the blood pressure-lowering drugs that are used in this emergency setting.

The management of hypertension in these emergency situations represents a significant therapeutic challenge. Many antihypertensive drug classes have been used with the objective of rapidly reducing blood pressure, and the expectation of reducing adverse clinical outcomes. This approach was first recommended by Gifford in 1959 based on a series of 8 cases with hypertensive encephalopathy that were treated with sodium nitroprusside. Based on this case series evidence this approach has become and remained the standard of care and is currently recommended by most, if not all, guideline committees (such as JNC-7). At issue in this review is whether RCT evidence supports this approach and which drug classes are the most effective.

---

1 A version of this chapter has been published. Perez MI, Musini VM, Wright JM. Pharmacological interventions for hypertensive emergencies. Cochrane Database of Systematic Reviews 2008, Issue 1 Art No. CD003653. DOI:10.1002/14651858.pub3. A version of this chapter has been co-published in the Journal of human hypertension 2008;22[9]:596-607
Two published systematic reviews attempted to address these issues. However, they have different methodology and some deficiencies. For example, Cherney et al 2002 accepted data from patients who were not part of a randomized controlled trial. In addition, they incorrectly placed some “urgency” trials in the “emergency” category of trials, even though the authors correctly defined and studied emergencies and urgencies as two separate settings. Hypertensive urgencies are defined as marked elevated blood pressure in an otherwise stable patient (i.e., without acute end organ damage). Hypertensive emergency patients are at higher risk of death than hypertensive urgency patients due to the presence of significantly more life-threatening circumstances in the former category. Because of these differences in risk the urgency and emergency settings need to be reviewed separately.

The second systematic review, a Cochrane review of interventions that alter blood pressure after acute stroke, is not limited to RCTs studying drugs to reduce blood pressure and includes RCTs involving interventions or approaches with the aim of increasing blood pressure. Therefore, it also does not answer the question raised here.

2.2 Objectives

2.2.1 General

To find and quantify the randomized controlled trial (RCT) evidence for antihypertensive drug treatment of patients with a hypertensive emergency, defined as marked hypertension associated with acute end organ damage.
2.2.2 Specific

To answer the following two questions: does anti-hypertensive drug therapy, as compared to placebo or no treatment, affect mortality and morbidity in patients with a hypertensive emergency; and does one first-line antihypertensive drug class offer a therapeutic advantage, in terms of mortality and morbidity, over another in patients with a hypertensive emergency?

2.3 Methods

2.3.1 Criteria for considering studies for this review

2.3.1.1 Types of studies

All unconfounded, truly randomized control trials* that compare a first-line antihypertensive drug class versus placebo, no treatment or another first-line antihypertensive drug class. Crossover trials are excluded. There is no language restriction.

* Trials where it is explicitly stated that randomization took place; quasi-randomization or pseudo-randomization methodology is not accepted for inclusion.

2.3.1.2 Types of participants

Participants must meet the following hypertensive emergency definition: any clinical setting where patients present with marked elevation of blood pressure in the presence of acute end organ damage. Examples of acute end organ damage are the following: myocardial infarction, unstable angina, acute left ventricular failure with pulmonary edema, acute aortic dissection, encephalopathy, stroke, and life-threatening bleeding (intracerebral hemorrhage, subarachnoid hemorrhage).
Thus, patients with marked elevation of blood pressure but without acute end organ damage (defined as urgencies) are not included.

There is no evidence as to what constitutes "marked blood pressure elevation". Therefore, we have chosen blood pressure level(s) commonly used in clinical practice to mandate the use of antihypertensive drugs (along with other acute therapy such as pain management) in relevant clinical settings. For example, for patients with acute myocardial infarction a SBP greater or equal to 180 and or DBP ≥ 110 mm Hg is the threshold above which thrombolysis is contraindicated [ACC/AHA-2004 6]. For patients with acute aortic dissection or with left ventricular failure and pulmonary edema a SBP greater or equal to 120 mm Hg and or DBP ≥ 70 mm Hg is the threshold for therapy 7;8. For patients with intracranial hemorrhage or subarachnoid hemorrhage a SBP ≥ 160 mm Hg is the threshold because of a higher incidence of re-bleeding above this level 9. For patients with any other acute end organ damage setting a SBP ≥ 180 and or DBP ≥ 110 mm Hg is the defined threshold.

We included all RCTs that included patients with these minimum or higher thresholds. In the case that a RCT does not define blood pressure inclusion criteria but had included only one category of patients (patients with pulmonary edema, for example), then the mean base-line blood pressure had to be equal to or greater than these defined thresholds. In the event that an RCT had included patients with different end organ damage clinical settings, a mean base-line blood pressure of SBP ≥180 and or DBP ≥ 110 mm Hg is acceptable for inclusion.

Note: Pregnancy-related hypertensive emergencies are excluded from this review.
2.3.1.3 Types of interventions

Intervention: A first-line anti-hypertensive drug class. (First-line anti-hypertensive drug classes included: nitrates, beta-blockers, ACE-inhibitors, diuretics, calcium channel blockers, dopamine agonists, alpha-adrenergic antagonists and direct vasodilators (diazoxide, hydralazine).

Control: placebo, no treatment or a different first-line anti-hypertensive drug class.

2.3.1.4 Types of outcome measures

**Primary**

- Total serious adverse events^  
- All cause mortality  
- Composite of non-fatal cardiovascular events including: myocardial infarction, unstable angina, dissection of aortic aneurysm, acute renal failure, stroke, and respiratory failure (necessitating mechanical ventilation).

^ Serious adverse events are defined as any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of hospitalization, or results in persistent or significant disability.

**Secondary**

- Weighted mean change in systolic blood pressure (SBP), diastolic blood pressure (DBP) and in heart rate (HR), during the treatment period.
- Withdrawal due to adverse events

2.4 Search methods for identification of studies

We searched randomized controlled trials of all antihypertensive drugs used for hypertensive emergencies through the following databases of articles published from
1966 to August 2007: MEDLINE, EMBASE, COCHRANE clinical trial register. A comprehensive search strategy was used to identify all relevant articles. Review articles and trials reference lists were also checked.

Key words: controlled clinical trial, randomized controlled trials, meta-analysis, severe/accelerated/crisis (es), hypertension, antihypertensive, emergencies: hypertensive encephalopathy, myocardial infarction, unstable angina, acute left ventricular failure, pulmonary (o)edema, stroke, subarachnoid / intracranial h (a)orrhage, aortic dissection.

For a complete search strategy see Appendix II: Search Strategy Chapter 2.

2.5 Data collection and analysis

2.5.1 Data abstraction

Two reviewers (M.I.P. & V.M.) independently decided whether or not a trial was included. They also independently extracted and entered the data from the included studies. Discrepancies were resolved by discussion. Absence of consensus was resolved by a third reviewer (J.M.W.).

A modified Cochrane quality scoring system was used for concealment of allocation and blinding: A (adequate & double-blind), B (unclear & single-blind or open label), C (clearly inadequate & open-label). The two reviewers (M.I.P. & V.M.) also independently assessed the quality of studies. Authors were contacted in case of missing information.
2.5.2 Analyses

For the synthesis and analysis of the data, Cochrane Review Manager 4.2.9 was used. Relative and absolute risk differences (with 95% confidence interval) were calculated for dichotomous outcomes for each trial on an intention to treat basis. Heterogeneity between trials results was tested using chi-squared test, where $p$ less than 0.05 was taken to indicate significant heterogeneity. The fixed effect model was used when there was homogeneity and the random effect model was used to test for statistical significance where there was heterogeneity.

Trials were not sub-classified according to dose or dosing regimen. Data for blood pressure was combined using a weighted mean difference method, whereby the trials are weighted according to the number of subjects in the trial and the within-study variance. Some of the trials did not report a within-study variance for blood pressure reduction. In these studies standard deviation (SD) was imputed using the following hierarchy:

1. Pooled standard deviation calculated either from the t-statistic corresponding to an exact $p$-value reported or from the 95% confidence interval of the mean difference between treatment group and comparative group.

2. Standard deviation of blood pressure/heart rate at the end of treatment

3. Standard Deviation of blood pressure/heart rate at baseline (except if this measure is used for entry criteria).

4. Weighted mean standard deviation of change in blood pressure/heart rate calculated from at least 3 other trials using the same drug and dose regimen.

5. Weighted mean standard deviation of change in blood pressure/heart rate calculated from other trials using the same drug.
6. Weighted mean standard deviation of change in blood pressure/heart rate calculated from all other trials (any drug and dose).

Several sensitivity analyses were pre-planned to test robustness including the use of both fixed and random effects models, 95 and 99% confidence intervals, and quality of trials. Also sensitivity analyses were pre-planned according to the clinical setting and to the class of drug.

### 2.6 Results

#### 2.6.1 Description of studies

Our search strategy yielded 86% of citations showing no relation to this work in the first screening stage by reading titles and abstracts (see Figure 2-1). Fifteen randomized controlled trials (869 patients) were found that satisfied the inclusion criteria (see Summary of Included Studies, Table 2-1). Two trials were placebo-controlled. Only one trial was confirmed to be double-blind, while the rest were open-label. No trial was designed for or had the power to detect differences in clinical outcomes. The largest trial consisted of 133 patients. The longest trial lasted 10 days. Most of the trials reported data for only two to six hours. (Please see appendix III: for full details of the characteristics of Included Studies). Seven drug classes were evaluated: nitrates (nine trials), ACE-inhibitors (seven), calcium channel blockers (six), peripheral alpha-1 blockers (four), diuretics (three), direct vasodilators (two) and dopamine agonists (one).
All included trials had patients with elevated blood pressure in the presence of acute end organ damage. Blood pressure entry criteria differed among trials. Four trials were included on the basis of their mean blood pressure values at baseline \(^{12;14;19;20}\). Seven trials included exclusively patients with acute pulmonary edema \(^{12;14;16;19;22;23;25}\). One trial included exclusively patients with hypertensive encephalopathy \(^{18}\). There was no trial that
included exclusively patients with acute aortic dissection or acute myocardial infarction. Thus, the rest of seven trials included a diverse population with different acute end organ damage. Only two trials\(^\text{11,17}\) reported the standard deviation of the change of blood pressure. In the rest of the trials this measure of variability was imputed from the standard deviation at endpoint.

Additional information was required and requested from all included trials. One trialist\(^\text{11}\) provided missing information in the original publication. The rest of the trialists did not reply to our request.

**Table 2-1. Summary of included studies.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Comparators and dose</th>
<th>n</th>
<th>Blood pressure (mm Hg) Inclusion Criteria</th>
<th>Mean SBP/DBP (mmHg) at baseline</th>
<th>Clinical inclusion criteria</th>
<th>Mean SBP/DBP (mmHg) at end-point</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angeli 1991(^\text{11})</td>
<td>Nifedipine 10 mg sublingual (sl) Captopril 25mg sl</td>
<td>10</td>
<td>DBP &gt; 140</td>
<td>247/158 245/145</td>
<td>Acute end organ damage(^\dagger)</td>
<td>204/115 190/116</td>
<td>0</td>
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<tr>
<td>Beltrame 1998(^\text{12})</td>
<td>Nitroglycerine 2.5-10 mcg IV infusion Furosemide 40mg IV boluses</td>
<td>37</td>
<td>Not defined*</td>
<td>161/ NR 164/ NR</td>
<td>Acute pulmonary edema</td>
<td>133/ NR 139/ NR</td>
<td>3</td>
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<tr>
<td>Elliot 1990(^\text{13})</td>
<td>Nitroprusside 0.5-mcg/kg/min IV infusion Fenoldopan 0.1 mcg/kg/min IV infusion</td>
<td>15</td>
<td>DBP &gt; 120</td>
<td>222/137 214/136</td>
<td>Acute end organ damage(^\dagger)</td>
<td>174/105 180/106</td>
<td>NR</td>
</tr>
<tr>
<td>Halminton 1996(^\text{14})</td>
<td>Placebo Captopril 25 mg sl</td>
<td>25</td>
<td>Not defined*</td>
<td>160/100 172/112</td>
<td>Acute pulmonary edema</td>
<td>NR</td>
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<td>Hirschl 1997(^\text{15})</td>
<td>Nitroprusside 0.5-3 mcg/kg/min IV infusion Urapidil 12.5 mg IV boluses</td>
<td>35</td>
<td>SBP&gt;200 and/or DBP&gt;110</td>
<td>211/109 215/107</td>
<td>Acute end organ damage(^\dagger)</td>
<td>151/74 162/88</td>
<td>NR</td>
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<td>Nitroglycerin</td>
<td>23</td>
<td>206/116</td>
<td>136/71</td>
<td></td>
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</tr>
<tr>
<td>Author</td>
<td>Comparators and dose</td>
<td>n</td>
<td>Blood pressure (mm Hg) Inclusion Criteria</td>
<td>Mean SBP/DBP (mmHg) at baseline</td>
<td>Clinical inclusion criteria</td>
<td>Mean SBP/DBP (mmHg) at end-point</td>
<td>DEATHS</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------</td>
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<td>------------------------------------------</td>
<td>---------------------------------</td>
<td>-----------------------------</td>
<td>---------------------------------</td>
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</tr>
<tr>
<td>1999</td>
<td>0.8 mg sl Enalapril</td>
<td>23</td>
<td>SBP&gt;200 or DBP&gt;100</td>
<td>211/115</td>
<td>Acute pulmonary edema</td>
<td>139/70</td>
<td>0</td>
</tr>
<tr>
<td>Marigliano</td>
<td>Nifedipine 10 mg sl</td>
<td>22</td>
<td>SBP&gt;210</td>
<td>208/139</td>
<td>Acute end organ damage†</td>
<td>154/70</td>
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<td>1986</td>
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<td>28</td>
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<td>Hypertensive encephalopathy</td>
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<td>Placebo</td>
<td>20</td>
<td>Not defined*</td>
<td>188/111</td>
<td>Acute end organ damage†</td>
<td>179/101</td>
<td>N</td>
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<tr>
<td>1999</td>
<td>Isosorbide aerosol</td>
<td>30</td>
<td>MAP &gt;130</td>
<td>187/121</td>
<td>Acute end organ damage†</td>
<td>153/92</td>
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<td>134/72</td>
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<td>Comparators and dose</td>
<td>n</td>
<td>Blood pressure (mm Hg)</td>
<td>Mean SBP/DBP (mmHg) at base-line</td>
<td>Clinical inclusion criteria</td>
<td>Mean SBP/DBP (mmHg) at end-point</td>
<td>Deaths</td>
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<tr>
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<td>Hydroalazine</td>
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<td>140/78</td>
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<td></td>
<td>198/122</td>
<td></td>
<td>134/78</td>
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<tr>
<td></td>
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<td></td>
<td>198/128</td>
<td></td>
<td>160/90</td>
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<td></td>
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<td></td>
<td>135/79</td>
<td>N</td>
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</table>

† As stated in the article reflecting the inclusion of patients with different acute end organ damage settings
*T this RCT was included on the basis of the mean blood pressure values at baseline according to our pre-defined thresholds for this category of patients

We excluded 27 clinical trials for several reasons:

- Several trials mixed patients with and without acute end organ damage in the same RCT [12 trials 26-37]
- Other trials included patients without explicitly stating whether patients had acute end organ damage or not [7 trials 38-44]
- Some trials included non-randomized participants in the trial's results [1 trial 45]
- One trial did not report any of the outcomes of interest [1 trial 46]
- Two trials did not fulfilling blood pressure threshold criteria 47;48.
- One was a cross-over trial 49.
• Two trials had wrong comparators (one compared different doses of the same combination therapy\textsuperscript{50}; another compared two drugs of the same class\textsuperscript{51}).

• RCT only included responders to a previously given antihypertensive therapy\textsuperscript{52}.

Two out of 27 excluded trials involved a beta-blocker arm and 18 / 27 excluded trials involved a calcium channel blocker arm. One excluded trial studied exclusively patients with acute aortic dissection\textsuperscript{51}.

2.6.2 Risk of bias in included studies

All studies, except one\textsuperscript{14}, were open-label trials. The method of randomization was not reported in eight trials. The method to achieve concealment of allocation was reported in only two trials\textsuperscript{14,18}.

2.6.3 Effects of interventions: comparisons according to outcomes

2.6.3.1 Total serious adverse events

No trial reported the total number of patients with at least one serious adverse event.

2.6.3.2 All-cause mortality

Mortality was reported in 7 trials\textsuperscript{11,12,16,18,19,22,23} and totaled 6 deaths in 3 RCTs. The group to which the dead patients were originally allocated was not reported for 5 of the deaths. In one RCT, a patient treated with hydralazine died of a rupture of the interventricular septum\textsuperscript{23}. In four trials mortality was reported as nil. In eight trials there was no mention of mortality. It is possible that there were no deaths during the short range of follow-up (6-24 hours), but it is impossible to be certain.
2.6.3.3 Non-fatal cardiovascular events

2.6.3.3.1 Composite

Cardiovascular events were reported in five trials\textsuperscript{12;14;16;18;22}. No trial reported cardiovascular events as a composite. It was not possible to extract events from the original trials and analyze them as a composite due to a risk of double-counting the events.

2.6.3.3.2 Myocardial infarction

One placebo-controlled trial\textsuperscript{14} reported this outcome. There was no statistically significant difference between ACE inhibitors and placebo (RR 0.72, 95\%CI 0.31 -1.72). Three head-to-head trials reported this outcome\textsuperscript{12;18;22}: there was no statistical difference in myocardial infarction between nitrates (2.7\%) and alpha-adrenergic antagonist (5\%) (RR 0.55, 95\%CI 0.09-3.17); nitrates (16\%) versus diuretics (12.5\%) (RR 1.30, 95\%CI 0.40-4.19); or diazoxide (3.5\%) versus dihydralazine (4\%), (RR 0.86, 95\%CI 0.06-12.98).

2.6.3.3.3 Pulmonary edema requiring mechanical ventilation

Three trials reported this outcome\textsuperscript{14;16;22}. There was no meta-analysis performed as there was only one trial for each comparison. There was no statistically significant difference between captopril and placebo (RR 0.40, 95\%CI 0.09 -1.86), nitrates and alpha-adrenergic antagonist (RR 4.12, 95\%CI 0.20-84.24) or between nitrates and ACE-Inhibitor (RR 0.33, 95\%CI 0.01-7.78).

Other than the above, the trials did not report any of our list of CV events (unstable angina, dissection of aortic aneurysm, acute renal failure, or stroke). An additional
cardiovascular event was reported that was not on our list: asystole, which happened in one patient randomized to an ACE inhibitor\textsuperscript{16}.

2.6.3.4 Withdrawal due to adverse events

Only one trial comparing an alpha-blocker with nitroglycerine reported withdrawal due to adverse events\textsuperscript{22}. There were no significant differences between these two drugs classes (5\% vs 2.7\%) (RR 3.38, 95\%,CI 0.17-68.84).

2.6.3.5 Weighted mean change in blood pressure and heart rate during treatment

For this secondary outcome all trials provided some data and we were able to pool these data.

2.6.3.5.1 Drug versus placebo or no treatment

Although we included two placebo-controlled trials, only one provided systolic or diastolic blood pressure (BP) data\textsuperscript{20} and this was limited to one hour of follow-up. In this trial, 3 classes of antihypertensives were included: calcium channel blocker, angiotensin converting enzyme inhibitors, and alpha-1 adrenergic antagonists. The pooled effect showed a statistically significant greater reduction in both systolic (WMD -13.14, 95\%CI, -19.48,-6.80) and diastolic (WMD -8.03, 95\%CI, -12.61,-3.45) blood pressure with antihypertensive therapy. There was no data on heart rate.

It was not possible to extract BP data from the other placebo-controlled trial\textsuperscript{14}. In addition to not reporting any measurement of variability, this trial reported BP data as change in mean arterial pressure (MAP).
2.6.3.5.2 *Nitrates versus diuretics*

Three trials compared nitrates to diuretics\(^{12,19,23}\). Furosemide was the common diuretic used in all of them with two nitrates, nitroglycerine and isosorbide as comparators. Neither systolic nor diastolic blood pressure lowering effect was statistically different between the two classes of drugs. However, in Beltrame 1998, the systolic blood pressure lowering effect of both drugs was greater (-21 mm Hg for furosemide; -23.75 mm Hg for nitroglycerin) than that reported in the other two trials (+1.0, +1.6 mm Hg for furosemide groups; and -6,-8 mm Hg for isosorbide groups, respectively). The reasons for that difference across trials are not clear. Despite these differences, heterogeneity was not present when pooling all these three trials. Heart rate change was also not significantly different for both classes of drugs.

2.6.3.5.3 *Nitrates versus alpha-1 antagonist*

Two trials compared the alpha-1 adrenergic antagonist (A1A), urapidil, with nitrates\(^{15,22}\). The first trial used nitroprusside and the second used nitroglycerine as comparator. The systolic blood pressure lowering effect of the two nitrates was similar (-58.4 mmHg for nitroprusside and -59.5 mmHg for nitroglycerine). However, the effect of urapidil (administrated at the same dose in both trials) was very different (-37.6 mmHg and -73.5 mmHg). A similar discrepancy was seen for diastolic blood pressure. This heterogeneity precluded the pooling of these trials in a meta-analysis for these outcomes.

2.6.3.5.4 *Nitrates versus dopamine agonist*

For this comparison one trial was included\(^{13}\). During 4 hours of treatment, nitrates were associated with a statistically significant greater reduction in systolic blood pressure as
compared with a dopamine agonist (WMD -14.00, 95% CI [-27.72, -0.28]). There were no differences between these classes in diastolic blood pressure or heart rate.

2.6.3.5.5 **Nitrates versus ACE-inhibitors**

One trial compared a nitrate with an ACE inhibitor\(^6\). No statistically significant difference was found between the two groups in systolic or diastolic blood pressure or heart rate.

2.6.3.5.6 **Nitrates versus calcium channel blockers**

By pooling two trials\(^{21,25}\) calcium channel blockers were not associated with statistically significant differences in systolic or diastolic blood pressure as compared to nitrates. Using the fixed effect model, CCBs were associated with statistically significant increase in heart rate as compared to the nitrates (WMD 11.76 95% CI [4.45, 19.07]). However there was significant heterogeneity across trials and this increase was no longer statistically significant when a random effect model was used.

2.6.3.5.7 **Nitrates versus direct vasodilator**

For this comparison one trial was included\(^23\). There was no statistical difference in systolic or diastolic blood pressure reduction between the two drugs. There was also no significant difference between these classes in heart rate change.

2.6.3.5.8 **ACE inhibitors versus calcium channel blockers**

Four trials\(^{11,17,20,24}\) compared an ACE-Inhibitor with a CCB. The pooled data shows that CCBs were associated with a significantly greater reduction in diastolic blood pressure as compared with ACE-I (WMD 7.86, 95% CI [4.92, 10.81]). No statistically significant
difference was found between the two groups in the reduction of systolic blood pressure.  
In three trials that reported heart rate changes\textsuperscript{11,17,24}, CCBs were associated with a significant increase in heart rate as compared with ACE-Inhibitors (WMD 22.91, 95% CI [19.8, 26.01]). However, there was significant heterogeneity across trials and this increase was no longer significant when a random effect model was used.

2.6.3.5.9 \textit{ACE inhibitors versus alpha-1 adrenergic antagonist}

Two trials\textsuperscript{20,24} compared an ACE-inhibitor with an alpha-1 adrenergic antagonist (A1A). Both trials used captopril as comparator but one trial used prazosin and the other used ketanserin. The pooled data shows that ACE-inhibitors were associated with a significantly greater reduction in both systolic and diastolic blood pressure as compared with A1A (SBP WMD -20, 95% CI [-22.85,-17.39]; DBP WMD -3.70, 95% CI [-7.08,-0.31]). For SBP outcome there was statistically significant heterogeneity across trials. However the difference was still significant when the random effects model was used. No statistically significant difference was found between the two groups in the heart rate change in the only trial reporting that outcome \textsuperscript{24}.

2.6.3.5.10 \textit{Diazoxide versus hydralazine}

For this comparison, one trial\textsuperscript{18}, which dealt with exclusively hypertensive encephalopathy patients, was included. During four hours of treatment, hydralazine was associated with a statistically significant greater reduction in both systolic (WMD 13.56, 95% CI [3.06, 24.06]) and diastolic (WMD 14.67, 95% CI [8.01, 21.33]) blood pressure as compared with diazoxide (WMD -14.00, 95% CI [-27.72, -0.28]). It is important to mention, though, that there was no measure of variability reported in this trial. Therefore,
we imputed the standard deviation of the change according to our hierarchy from other trials (last option: weighted mean standard deviation of change from all trials; any drug any dose). There was no heart rate data reported.

2.7 Discussion

This is the first systematic review investigating mortality and morbidity outcomes for all RCTs of drug treatment for hypertensive emergencies. A systematic review that combined hypertensive emergencies and urgencies did not include 11 trials included in our systematic review. Furthermore, Cherney's review mixed randomized with non-randomized trials.

The only other relevant systematic review in relation to hypertensive emergencies is that conducted for acute stroke by BASC 2001. We excluded one trial [n =16 patients] that the BASC 2001 systematic review had included. The reason for excluding it was because the blood pressure criteria in this trial (>170/95 mmHg) did not meet our blood pressure threshold criteria (SBP ≥ 180 and or DBP ≥ 110 mm Hg). This exclusion does not affect our conclusion for clinical outcomes as this trial did not report clinical outcomes. The other BASC 2001 trials were not included because blood pressure at baseline was not elevated. Thus, these clinical trials did not include hypertensive emergency patients as we have defined them.

One of the limitations in our review is that most of the included trials were small (average 58 patients per trial). Furthermore, with the exception of Hamilton (1996) all trials were of poor quality.

Three included trials deserve further discussion. Hamilton 1996, the only double-blind trial, includes patients with acute pulmonary edema and high blood pressure, and it
compared captopril versus placebo. It demonstrates that this high quality and double-blind trial was ethical and feasible. The DANISH II 1986\textsuperscript{18} trial was the only trial that included patients exclusively with hypertensive encephalopathy. This was a well-organized multicentre trial, conducted in Denmark, comparing diazoxide to dihydralazine. Due to its study design, the ethical committee accepted that the informed consent could not be obtained from patients as all of them had symptoms of hypertensive encephalopathy. A downside of this study is the fact that the trialists reported their results in duplicate publications that did not cite the other publications (the original publication, Krogsgaard 1983\textsuperscript{53}, is not cited in the other duplicate publications,\textsuperscript{18;54;55}). In addition, blood pressure values were not the same in the different publications, and none of the publications reported measures of systolic or diastolic blood pressure variability. The largest trial, Schreiber 1998\textsuperscript{22}, included 133 patients with acute pulmonary edema plus high blood pressure, in an out-of-hospital setting, who were randomized to receive either nitroglycerin or urapidil. The ethical committee (Vienna, Austria) agreed that no informed consent had to be obtained at the time of inclusion for randomization. However, the pitfall of this trial is that 16% of all randomized patients were excluded from the analyses, which potentially biased the results. Consistent with this, there was significant heterogeneity when this trial was combined with another trial studying the same comparison groups.

In 19 of the excluded trials\textsuperscript{26-44} it was not possible to determine how many patients had acute end organ damage or merely had elevation of blood pressure. We believe that it would be misleading to include these trials in this review as the impact of
antihypertensive drugs is potentially different. If individual patient data could be obtained, the patients with acute end organ damage could be added to our review. It was perhaps surprising and definitely disappointing that we could find no randomized controlled trial evidence to answer the first question we have posed: Does antihypertensive therapy as compared to placebo or no treatment change mortality and morbidity in patients with hypertensive emergencies? The one available placebo-controlled trial demonstrated that blood pressure was reduced with drugs as compared to the control treatment, however, it was too small and of too short duration to assess morbidity and mortality. We feel it is important for physicians to know that this is one of the clinical settings where treatment is not supported by RCT evidence. Despite the lack of evidence it is not hard to accept the necessity of lowering blood pressure in those clinical settings where the excessive increases in blood pressure are the cause of the end organ damage. However, this is not necessarily the best approach in settings where the excessive elevations of blood pressure are probably caused by end organ damage such as high BP in the presence of a cerebrovascular accident. The presently accepted approach for the immediate treatment of hypertensive emergencies in clinical practice is primarily based on a series of cases published in 1959 (Gifford 1959). In this study, carried out over a period of 18 months, the author demonstrated the ability to reduce blood pressure with nitroprusside, within minutes, in eight patients with hypertensive emergencies (mostly patients with hypertensive encephalopathy), whose blood pressures had remained elevated after treatment with reserpine or hydralazine. However, he did not report clinical outcomes so we do not know whether these patients did better as a result of the blood pressure lowering. Gifford recommended prompt blood
pressure reduction in clinical settings other than hypertensive encephalopathy such as intracerebral or subarachnoid hemorrhage or acute left ventricular failure. The lack of RCT evidence leaves the distinct possibility that in some clinical settings defined as hypertensive emergencies immediate antihypertensive therapy could be doing more harm than good.

These is a hypertensive emergency not included in the present systematic review, eclampsia. Due to its pathophysiology and the involvement of the infant as well as the mother, we felt this clinical entity must be studied separately from other hypertensive emergencies and include outcomes in the infant as well as the mother. There is a Cochrane systematic review [Duley 200656] that has studied the drugs for treatment of very high blood pressure during pregnancy. However, Duley's systematic review was not limited to patients with eclampsia and did not separately report outcomes in the eclampsia patients. To the best of our knowledge, there is no systematic review dealing exclusively with eclampsia and anti-hypertensive treatment. Thus, a systematic review in this specific area is currently needed.

The present review also does not provide any mortality and morbidity evidence from RCTs to inform clinicians as to which first-line antihypertensive drug class provides more benefit than harm in hypertensive emergencies. This lack of evidence was due to the fact that the trials were too small, did not follow the patients for a long enough period of time and frequently failed to report all important outcomes. In addition all the RCTs except one were open-label trials and therefore concealment of allocation was not possible in most cases. Although, these shortcomings of the trials would not likely affect mortality and morbidity outcomes, they could bias blood pressure and heart rate data.
Neither did we find RCTs that compared different strategies to reduce blood pressure. Thus, how fast or how much blood pressure should be lowered in hypertensive emergencies remains unknown.

Although it is unproven, it is highly likely that antihypertensive therapy is an overall benefit in a hypertensive emergency and therefore a placebo controlled trial to prove this would be unethical. What is clear is that this is a clinical area where properly conducted randomized trials are badly needed. At the present time RCTs could be conducted to compare different drug classes and treatment strategies; for example, aggressive rapid lowering of blood pressure to a target versus lowering the blood pressure slowly at a defined rate such as 5-10 % every 2 hours. What is also clear from this review is that any trial must follow patients in the long term and document mortality and morbidity. One of the best examples of an adequate RCT in an emergency setting is the CRASH trial\textsuperscript{57} where 10,000 patients with acute head injury were randomized to intravenous steroids or placebo. Its approach to handle ethical issues could serve as a model when conducting a trial with hypertensive emergency patients.

### 2.8 Authors’ Conclusions

#### 2.8.1 Implications for practice

There is no evidence from RCTs that anti-hypertensive drugs reduce mortality or morbidity in patients with hypertensive emergencies, defined as marked hypertension associated with acute end organ damage. Furthermore, there is insufficient RCT evidence to determine which drug or drug class is most effective in reducing mortality and morbidity. There were some minor differences in degree of blood pressure lowering between drug classes; however, the clinical significance of this is unknown.
This review demonstrates blood pressure-lowering efficacy for nitrates, ACE inhibitors, diuretics, alpha-adrenergic antagonist, calcium channel blockers and dopamine agonists. Nitrates (including nitroprusside) have been the most studied. Therefore, if a hypertensive emergency patient cannot be treated as part of an RCT and a nitrate is available, it is a reasonable choice of therapy.

2.8.2 Implications for research

Randomized controlled trials are needed to assess different blood pressure lowering strategies and different first-line drug classes in patients with hypertensive emergencies. Outcomes in such trials must be mortality and total serious adverse events at different times of follow-up such as seven days, one month and including at least six months of follow-up of all patients.
2.9 References


10. ICH-FDA. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. Clinical safety data


3 EFFECT OF EARLY TREATMENT WITH ANTI-
HYPERTENSIVE DRUGS ON SHORT AND LONG-
TERM MORTALITY IN PATIENTS WITH AN ACUTE 
CARDIOVASCULAR EVENT\textsuperscript{2}

3.1 Background

Acute cardiovascular events represent a significant therapeutic challenge as they are the number one cause of hospitalizations in many countries, including Canada\textsuperscript{1}. A wide range of pharmacological interventions administrated for these conditions have been studied in great detail, worldwide. However, some questions remain unanswered. For instance, it is not known whether blood pressure-lowering drugs given in the early phase of these events is beneficial or harmful. The best time of initiation of treatment with these drugs is also not known, although most clinical guidelines recommend starting treatment within 24 hour of the onset. For example, it is recommended that ACE inhibitors be started within the first 24 hours of an acute myocardial infarction\textsuperscript{2}. In the setting of an acute cardiovascular event, blood pressure is often not elevated and sometimes it is low. Thus, the rationale for the early administration of a blood pressure-lowering drug is not completely clear. The objective of this review is to find randomized controlled trial (RCT) evidence for the use of blood pressure-lowering drugs in this early phase of an acute CVE.

\textsuperscript{2} A version of this chapter has been published. Perez MI, Musini VM, Wright JM. Cochrane Database of Systematic Reviews 2009, Issue 4 Art No. CD006743. DOI:10.1002/14651858.pub2. Effect of early treatment with anti-hypertensive drugs on short and long-term mortality in patients with an acute cardiovascular event.
An acute cardiovascular event is a sudden manifestation of a cardiovascular disease (e.g., myocardial infarction or stroke). According to the World Health Organization, cardiovascular diseases are the leading cause of death in the world. Acute cardiovascular events include acute myocardial infarction (AMI), unstable angina (UA), acute stroke, acute aortic dissection, and left-ventricular failure with acute pulmonary edema. Although these could be considered different clinical entities they share one thing in common; they are life-threatening and have a high rate of initial mortality if left untreated. For example, epidemiological studies from the 1960's showed that 75% of patients died within 24 hours of the onset of acute myocardial infarction.

The best way to understand the rationale for this review is to consider another well-studied intervention, fibrinolysis, which is administered in the early phase of an acute myocardial infarction or stroke. Consider the example of a large RCT [ISIS-2 1988] where 17,187 patients within 24 hours of the onset of a suspected acute myocardial infarction were randomized to receive one-hour streptokinase IV infusion or placebo. The patients were followed for 35 days and relative mortality between the two groups was measured over time. By inspecting the survival curves it was possible to determine that 75% of the deaths in the placebo group occurred during the first 10 days. Streptokinase had no effect on mortality at 48 hours (RR=1.04, 95%CI [0.89,1.21]), but reduced mortality at 10 days (RR= 0.82, 95%CI[0.74,0.91]) and at 35 days (RR=0.77, 95%CI [0.70,0.84]). From this it can be deduced that this immediate and short treatment had a beneficial effect, but this was only manifest when measured at 10 days and 35 days. This trial, therefore, represents the ideal design we are looking for in this review where an early (within 24 hours) antihypertensive intervention is given for a short time (up to 48
hours) to patients with an acute cardiovascular event, and the key outcomes are reported at 48 hours, 10 days and ≥30 days. We have chosen these times as it has been emphasized that when the severity of a disease changes quickly over time, the follow-up periods need to be subdivided into an early period, an intermediate period and a late period. In addition to this ideal trial design, we have also studied and analyzed trials in which the intervention was started within 24 hours and continued for up to 10 days. We refer to the 1 - 48 hour intervention as "immediate" and the intervention started within 24 hours and continued up to 10 days as “short-term”.

For trials where the experimental treatment and control was continued for more than 10 days we limited our analysis to the 2 day and 10 day mortality. Most patients are stable after 10 days and drug effects occurring after the acute period are not within the purview of this review.

3.2 Description of the intervention

Anti-hypertensive or blood pressure-lowering drugs are defined as those pharmacological agents indicated and used to treat elevated blood pressure or hypertension. According to the World Health Organization (WHO) / International Society of Hypertension (ISH), and other international guideline committees (such as ESH-ESC 2007, BHS-IV 2004, JNC-7, 2003) these include angiotensin converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARBs), beta-adrenergic receptor blockers (BB), calcium channel blockers (CCB), diuretics, nitrates (including nitroprusside).

It is important to emphasize that anti-hypertensive drugs have the potential to cause pharmacological actions other than lowering BP (for example, reducing heart rate) when administrated to humans, which makes them usable for indications other than treating
hypertension. In contrast, there are drugs that have the potential to reduce blood pressure (for example: morphine in certain doses and settings) but are not classified as anti-hypertensive drugs. The latter types of drugs are not considered in this review.

Anti-hypertensive drugs are commonly used and recommended in the early phase of an acute cardiovascular event. The most common anti-hypertensive drugs that are recommended are ACEI [for acute myocardial infarction\(^2\);\(^\text{12}\); and for unstable angina or non-ST elevation myocardial infarction (UA/NSTEMI)\(^1\);\(^\text{13}\), BB [for AMI\(^2\);\(^\text{12}\); for UA/NSTEMI\(^1\);\(^\text{13}\), and for Stroke (hypertensive)\(^1\);\(^\text{14}\), CCB [for AMI\(^2\), and for Stroke (hypertensive)\(^1\);\(^\text{14}\), diuretics [for AMI with acute pulmonary edema\(^2\), and nitrates [ for AMI\(^2\);\(^\text{8}\), for UA/NSTEMI\(^1\);\(^\text{13}\), and for Stroke (hypertensive)\(^1\);\(^\text{14}\).

### 3.2.1 How do the interventions might work?

The exact mechanism of action of blood pressure-lowering drugs, antihypertensives, is often not known with certainty, but each of the different classes of drugs acts at different sites and by different mechanisms.

#### 3.2.1.1 Angiotensin converting enzyme inhibitors (ACE-I)

ACE-I inhibit the conversion of angiotensin I, a relatively inactive peptide, to angiotensin II, which is a potent vasoconstrictor and causes release of aldosterone from the adrenal cortex. The ACE-I probably lower blood pressure by reducing the blood pressure-increasing effects of Angiotensin II.
3.2.1.2 Angiotensin II receptor blockers (ARBs)

ARBs inhibit the binding and action of Angiotensin II at the angiotensin II type 1 (AT1) receptor, which is the site of action to cause vasoconstriction and release of aldosterone. They, thus, also probably reduce blood pressure by blocking the blood pressure-increasing effects of Angiotensin II.

3.2.1.3 Beta-adrenergic receptor blockers (BB)

In general, beta-adrenergic receptor-blocking drugs or beta-blockers (BB) are drugs that competitively inhibit the effect of the catecholamines, noradrenaline and adrenaline, on beta-adrenergic receptors. There are subtypes of beta-blockers depending on their relative affinity for B1 and B2 receptors, partial agonist activity, and ability to also block alpha-adrenergic receptors. Catecholamines have a positive chronotropic and inotropic actions on the heart, can cause vasoconstriction or vasodilatation of blood vessels and stimulate renin release from the kidney. Thus, BB drugs could lower blood pressure by a number of these differing effects. The exact mechanism by which beta-blockers lower blood pressure in humans is not known.

3.2.1.4 Calcium channel blockers (CCB)

Calcium channel blockers reduce the cytosolic free-calcium concentrations by blocking transmembrane calcium influx through L-type calcium channels. Dihydropyridines (such as nifedipine), benzothiazepines (diltiazem) and phenylalkylamines (verapamil) bind to the pore-containing the α1 subunit of the L-type calcium channel. In general, calcium channel blockers relax arteriolar smooth muscle, resulting in vasodilatation and decreased peripheral resistance. The decreased systemic resistance is thought to cause the blood pressure reduction. Agents that slow the rate of recovery of L-type calcium channels
(verapamil, diltiazem) have negative chronotropic and dromotropic effects on the heart's conducting system. The CCBs also have a natriuretic effect on the kidney that may contribute to their ability to lower blood pressure.

3.2.1.5 Diuretics

Thiazide diuretics inhibit the Na⁺Cl⁻ co-transporter in the proximal part of the distal convoluted tubule of the kidney. This decreases tubular reabsorption of sodium and chloride, and increases urinary excretion of sodium and water.

Furosemide and other loop diuretics inhibit sodium reabsorption in the ascending limb of the loop of Henle as well as in both proximal and distal tubules.

The mechanism by which diuretics lower blood pressure has not been established.

3.2.1.6 Nitrates (including nitroprusside)

Organic nitrates and sodium nitroprusside (SNP) are nitric oxide (NO) donors. Organic nitrates, such as glyceryl trinitrate (nitroglycerine) require enzymatic metabolism to generate NO. In contrast SNP spontaneously generates this NO. There are a number of theories about how nitrates cause vasodilatation:

Nitrates act on specific nitrate receptor (containing a sulphhydryl group-SH),

NO exerts a potassium channel activation (hyperpolarizing the cell membrane); and

NO activates the enzyme guanylate cyclase increasing cGMP levels, which in turn inhibits Ca⁺⁺ entry into smooth muscle cells and increases Ca⁺⁺ uptake by the smooth endoplasmic reticulum resulting in vascular smooth muscle relaxation.
3.3 Why is it important to do this review?

The main goal is to answer the question, “does blood pressure-lowering by all classes of blood pressure-lowering drugs during the early phase of an acute cardiovascular event affect mortality and morbidity?”

It is important to appreciate that during the first hours after an acute cardiovascular event, complex hemodynamic changes are occurring, making the organs involved especially vulnerable to local and systemic changes. Blood pressure reduction during this time could be beneficial, but it is equally likely that it is detrimental.

Recently, thanks to the advances in the understanding of the underlying pathophysiological mechanisms involved in some acute cardiovascular events (such as the thrombotic occlusion at the site of atherosclerotic plaques in AMI) different pharmacological interventions have been implemented and proven beneficial. For example, randomized controlled trial (RCT) evidence has demonstrated a reduction in mortality with the use of thrombolytic drugs\textsuperscript{15,16} and anti-platelet drugs\textsuperscript{17} in acute AMI. There is also RCT evidence for benefit with the use of anti-platelet drugs\textsuperscript{17} in the acute treatment of stroke. The benefits of these pharmacological therapies have been claimed to be greater when they are administrated in the early phase (for example: thrombolysis within 6 hours) of the onset of the acute cardiovascular event. Thus, the time of the administration can be an important determinant as to whether an intervention is beneficial or harmful to patients with an acute cardiovascular event.

The rationale for administering blood pressure lowering drugs in the early phase of an acute cardiovascular event is less well understood. In acute cardiovascular events associated with marked elevation of blood pressure (defined as hypertensive emergencies
by JNC-7, 2003\textsuperscript{10}) blood pressure lowering makes some pathophysiological sense as if the elevated blood pressure is causing organ damage, reducing blood pressure is likely to be beneficial. However, there is no RCT evidence to demonstrate mortality and morbidity benefits of the use of blood pressure lowering drugs in hypertensive emergencies\textsuperscript{18}. This lack of evidence for situations where blood pressure is elevated emphasizes the importance of attempting to assess the benefits and harms in acute cardiovascular events in general. In the setting of acute cardiovascular event in general most of the time blood pressure is not elevated and sometimes it is low.

We have deliberately chosen outcomes in this review that are a measure of both benefit and harm in order to avoid selective reporting bias. Due to the standardized definition of serious adverse events, SAEs, (any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of hospitalization, or results in persistent or significant disability\textsuperscript{19}), measuring total number of people with at least one serious adverse event would provide a pretty close estimate of the net health effect (benefit minus harm) of an intervention\textsuperscript{20}. However, in acute, critically-ill hospitalized patient settings, measuring SAE could be problematic and/or impractical. The main reason for this is because physician must make a judgment as to whether an event led to prolongation of hospitalization. Therefore, in these acute clinical settings total all-cause mortality, a subgroup of total SAEs, is the best measure of net health effect\textsuperscript{21}. All cause mortality is an outcome measure that is not subject to physician judgment and which is usually reported in trials. It is easy to appreciate that an intervention that decreases mortality as compared to placebo is beneficial, while an intervention that increases mortality compared to placebo is harmful. Thus, we have chosen all-cause mortality as
our primary outcome and total non-fatal serious adverse event as one of our secondary outcomes anticipating that trials might not consistently report this outcome.

Secondly to answer, whether blood pressure lowering by the different subclasses of blood pressure-lowering drugs during the early phase of an acute cardiovascular event affects mortality and morbidity? This question can be answered by performing a subgroup analysis where the effect of the drugs in the different classes of blood pressure lowering drugs are analyzed separately and compared with each other.

There are other published systematic reviews of randomized controlled trials dealing with antihypertensive drugs for acute cardiovascular events (specifically for acute myocardial infarction or stroke). For acute myocardial infarction, reviews have been published for each different class of anti-hypertensive drug: for CCB\(^{22}\); for BB\(^{23-25}\); for nitrates\(^{26}\), and ACE inhibitors\(^{27,28}\). In addition, there are three published systematic reviews dealing with acute stroke: Horn et al 2000\(^{29}\) for CCB, Bath et al 2002 for nitrates\(^{30}\), and Geeganage et al 2008\(^{31}\) for diverse interventions.

These systematic reviews all have significant drawbacks and none were designed to assess the specific objective of this review. Some were not limited to immediate treatment (Rodrigues 2003\(^{28}\); AMICG 1998\(^{27}\); Held 1989\(^{22}\); Yusuf 1985\(^{26}\); Al-Reesi 2008\(^{25}\); Bath 2002\(^{30}\); Freemantle 1999\(^{24}\)) and included trials where the treatment started days after the onset of the acute cardiovascular event. One review mixed trials with control group (no treatment or placebo) with trials that have an active comparator as control, Yusuf 1988\(^{26}\). Except for Geeganage 2008\(^{31}\), all these reviews are limited by not being up-to-date.
This is the first systematic review with the objective to assess the effects of all blood pressure lowering drugs administrated as immediate treatment (starting within 24 hours) in patients with an acute cardiovascular event, on mortality, morbidity and blood pressure outcomes.

### 3.4 Objectives

#### 3.4.1 Primary

To determine the effect of immediate\(^\wedge\) and short-term\(^{\wedge\wedge}\) treatment with antihypertensive drugs on mortality at 2 days, 10 days and \(\geq 30\) days in patients with an acute cardiovascular event.

\(^\wedge\) Immediate treatment is defined as treatment started within 24 hours of the onset of an acute cardiovascular event and lasting for a maximum of 2 days.

\(^{\wedge\wedge}\) Short-term treatment is defined as treatment started within 24 hours of the onset of an acute cardiovascular event and lasting for a maximum of 10 days.

#### 3.4.2 Secondary

To determine the effect of anti-hypertensive drugs on blood pressure and heart rate during the first 24 hours of treatment in patients with an acute cardiovascular event.
3.5 Methods

3.5.1 Criteria for considering studies for this review

3.5.1.1 Types of studies
Randomized controlled trials (RCTs) with parallel design, comparing an anti-hypertensive drug with placebo, or no treatment, in patients with an acute cardiovascular event.
The intervention (anti-hypertensive treatment) must be started within 24 hours of the onset of the acute cardiovascular event.
Patient must be followed for at least 24 hours and mortality or SAE data must be provided at least one of the specified time periods, 2 days, 10 days or ≥ 30 days.

3.5.1.2 Types of participants
Participants with any of the following acute cardiovascular events: myocardial infarction, unstable angina, acute left-ventricular failure with pulmonary edema, acute aortic dissection, stroke, intracranial hemorrhage, sub-arachnoid hemorrhage

3.5.1.3 Types of interventions
Intervention: any anti-hypertensive drug
Anti-hypertensive drug belonging to any of the following classes of drugs: Nitrates (including nitroprusside), beta adrenergic antagonists (BB), angiotensin converting enzyme inhibitors (ACE-I), calcium channel blockers (CCB), dopamine agonists, alpha-adrenergic antagonists, diuretics [furosemide and thiazides], direct vasodilators (diazoxide, hydralazine) and others (reserpin, clonidine, alpha-methylldopa, trimethaphan)
Control: Placebo or no early antihypertensive treatment

Placebo is defined as inert substance designed to resemble the drug being tested but which has no active ingredient and has no treatment effect. In trials, where a placebo is used as a comparator, all patients in the placebo group usually receive the same medical treatment, except for the drug being tested, as the experimental group. This is achieved by the utilization of a double-blind study design in these trials. In trials where no treatment is used as a comparator it is assumed that all medical treatments other than antihypertensive treatment intervention being studied are the same in both groups. In these trials the design is open-label and not blinded.

3.5.1.4 Types of outcome measures

**Primary outcome**

All-cause mortality at 2 days, 10 days and ≥ 30 days.

**Operational definitions:**

- At 2 days also accepts cumulative mortality at times less than 48 hours if that is the only data available.
- At 10 days also accepts cumulative mortality reported after 2 days and at times less than 10 days if that is the only data available.
- At ≥ 30 days also accepts cumulative mortality reported as 1-month or 4-week mortality and for any duration of follow up longer than 30 days.

**Secondary outcome**

Total number of patients with at least one non-fatal Serious Adverse Event (SAE) at the same time periods for all cause mortality.
Weighted mean change in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR), during the first 24 hours of treatment.

3.5.2 Search methods for identification of studies

3.5.2.1 Search strategy

We used wild symbols and letters for this extensive search. MEDLINE, EMBASE, and Cochrane clinical trial register from Jan 1966 to February 2009 was searched for randomized controlled trials. We also browsed the reference lists in review articles and trials for any studies that may have not been identified by the search strategy. In case of missing information in the retrieved articles, authors were contacted.

The search strategy applied to identify all antihypertensive drugs and trials using a comprehensive search strategy and key words: controlled clinical trial, randomized controlled trials and other terms listed in the search strategies.

3.5.2.2 Medline search

Please see appendix IV: MEDLINE and EMBASE Searches for a detailed list of search criteria.

3.5.2.3 EMBASE search

Please see appendix IV: MEDLINE and EMBASE Searches for a detailed list of search criteria.

3.5.2.4 CENTRAL search

This search was identical to EMBASE and MEDLINE searches but without the "trials" component as CENTRAL only deals with randomized-related studies.
3.5.3 Data collection and analysis

3.5.3.1 Data extraction

Two reviewers (MIP & VM) independently decided whether a trial was included. They also extracted and verified data entry from included studies. Discrepancies were resolved by discussion. Absence of consensus was resolved by a third reviewer (JMW).

3.5.3.2 Analysis

For the analysis of the data, Cochrane review manager software, RevMan 5 was used. Quantitative analyses of outcomes were based on intention-to-treat principles as much as possible. We used weighted mean difference to combine continuous variables and expressed relative and absolute risk difference (with 95% confidence interval) for dichotomous outcomes to accept significant differences. Pooled risk differences obtained from Mantel-Haenszel fixed effect model were converted to numbers needed to treat (NNTs) where appropriate.

Heterogeneity between trial results was tested using the $I^2$ statistic where percentages greater than 50% were taken to indicate significant heterogeneity.

The effects of immediate treatment with antihypertensive drugs on 2 day, 10 day and $\geq$30 day mortality in patients with an acute cardiovascular event were explored. The effects of short-term treatment with antihypertensive treatment were explored at 10 days and $\geq$30 days. In trials where the study treatment was continued longer than day 10, data was not included for the $\geq$30 day time period. To quantify the occurrences of deaths the cumulative incidence reported in each trial (based on full Intention to Treat principles) was used. For example, for our day-10 mortality measure we included the cumulative incidence from time of randomization to day-10 inclusive (or at discharge from hospital
when trial did not report the time - the assumption here is that the average hospitalization is about 7-10 days).

A sensitivity analysis was performed to test the impact of the design of the trial, double-blind vs. open label trials. Sensitivity analysis was also performed according to the class of drug, clinical condition, dose regimen, duration of treatment and concomitant pharmacological interventions.

Non-fatal serious adverse events (NF-SAEs) were included only if they were reported as total, not as individual non-fatal SAE. The reason for doing this was to avoid double counting individual NF-SAE (as one patient may suffer from one or more NF-SAE and could be included more than once in the original report) and to prevent selection reporting bias (as many trials could omit certain NF-SAEs).

Data for blood pressure and heart rate were combined using a weighted mean difference method, whereby the trials are weighted according to the number of subjects in the trial and the within-study variance. Some of the trials did not report a within-study variance for blood pressure change; in these studies standard deviation (SD) of change was imputed using the following hierarchy.

1. Pooled standard deviation calculated either from the t-statistic corresponding to an exact p-value reported or from the 95% confidence interval of the mean difference between treatment group and comparative group.


3. Standard deviation of blood pressure/heart rate at baseline (except if this measure is used for entry criteria).
4. Weighted mean standard deviation of change in blood pressure/heart rate calculated from at least 3 other trials using the same drug and dose regimen.
5. Weighted mean standard deviation of change in blood pressure/heart rate calculated from other trials using the same drug.
6. Weighted mean standard deviation of change in blood pressure/heart rate calculated from all other trials (any drug and dose).
7. Weighted mean standard deviation in blood pressure/heart rate at end of treatment calculated from at least 3 other trials using the same drug and dose regimen.
8. Weighted mean standard deviation in blood pressure/heart rate at end of treatment calculated from all other trials (any drug and dose).

3.6 Results

3.6.1 Description of studies

3.6.1.1 Results of the search
The search strategy yielded 3412 citations and 82% of these were excluded after reading titles and abstracts. The remaining 623 citations were retrieved for detailed evaluation and 410 were excluded for the reasons shown in (see Figure 3-1). Of the 213 citations of randomized controlled trials we identified, 102 (65 trials) were included in this review. The specific reasons for exclusion of the other 111 (70 trials) are explained in Table 3-1. Most of these trials had to be excluded because they did not report mortality data.
Figure 3-1 Quorum Flowchart or Citations (RCTs)

Citations identified in literature search*: N= 3,412

Citations excluded by reading title and abstract [clearly no relation to our work]: n=2,791

Citations retrieved for more detailed evaluation: n=621

Excluded: n= 410 (103)
Reasons:
- Reviews/ sec. analysis: n=125
- Active comparator: n=18 (17)
- Included patients after 24 hours of symptom onset: n=210 (86)
- Other (non-randomized, non-acute setting, etc): n=57

Citations of potentially appropriate randomized controlled trials: n= 211

Excluded: n= 111 (70)
Reasons:
- Follow-up < 24 h: n=8 (5)
- Uncertain time of patient’s inclusion: n=26 (18)
- Primary outcome not reported: n=77 (47)

Included: n= 100 (65)
3.6.1.2 Excluded studies

There were 70 excluded trials. Although these trials could have been excluded for several reasons, the following are the primary reasons:

- Mortality not reported or not reported in a form or time period that we could use: 47 trials.
- Uncertain time of patient inclusion following the acute event: 18 trials.
- Follow-up of less than 24 hours: 5 trials.

Forty-seven trials were excluded due to lack of mortality data or mortality data that were not reported in a form or time period that we could use. There were three sub-types:

A) Not reporting mortality at all, in either original, additional publications or after being requested to provide such data [18 trials]. B) Reporting mortality but not according to our pre-specified time-frame [22 trials]; or reporting it in an abstract but not confirmed by additional publications or after being requested it [2 trials]; and C) Reporting mortality but not based on intention to treat (ITT) principles [7 trials]. An example of the latter sub-category is a multicenter double-blind trial conducted by Walker 1988 et al. Mortality rate was reported as 7/106 in the nifedipine group and 7/120 in the placebo group. After detailed reading of Walker's original and additional publications, it was found that the actual number of randomized patients was 217 in each group. Thus, the investigators failed to report mortality in approximately 50% of the randomized patients. As this population represents a selected sub group of patients, if the information in this trial had been included in our review, it would have been misleading. Other trials that fell into this category were Eveson 2007, Szczechowski 1994, DAVIT I 1984, HINT 1986, Barber 1976 and Balcon 1966 et al.
Our justification for excluding those trials, which had an uncertain time of patient inclusion following the acute event, was to avoid having a heterogeneous population that could lead to erroneous conclusions. The uncertain time inclusion applies to those trials that failed to explicitly state a specific time for inclusion, or trials that included their patients "on admission" or "immediately after admission". We believe that this is too imprecise to determine the exact time that had elapsed from symptom onset to the inclusion of the patient and therefore to the initiation of therapy. It is possible that some patients could have had a delayed admission (symptoms began > 24 hours). This also would likely bias for survivors. In addition, having a delayed admission was more common in trials conducted before 1980-90, when infrastructure for emergency response to assist patients with acute cardiovascular event was not as uniformely developed as it is today. An illustrative example of this category of excluded trials is that of a double-blind trial where patients were to be included "immediately after admission" in 16 Danish centres (DAVIT I 1984\textsuperscript{35}). It was determined that the treatment was started after 24 hours in >15% of patients with AMI; mortality data were not reported separately for these patients.

Therefore, data from 65 trials (those excluded due to uncertain timing and those due to improper or non-extractable mortality data) out of 70 excluded trials could potentially be added to our review. Of these 65 excluded trials, 14 involved an ACE inhibitor (N=4,407); 21 trials involved a B-adrenergic Blocker (N=2,524); 8 trials involved a nitrate (N=1,475) and 20 trials involved a CCB (N=10,958). If these excluded patients were added to the included patients it would have only a small impact on the ACE inhibitor data (increase by 5.2%), BB data (increase by 3.5%), and nitrate data (increase
by 1.7%). However, it could have a large impact on the calcium channel blocker data (increase by ~600%, from 2,141 to 13,099). There were 3/65 studies (N=126) that involved other classes of blood pressure lowering drugs (2 trials for the alpha-1 adrenergic antagonist, prazosin\textsuperscript{39,40}; and 1 trial for alpha-2 centrally acting agonist, clonidine\textsuperscript{41})

Of 70 excluded studies, 52 trials involved patients with AMI, 9 trials included patients with acute stroke, 6 trials- unstable angina, 3 trials- acute pulmonary edema, and 1 trial - subarachnoid hemorrhage patients (See Table 3-1).

There was no trial identified that included patients with acute aortic dissection and compared an active drug vs. placebo or no treatment within 24 hours of the onset. To the best of our knowledge there is only one randomized controlled trial that has included exclusively patients with acute aortic dissection and randomized their patients within 24 hour of the onset, Yoshida 1998\textsuperscript{42}. However, this trial compared two active treatments.

**Table 3-1 Reasons for exclusion of studies**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reason for exclusion</th>
</tr>
</thead>
</table>
| Annane 1996\textsuperscript{43} | Follow-up less than 24 hours. A secondary reason for exclusion was that this trial only included responders to another anti-hypertensive before entering to the trial  
Setting: Acute cardiogenic pulmonary edema |
| Ardissino 1997\textsuperscript{44} | Uncertain time of inclusion of patients  
Setting: unstable angina |
| Azancot 1982\textsuperscript{46} | Mortality not reported  
Setting: AMI |
| Azcona 1990\textsuperscript{46} | Mortality not reported. No publication was found for the results of the trial.  
Setting: acute stroke |
| Balcon 1966\textsuperscript{38} | Mortality not reported according to our time-frame. A secondary reason for exclusion was that results are not given on an intention to treat basis.  
Setting: AMI |
| Basu 1997\textsuperscript{47} | Mortality not reported according to our time-frame.  
Setting: AMI |
| Blanc 1989\textsuperscript{48} | Mortality not reported.  
Setting: AMI |
<table>
<thead>
<tr>
<th>Trial</th>
<th>Reason for exclusion</th>
</tr>
</thead>
</table>
| Briant 1970<sup>46</sup>    | Uncertain time of inclusion of patients  
Setting: AMI                                                                                                                                       |
| Bussmann 1984<sup>50</sup>  | Mortality not reported.  
Setting: AMI                                                                                                                                         |
| CATS 1994<sup>41</sup>      | Mortality not reported according to our time-frame. Letter sent to trialists on July 19, 2008, trying to obtain data. We have not got a response yet |
| CHHIPS 2005<sup>52</sup>    | Mortality not reported. Publication of the trial results were never found published  
                                                                                                                                                |
| Davalos 1992<sup>53</sup>   | Mortality not reported according to our time-frame  
                                                                                                                                                |
| DAVIT I 1984<sup>35</sup>   | Uncertain time of inclusion of patients. For example, It is stated that patients were to be included "on admission", but treatment started after 24 hours in >15% of patients with AMI and mortality data was not reported separately for those starting earlier or later than the 24 hours. An additional problem was that these AMI patients were part of a subset of the entire randomized patients (AMI-41% + suspected AMI-59%) based on intention to treat analysis. Therefore, it should not be dismissed the possibility of the inclusion of additional patients being admitted later than 24 hours if all randomized patients were considered  
                                                                                                                                                |
| Emanuelsson 1984<sup>54</sup> | Mortality was not reported  
                                                                                                                                                |
| EMIP 1994<sup>55</sup>      | Mortality not reported according to our time-frame.  
                                                                                                                                                |
| Evemy 1978<sup>56</sup>     | Uncertain time of inclusion of patients  
                                                                                                                                                |
| Eveson 2007<sup>33</sup>    | Mortality results are not given on an intention to treat basis. Letter sent to trialists on March 4, 2008, trying to obtain data. We have not got a response yet  
                                                                                                                                                |
| FAMIS 1998<sup>57</sup>     | Mortality not reported according to our time-frame. Sent letter to trialists on June 20,2008, trying to obtain data. We've got no response yet  
                                                                                                                                                |
| Franke 1996<sup>58</sup>    | Mortality not reported according to our time-frame. Sent letter to trialists on August 12,2008, trying to obtain data. We have not got a response yet  
                                                                                                                                                |
| French 1999<sup>59</sup>    | Mortality not reported according to our time-frame. Sent letter to trialists on July 1, 2008, trying to obtain data. We have not got a response yet  
                                                                                                                                                |
| Gardtman 1999<sup>70</sup>  | Uncertain time of inclusion of patients  
                                                                                                                                                |
| Gebalska 2000<sup>51</sup>  | Mortality not reported  
                                                                                                                                                |
| Gelmers 1984<sup>62</sup>   | Uncertain time of inclusion of patients  
                                                                                                                                                |
| Gerstenblith 1982<sup>63</sup> | Uncertain time of inclusion of patients. Chronic Unstable angina  
                                                                                                                                                |
| GISSI-3p 1994<sup>64</sup>  | Mortality not reported according to our time-frame. Pilot trial for AMI  
                                                                                                                                                |
| Gonzalez-Fernandez 1993<sup>65</sup> | Uncertain time of inclusion of patients  
                                                                                                                                                |
| Gordon 1984<sup>66</sup>   | Mortality not reported  
                                                                                                                                                |
| Gottlieb 1986<sup>67</sup>  | Mortality not reported according to our time-frame.  
                                                                                                                                                |
| Gottlieb 1988<sup>68</sup>  | Mortality not reported according to our time-frame. Letter sent to trialists on August 13, 2008, trying to obtain data. We have not got a response yet  
                                                                                                                                                |
| Gupta 1984<sup>69</sup>     | Incomplete reporting- only abstract  
                                                                                                                                                |
| Gupta 1985<sup>70</sup>     | Mortality not reported according to our time-frame.  
                                                                                                                                                |
| Hamilton 1996<sup>71</sup>  | Follow-up less than 24 hours.  
                                                                                                                                                |
| Haude 1991<sup>72</sup>     | Follow-up less than 24 hours.  
<pre><code>                                                                                                                                            |
</code></pre>
<table>
<thead>
<tr>
<th>Trial</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEART 1997</td>
<td>Mortality not reported. Letter sent to trialists on August 4, 2008, trying to obtain data. We have not got a response yet</td>
</tr>
<tr>
<td>HINT 1986</td>
<td>Uncertain time of inclusion of patients, A secondary reason for exclusion was that results are not given on an intention to treat basis</td>
</tr>
<tr>
<td>Jaffe 1987</td>
<td>Mortality not reported</td>
</tr>
<tr>
<td>Just 1986</td>
<td>Mortality not reported</td>
</tr>
<tr>
<td>Kahler 1995</td>
<td>Mortality not reported according to our time-frame.</td>
</tr>
<tr>
<td>Karlberg 1998</td>
<td>Mortality not reported according to our time-frame.</td>
</tr>
<tr>
<td>Kolettis 1983</td>
<td>Mortality not reported according to our time-frame.</td>
</tr>
<tr>
<td>Kumada 1995</td>
<td>Uncertain time of inclusion of patients</td>
</tr>
<tr>
<td>Lejmetel 1993</td>
<td>Mortality not reported. Letter sent to trialists on July 20, 2008, trying to obtain data. We have not got a response yet. Publication of the trial results were never published</td>
</tr>
<tr>
<td>Lloyd 1988</td>
<td>Mortality not reported</td>
</tr>
<tr>
<td>Loogna 1985</td>
<td>Mortality not reported</td>
</tr>
<tr>
<td>Macleod 1980</td>
<td>Mortality not reported. There was only an abstract reported</td>
</tr>
<tr>
<td>Manolis 1999</td>
<td>Uncertain time of inclusion of patients. It could be argued that it was within 24 hours since study treatment was given right after thrombolysis, but we could not confirm this</td>
</tr>
<tr>
<td>Matias-Gutierrez 1992</td>
<td>Mortality not reported according to our time-frame.</td>
</tr>
<tr>
<td>McGrath 1986</td>
<td>Mortality not reported.</td>
</tr>
<tr>
<td>Morris 1995</td>
<td>Mortality not reported according to our time-frame. Letter sent to trialists on August 13, 2008, trying to obtain data. We have not got a response yet</td>
</tr>
<tr>
<td>Mueller 1980</td>
<td>Uncertain time of inclusion of patients</td>
</tr>
<tr>
<td>Murdock 1990</td>
<td>Uncertain time of inclusion of patients</td>
</tr>
<tr>
<td>Oldroyd 1991</td>
<td>Mortality not reported according to our time-frame. Letter sent to trialists on July 24, 2008, trying to obtain data. We have not got a response yet.</td>
</tr>
<tr>
<td>Oshima 1997</td>
<td>Mortality not reported according to our time-frame.</td>
</tr>
<tr>
<td>Osuna 1985</td>
<td>Uncertain time of inclusion of patients</td>
</tr>
<tr>
<td>Ramsdale 1988</td>
<td>Mortality not reported</td>
</tr>
<tr>
<td>Reinert 2004</td>
<td>Uncertain time of inclusion of patients</td>
</tr>
<tr>
<td>Renard 1987</td>
<td>Follow-up less than 24 hours</td>
</tr>
<tr>
<td>Reynolds 1972</td>
<td>Uncertain time of inclusion of patients. A secondary reason for exclusion was that results were not given on intention to treat basis.</td>
</tr>
<tr>
<td>Schrader 2003</td>
<td>Mortality not reported according to our time-frame. This trial included patients within 24h and within 36 h, but results are not reported separately for those two categories. Letter sent to trialists on May 1, 2008, trying to obtain data. We have not got a response yet</td>
</tr>
<tr>
<td>Sloman 1967</td>
<td>Uncertain time of inclusion of patients</td>
</tr>
<tr>
<td>SMILE 1995</td>
<td>Mortality not reported according to our time-frame. Letter sent to trialists on June 20, 2008, trying to obtain data. We have not got a response yet.</td>
</tr>
<tr>
<td>Szczechowski 1994</td>
<td>Mortality results are not given on an intention to treat basis</td>
</tr>
<tr>
<td>Waagstein 1976</td>
<td>Follow-up less than 24 hours</td>
</tr>
<tr>
<td>Trial</td>
<td>Reason for exclusion</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Walker 1988</td>
<td>Mortality results are not given on an intention to treat basis. Letter sent to trialists on August 13, 2008, trying to obtain data. We have not got a response yet</td>
</tr>
<tr>
<td>Wilcox 1980a</td>
<td>Mortality not reported according to our time-frame.</td>
</tr>
<tr>
<td>Wilcox 1980b</td>
<td>Mortality not reported according to our time-frame</td>
</tr>
<tr>
<td>Wilcox 1986</td>
<td>Mortality not reported according to our time-frame. Last letter sent to trialists on August 13, 2008, trying to obtain data. We have not got a response yet</td>
</tr>
<tr>
<td>Wimalaratna 1994</td>
<td>Mortality not reported. Letter sent to trialists on August 13, 2008, trying to obtain data. We have not got a response yet</td>
</tr>
<tr>
<td>Zochowski 1986</td>
<td>Uncertain time of inclusion of patients</td>
</tr>
</tbody>
</table>

### 3.6.1.3 Included studies

Sixty-five randomized controlled trials (N=166,206) were found that satisfied the inclusion criteria. Of those, 40 (60%) were double-blind placebo-controlled trials, involving 75% (N=125,487) of the entire studied population (Table 3-2). All included trials reported mortality for at least one of the time points of interest (please see appendix V for details of all included studies); none of the trials reported the total number of non-fatal serious adverse events. The largest trial included 58,050 patients. Twenty-one trials studied immediate treatment and 44 trials studied short-term treatment. The duration of treatment was for more than 10 days in 27/65 trials. We were able to extract short-term mortality (at day 10) in 62 trials. Four classes of blood pressure lowering drugs were evaluated: ACE inhibitors (12 trials), B-blockers (20 trials), Calcium channel blockers (18 trials) and nitrates, including nitroprusside (18 trials). The included trials studied patients with only 2 types of cardiovascular events: acute myocardial infarction (59 trials) and stroke (6 trials) (Table 3-3).

All included trials enrolled their patients within 24 hours of the onset of an acute cardiovascular event. In this review, we have assumed that enrollment, randomization and administration of the study drug occurred simultaneously. The details of the process
involved were not described in any of the trial reports. The objective for accepting these types of trials was to evaluate the effects of early anti-hypertensive treatment in an acute setting. In the acute myocardial infarction (AMI) trials the average time of initiation of the study drug was 6.35 ± 4.74 hours after the onset. No stroke trial reported the time that treatment started. However, the included AMI studies scheduled their randomization 5 hours earlier than the stroke studies (12.6 ± 7.8 and 17 ± 8, respectively). We did find trials dealing with acute pulmonary edema and acute aortic dissection where patients were randomized within 24 hours. However, these trials had to be excluded for different reasons (see above, Excluded Studies).
### Table 3-2 Overview of included studies according to group

<table>
<thead>
<tr>
<th>Participants in trials* involving (No.of trials):</th>
<th>Active drug</th>
<th>Placebo or No treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors(12)</td>
<td>42,260</td>
<td>42,196</td>
</tr>
<tr>
<td>B-blockers(20)</td>
<td>36,338</td>
<td>36,262</td>
</tr>
<tr>
<td>CCB(18)</td>
<td>1,111</td>
<td>1,030</td>
</tr>
<tr>
<td>Nitrates(18)</td>
<td>42,206</td>
<td>42,207</td>
</tr>
<tr>
<td>All trials (65)^</td>
<td>83,234^</td>
<td>82,972^</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants in trial design (No. of trials):</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-blind (40)</td>
<td>62,849 (76%)</td>
<td>62,638 (75%)</td>
</tr>
<tr>
<td>Not double-blind (25)</td>
<td>20,385 (24%)</td>
<td>20,334 (25 %)</td>
</tr>
<tr>
<td>Weighted mean age (years) [trials / participants with data]</td>
<td>60.91</td>
<td>60.85</td>
</tr>
<tr>
<td>Weighted mean blood pressure (mm Hg) @ baseline [trials / participants with data]</td>
<td>133.7 [34 / 41,862]</td>
<td>133.7 [34 / 41,669]</td>
</tr>
<tr>
<td>Systolic</td>
<td>82.2</td>
<td>82.7</td>
</tr>
<tr>
<td>Diastolic</td>
<td>[25 / 7,125]</td>
<td>[25 / 7,043]</td>
</tr>
<tr>
<td>Female patients (%) [Based on trials reporting gender]</td>
<td>26% [47 / 82,342]</td>
<td>25% [47 / 82,036]</td>
</tr>
</tbody>
</table>

^ This total is less than the sum of all four categories as 2 trials (GSSI-3, ISIS-4) used 2x2 factorial design and one trial (Hargreaves 1992) compare drugs from two different categories of anti-hypertensive with the same placebo or control group.
High blood pressure at baseline was not part of the inclusion criteria in any of the 65 included trials. However, most of the trials explicitly stated that patients had to be free from shock or had a minimum BP (in general, SBP of 90-110 mmHg and/or DBP of 50-60 mm Hg) to enter the trial. For the included trials the overall weighted mean blood pressure at baseline was 133/82.2 mm Hg for those randomized to an active drug and 133/82.7 mm Hg for those randomized to the placebo or no treatment group. One quarter of patients was female and the overall weighted mean age was 60.85 years. (See Table 3-2 for generalities; See Appendix V for full details of the characteristics of included studies)
### Table 3-3 Acute event and timing of inclusion in included studies

<table>
<thead>
<tr>
<th>Included Trial</th>
<th>Cardiovascular event</th>
<th>Patients included within hours of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beaufils 1988</td>
<td>Acute myocardial infarction</td>
<td>6</td>
</tr>
<tr>
<td>Branagan 1986</td>
<td>Acute myocardial infarction</td>
<td>6</td>
</tr>
<tr>
<td>Bussmann 1981</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>Bussman 1992</td>
<td>Acute myocardial infarction</td>
<td>18</td>
</tr>
<tr>
<td>Charvat 1990</td>
<td>Acute myocardial infarction</td>
<td>6</td>
</tr>
<tr>
<td>Chiche 1979</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Clausen 1966</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>Cohn 1982</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>COMMIT 2005</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>CONSENSUS-II 1992</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>Crea 1985</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Di Pasquale 1994</td>
<td>Acute myocardial infarction</td>
<td>4</td>
</tr>
<tr>
<td>Di Pasquale 1997</td>
<td>Acute myocardial infarction</td>
<td>4</td>
</tr>
<tr>
<td>Durrer 1982</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Eichler 1985</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Erbel 1988</td>
<td>Acute myocardial infarction</td>
<td>6</td>
</tr>
<tr>
<td>ESPRIM 1994</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>Fitzgerald 1990</td>
<td>Acute myocardial infarction</td>
<td>8</td>
</tr>
<tr>
<td>Flaherty 1983</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Galcera 1993</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>Gelmers 1988</td>
<td>Acute Stroke</td>
<td>24</td>
</tr>
<tr>
<td>GISSI-3 1994</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>Hargreaves 1992</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>Heber 1987</td>
<td>Acute myocardial infarction</td>
<td>6</td>
</tr>
<tr>
<td>Hildebrandt 1992</td>
<td>Acute myocardial infarction</td>
<td>8</td>
</tr>
<tr>
<td>ICSG 1984</td>
<td>Acute myocardial infarction</td>
<td>4</td>
</tr>
<tr>
<td>Infeld 1999</td>
<td>Acute stroke</td>
<td>12</td>
</tr>
<tr>
<td>Included Trial</td>
<td>Cardiovascular event</td>
<td>Patients included within hours of onset</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>INWEST 1994 (^{131})</td>
<td>Acute myocardial infarction (^6)</td>
<td>24</td>
</tr>
<tr>
<td>ISIS-1 1986 (^{132})</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>ISIS-4 1995 (^{103})</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>Jaffe 1983 (^{133})</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Johannessen 1987 (^{134})</td>
<td>Acute myocardial infarction</td>
<td>6</td>
</tr>
<tr>
<td>Jugdutt 1983 (^{135})</td>
<td>Acute myocardial infarction</td>
<td>6</td>
</tr>
<tr>
<td>Jugdutt 1988 (^{136})</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Limburg 1990 (^{137})</td>
<td>Acute stroke</td>
<td>24</td>
</tr>
<tr>
<td>Lis 1984 (^{138})</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>Marangelli 2000 (^{139})</td>
<td>Acute myocardial infarction</td>
<td>4</td>
</tr>
<tr>
<td>MIAMI 1985 (^{140})</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>MILIS 1984 (^{141})</td>
<td>Acute myocardial infarction</td>
<td>18</td>
</tr>
<tr>
<td>Mitchell 2002 (^{142})</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Muller 1984 (^{143})</td>
<td>Acute myocardial infarction</td>
<td>6</td>
</tr>
<tr>
<td>Nabel 1991 (^{144})</td>
<td>Acute myocardial infarction</td>
<td>6</td>
</tr>
<tr>
<td>Natale 1999 (^{145})</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Norris 1978 (^{146})</td>
<td>Acute myocardial infarction</td>
<td>4</td>
</tr>
<tr>
<td>Norris 1980 (^{147})</td>
<td>Acute myocardial infarction</td>
<td>4</td>
</tr>
<tr>
<td>Norris 1984 (^{148})</td>
<td>Acute myocardial infarction</td>
<td>4</td>
</tr>
<tr>
<td>Owensby 1985 (^{149})</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Paci 1989 (^{150})</td>
<td>Acute stroke</td>
<td>12</td>
</tr>
<tr>
<td>Peter 1978 (^{151})</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Pimenta 1985 (^{152})</td>
<td>Acute myocardial infarction</td>
<td>6</td>
</tr>
<tr>
<td>Pizzetti 2001 (^{153})</td>
<td>Acute myocardial infarction</td>
<td>3</td>
</tr>
<tr>
<td>PRACTICAL 1994 (^{154})</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>Salathia 1985 (^{155})</td>
<td>Acute myocardial infarction</td>
<td>6</td>
</tr>
<tr>
<td>Schulman 1995 (^{156})</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>Sirnes 1984 (^{157})</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Included Trial</td>
<td>Cardiovascular event</td>
<td>Patients included within hours of onset</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Theroux 1998¹⁵⁸</td>
<td>Acute myocardial infarction</td>
<td>6</td>
</tr>
<tr>
<td>TIMI-IIB 1991¹⁵⁹</td>
<td>Acute myocardial infarction</td>
<td>4</td>
</tr>
<tr>
<td>Tonkin 1981¹⁶⁰</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>Van-de 1993¹⁶¹</td>
<td>Acute myocardial infarction</td>
<td>5</td>
</tr>
<tr>
<td>VENUS 2001¹⁶²</td>
<td>Acute Stroke</td>
<td>6</td>
</tr>
<tr>
<td>von Essen 1982¹⁶³</td>
<td>Acute myocardial infarction</td>
<td>24</td>
</tr>
<tr>
<td>Wagner 2002¹⁶⁴</td>
<td>Acute myocardial infarction</td>
<td>6</td>
</tr>
<tr>
<td>Yusuf 1983¹⁶⁵</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
<tr>
<td>Zannad 1988¹⁶⁶</td>
<td>Acute myocardial infarction</td>
<td>6</td>
</tr>
<tr>
<td>Zharov 1991¹⁶⁷</td>
<td>Acute myocardial infarction</td>
<td>12</td>
</tr>
</tbody>
</table>

Of the 22 trials for which we requested additional information, only 4 trialists responded to our request and provided additional information.

Blood pressure changes during the first 24 hours of treatment were reported in 19 trials (N=3,261). However, none of the trials reported on standard deviation of the change.

Thus, this measure of variability was imputed from: the end point standard deviation (second-choice in our pre-specified hierarchy) in 14 trials; from the baseline value (third-choice) in 1 trial; and from the weighted mean standard deviation at end point (last-choice) in 4 trials.

### 3.6.2 Risk of bias in included studies

Forty trials (60%) of the 65 included studies were double-blind, involving 75% (N=125,487) of the entire studied population. Less than 50% of the included trials reported adequate sequence generation, and only 23 trials (35%) reported concealment of
allocation (see Figure 3-2). Although the number of trials reporting adequate concealment of allocation was relatively small [13/40(32%) for double-blind and 10/25(40%) for open-label design trials], the number of patients randomized with adequate concealment of allocation was very high (121,618 patients out of the total 125,487 in double-blind trials and 37,055 out of the total 40,719 in open-label trials); in other words the trials that did not report concealment of allocation were small in sample size. Thus, this type of risk of bias is considered to be low in this review. Similarly, although more than 75% of trials had an incomplete reporting or did not report on immediate all-cause mortality (Figure 3-2), the studies that reported it were large enough (N=131,603) to keep this risk of incomplete outcome bias to a minimum. That was not the case for the ≥ 30 day mortality in which less than 25% reported mortality at times equal or greater than day 30 and the trials that reported it were small, therefore there is a significant risk of bias for mortality data at this time. Selective outcome reporting bias was not an issue in this review by limiting to include trials where our primary outcome, mortality, was reported in the RCTs.
3.6.3 Effects of interventions according to outcomes

3.6.3.1 Primary outcome: all-cause mortality

Foundation: Twelve trials (N=152,029) were designed for or had the power to detect differences in mortality (CONSENSUS-II 1992\textsuperscript{113}; GISSI-3 1994\textsuperscript{125}; ISIS-4 1995\textsuperscript{103}, COMMIT 2005\textsuperscript{112}; ISIS-1 1986\textsuperscript{132}; MIAMI 1985\textsuperscript{140}; Norris 1984\textsuperscript{148}; Salathia 1985\textsuperscript{155}; VENUS 2001\textsuperscript{162}; Cohn 1982\textsuperscript{111}; Durrer 1982\textsuperscript{117}; ESPRIM 1994\textsuperscript{120}) but any trial reporting mortality, regardless of its design and size, was included in our meta-analysis. We were able to assess the effects of immediate or short-term treatment with 4 antihypertensive classes of drugs: ACE inhibitors, B-blockers, calcium channel blockers and nitrates, on all-cause mortality data at 2, 10 or ≥ 30 days; in patients presenting with acute myocardial infarction or stroke.
3.6.3.1.1 Nitrates

Immediate treatment (started within 24 hours of the onset and lasting for maximum 2 days)

- All-cause mortality at 2 days (18 eligible trials, N=84,413):

Six trials (N=82,624) reported mortality at day 2. Nitrates were associated with a statistically significant reduction in all-cause mortality (RR 0.81, 95%CI [0.74, 0.89], p<0.0001; I² = 0%) (Figure 3-3).

Figure 3-3 Meta-analysis of the effect of nitrates in all-cause mortality at two days
All-cause mortality at 10 days (10 eligible trials, N=6,007):

All 10 trials (N=6,007) reported mortality at day 10. Nitrates were not associated with a statistically significant delayed reduction in all-cause mortality (RR 0.84, 95%CI [0.69, 1.01], p=0.07, I² = 63%).

All-cause mortality at ≥30 days (10 eligible trials, N=6,007):

Seven trials (N=5,771) reported mortality at ≥30 days. Nitrates were not associated with a statistically significant delayed reduction in all-cause mortality (RR 0.92, 95%CI [0.82, 1.04], p=0.20, I² = 42%) during a weighted average of 12 months of follow-up.

**Short-term treatment (started within 24 hours of the onset and lasting for a maximum of 10 days)**

All-cause mortality at 10 days: (8 eligible trials, N=78,406):

Six trials (N=78,178) reported mortality at 10 days. Nitrates were associated with a statistically significant reduction in all-cause mortality (RR 0.91, 95%CI [0.86, 0.97], p=0.003; I²=0%)

All-cause mortality at ≥30 days (5 eligible trials, N=969):

Three trials (N=570) reported mortality at ≥30 days. Nitrates were not associated with a statistically significant delayed reduction in all-cause mortality (RR 0.72, 95%CI [0.48, 1.10], p=0.13, I²=81%) during a weighted average of 4 months of follow-up.
3.6.3.1.2 Angiotensin converting enzyme (ACE) inhibitors

**Immediate treatment** (started within 24 hours of the onset and lasting for maximum 2 days)

- All-cause mortality at 2 days: (12 eligible trials, N=84,456):
  
  Three trials (N=77,414) reported mortality at 2 days. ACE inhibitors were not associated with statistically significant reduction in all-cause mortality (RR 0.91, 95%CI [0.82, 1.00]), p=0.05, I²=0% (Figure 3-4)

  - All-cause mortality at 10 days (2 eligible trials:\textsuperscript{107,164}, N=145):
    
    Both trials (N=145) reported mortality at 10 days. ACE inhibitors were not associated with a statistically significant delayed reduction in mortality at 10 days (RR 0.68, 95%CI [0.12, 3.98], p=0.67). (Figure 3-5)

  - All- cause mortality at ≥ 30 days (2 eligible trials, N=145):
    
    No trial reported mortality at this time.

**Short-term treatment** (started within 24 hours of the onset and lasting for a maximum of 10 days)

- All-cause mortality at 10 days (10 eligible trials, N=84,311):
  
  All 10 trials (N=84,311) reported mortality at 10 days. ACE inhibitors were associated with a statistically significant reduction in all cause mortality as compared to placebo (RR 0.93, 95%CI [0.87, 0.98] p=0.01). (Figure 3-5)

  - All- cause mortality at ≥ 30 days (2 eligible trials:\textsuperscript{115,116}, N=432):
    
    No trial reported mortality at ≥ 30 days
Figure 3-4 Meta-analysis of the Effect of ACE-inhibitors in All-cause Mortality at two days.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Bussmann 1992</td>
<td>0</td>
<td>22</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>GISSI-3 1994</td>
<td>200</td>
<td>9646</td>
<td>234</td>
<td>9672</td>
</tr>
<tr>
<td>ISIS-4 1995</td>
<td>549</td>
<td>29028</td>
<td>593</td>
<td>29022</td>
</tr>
</tbody>
</table>

Total (95% CI) 38696 | 38718 | 100.0% | 0.91 [0.82, 1.00] |

Total events 749 | 828

Heterogeneity: Chi² = 0.80, df = 2 (P = 0.67); I² = 0%

Test for overall effect: Z = 1.99 (P = 0.05)

Favours experimental Favours control
## 3.6.3.1.3 Beta-adrenergic antagonist or beta-blockers (BB)

### Immediate treatment (started within 24 hours of the onset and lasting for maximum 2 days)

- All-cause mortality at 2 days (20 eligible trials, N=72,600):
Six trials (N=68,007) reported mortality at 2 days. BB drugs were not associated with a statistically significant reduction in all-cause mortality (RR 0.95, 95%CI [0.85, 1.07], p=0.39, I²=67%). (Figure 3-6)

- All-cause mortality at 10 days (6 eligible trials, N=1,143):

  All 6 trials (N=1,143) reported mortality at 10 days. BB drugs were not associated with a statistically significant delayed reduction in all-cause mortality (RR 1.12, 95%CI [0.60, 2.07], p=0.73, I²=0%). (Figure 3-7)

- All-cause mortality at ≥ 30 days (6 eligible trials, N=1,143):

  Only one trial (N=108) reported mortality at ≥30 days. There were no deaths in either group.

**Short-term treatment** (started within 24 hours of the onset and lasting for a maximum of 10 days)

- All-cause mortality at 10 days (14 eligible trials, N=71,457):

  All 14 trials (N=71,457) reported mortality at 10 days. BB drugs were not associated with a statistically significant reduction in all-cause mortality (RR 0.96, 95%CI [0.91, 1.02], p=0.21, I²=0%). (See Figure 3-7)

- All-cause mortality at ≥ 30 days (8 eligible trials, N=18,645):

  Five trials (N=18,373) reported mortality at ≥ 30 days. BB drugs were associated with a statistically significant reduction in all-cause mortality (RR 0.91, 95%CI [0.84, 0.99], p=0.03, I²=0%) during a weighted average of 12 months of follow-up.
Figure 3-6 Meta-analysis of the Effect of Immediate Treatment with Beta-blockers on Mortality at Two Days

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Treatment Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMMIT 2005</td>
<td>395</td>
<td>22929</td>
<td>364</td>
<td>22923</td>
<td>62.7%</td>
<td>1.08 [0.94, 1.25]</td>
</tr>
<tr>
<td>Heber 1987</td>
<td>5</td>
<td>83</td>
<td>1</td>
<td>83</td>
<td>0.2%</td>
<td>5.00 [0.60, 41.88]</td>
</tr>
<tr>
<td>ICSG 1984</td>
<td>1</td>
<td>73</td>
<td>3</td>
<td>71</td>
<td>0.5%</td>
<td>0.32 [0.03, 3.04]</td>
</tr>
<tr>
<td>ISIS-1 1986</td>
<td>121</td>
<td>8037</td>
<td>171</td>
<td>7990</td>
<td>29.5%</td>
<td>0.70 [0.56, 0.89]</td>
</tr>
<tr>
<td>Johannis 1987</td>
<td>1</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0.1%</td>
<td>3.00 [0.13, 69.52]</td>
</tr>
<tr>
<td>MIAMI 1985</td>
<td>29</td>
<td>2877</td>
<td>41</td>
<td>2901</td>
<td>7.0%</td>
<td>0.71 [0.44, 1.14]</td>
</tr>
</tbody>
</table>

Total (95% CI) 34019 33988 100.0% 0.95 [0.85, 1.07]

Total events 552 580

Heterogeneity: Chi² = 15.06, df = 5 (P = 0.01); I² = 67%
Test for overall effect: Z = 0.86 (P = 0.39)
Figure 3-7 Meta-analysis of the Effect of Immediate Treatment and Short-Term Treatment with Beta-blockers on Mortality at 10 Days

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Total Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.2.1 Immediate treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norris 1978</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>23</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Norris 1980</td>
<td>1</td>
<td>33</td>
<td>0</td>
<td>29</td>
<td>2.65 [0.11, 62.56]</td>
<td></td>
</tr>
<tr>
<td>Norris 1984</td>
<td>15</td>
<td>364</td>
<td>14</td>
<td>371</td>
<td>1.09 [0.53, 2.23]</td>
<td></td>
</tr>
<tr>
<td>Owensby 1985</td>
<td>1</td>
<td>50</td>
<td>1</td>
<td>50</td>
<td>1.00 [0.06, 15.55]</td>
<td></td>
</tr>
<tr>
<td>Peter 1978</td>
<td>1</td>
<td>47</td>
<td>2</td>
<td>48</td>
<td>0.51 [0.05, 5.44]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>569</td>
<td>574</td>
<td></td>
<td>0.9%</td>
<td>1.12 [0.60, 2.07]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>20</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.92, df = 4 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.73)

| **3.2.2 short-term treatment** | | | | | | |
| Clausen 1966       | 13               | 66           | 13   | 64     | 0.7% 0.97 [0.49, 1.93] |                             |
| COMMIT 2005        | 1441             | 22929        | 1449 | 22923  | 71.4% 0.99 [0.93, 1.07] |                             |
| Heber 1987         | 5                | 83           | 1    | 83     | 0.0% 5.00 [0.60, 41.88] |                             |
| ICSG 1984          | 3                | 73           | 4    | 71     | 0.2% 0.73 [0.17, 3.14]  |                             |
| ISIS-I 1986        | 317              | 8037         | 367  | 7990   | 18.1% 0.86 [0.74, 0.99]  |                             |
| Johannessen 1987   | 2                | 20           | 0    | 20     | 0.0% 5.00 [0.26, 98.00]  |                             |
| MIAMI 1985         | 100              | 2877         | 110  | 2901   | 5.4% 0.92 [0.70, 1.20]  |                             |
| MILS 1984          | 4                | 134          | 8    | 135    | 0.4% 0.50 [0.16, 1.63]  |                             |
| Salatka 1985       | 25               | 416          | 20   | 384    | 1.0% 1.15 [0.65, 2.04]  |                             |
| TMMH-IIB 1991      | 17               | 720          | 17   | 714    | 0.8% 0.99 [0.51, 1.93]  |                             |
| Tonkin 1981        | 1                | 42           | 1    | 46     | 0.0% 1.10 [0.07, 16.96] |                             |
| Van-de 1993        | 1                | 103          | 2    | 98     | 0.1% 0.48 [0.04, 5.16]  |                             |
| von Essen 1982     | 1                | 25           | 1    | 26     | 0.0% 1.04 [0.07, 15.74] |                             |
| Yusuf 1983         | 7                | 244          | 16   | 233    | 0.8% 0.42 [0.18, 1.00]  |                             |
| **Subtotal (95% CI)** | 35769           | 35688        |       | 99.1% 0.96 [0.91, 1.02] |                             |
| **Total events**   | 1937             | 2009         |       |        |                   |                             |

Heterogeneity: Chi² = 12.32, df = 13 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)

| **Total (95% CI)** | 36338           | 36262        | 100.0% | 0.96 [0.91, 1.02] |                             |
| **Total events**   | 1957            | 2027         |        |        |                   |                             |

Heterogeneity: Chi² = 13.44, df = 16 (P = 0.76); I² = 0%
Test for overall effect: Z = 1.21 (P = 0.23)
3.6.3.1.4 Calcium channel blockers (CCB)

**Immediate treatment** (started within 24 hours of the onset and lasting for maximum 2 days)

- All-cause mortality at 2 days (18 eligible trials, N=2,141):

  Only 3 trials (N=242, Erbel 1988\(^{119}\); Theorox 1998\(^{158}\); Zannad 1988\(^{166}\)) reported mortality at 2 days. CCB were not associated with a statistically significant reduction in all-cause mortality (RR 2.33, 95%CI [0.62, 8.78], p=0.21, I\(^2\)=2%).

- All cause mortality at 10 days (3 eligible trials\(^{105,118,139}\), N=241):

  Only one trial Marangelli 2000\(^{139}\) (N=88) reported mortality at 10 days. There was one death in the CCB group and none in the control group.

- All cause mortality at ≥ 30 days (3 eligible trials, N=241):

  Only one trial Branagan 1986\(^{105}\) (N=108) reported mortality at ≥ 30 days. There were 7/54 deaths in the CCB group and 5/54 in the control group. The relative risk for this trial was 1.40, 95%CI [0.47,4.14].

**Short-term treatment** (started within 24 hours of the onset and lasting for a maximum of 10 days)

- All-cause mortality at 10 days (15 eligible trials, N=1,900):

  All 15 trials (N=1,900) reported mortality at 10 days. CCB were not associated with a statistically significant effect on all-cause mortality (RR 1.01, 95%CI [0.73, 1.38], I\(^2\)=0%)

- All-cause mortality at ≥ 30 days (5 eligible trials, N=730):

  One trial (N=90), Pizzetti 2001 reported mortality at ≥ 30 days. There were three deaths in the CCB group and two in the placebo group.
3.6.3.2 Secondary outcome: total non-fatal serious adverse events

No trial reported total non-fatal serious adverse events (SAE). It was not possible to extract individual non-fatal SAE from the original trials and analyze them as a composite due to a risk of double-counting the events and due to the risk of missing particular non-fatal SAEs that were not reported.

3.6.3.3 Secondary outcome: weighted mean change in blood pressure and heart rate during the first 24 hours of treatment

Many trials did not report these secondary outcomes. In general, trials that reported blood pressure data and also mortality data were small trials (average 170 patients). We carefully looked at all trials to see if they have blood pressure data for the entire population or for a subset of the entire study. Cohn 1982 was the only trial designed to detect mortality differences and that reported blood pressure data. The MIAMI 1985 trial had a subset study with blood pressure data and was included in our meta-analysis. It was not possible to do a secondary analysis (meta-regression or correlation) comparing the effects of blood pressure lowering during the first 24 hours and health outcomes. No trial reported the standard deviation of the change for blood pressure or heart rate. Thus, this measure of variability was imputed from: the end point (second-top choice in our pre-specified hierarchy) in 14 trials; from the baseline value (third choice) in 1 trial; and from the weighted mean standard deviation at end point (last choice) in 4 trials.
3.6.3.3.1 Nitrates

Systolic blood pressure change
There were 7 trials (N=1,958) included in the systolic meta-analysis. The pooled effect showed a statistically significant greater reduction in SBP with nitrates drugs compared to placebo or no treatment during the first 24 hours of an acute myocardial infarction (WMD -12.67, 95%CI [-14.51, -10.83], p<0.00001; I²=81%). The statistical significance remained when random effects model was applied.

Diastolic blood pressure change:
There were 6 trials (N=1146) included in the diastolic meta-analysis. The pooled effect showed a statistically significant greater reduction in DBP with nitrates drugs as compared to placebo or no treatment during the first 24 hours of an acute myocardial infarction (WMD -7.50, 95%CI [-9.07,-5.93], p<0.0001; I²=75%). The statistical significant effect remained when a random effect model was applied.

Heart rate change:
There were 6 trials (N=810) included in the heart rate change meta-analysis. There was no significant difference in heart rate change between nitrates and placebo or no treatment during the first 24 hours of a cardiovascular event (WMD -0.83, 95%CI [-2.83,1.17], p=0.42; I²=57%).

3.6.3.3.2 Angiotensin converting enzyme inhibitors (ACEi)

Systolic blood pressure change:
There were no included trials providing SBP data for ACEi.

Diastolic blood pressure change:
There were no included trials providing DBP data for ACEi
Heart rate change:

There were no included trials providing HR data for ACEi.

3.6.3.3 Beta-adrenergic antagonist or beta-blockers (BB)

Systolic blood pressure change:

There were 6 trials (N=738) included in the systolic meta-analysis. The pooled effect showed a statistically significant greater reduction in SBP with beta-blockers drugs compared to placebo or no treatment during the first 24 hours of a cardiovascular event (WMD -12.54, 95%CI [-15.63,-9.45], p<0.00001; I²=0%).

Diastolic blood pressure change:

There were 6 trials (N=738) included in the diastolic meta-analysis. The pooled effect showed a statistically significant greater reduction in DBP with beta-blockers drugs as compared to placebo or no treatment during the first 24 hours of a cardiovascular event (WMD -3.35, 95%CI [-5.43,-1.28], p=0.002; I²=60%). The statistically significant difference persisted when a random effects model was applied.

Heart rate change:

There were 5 trials (N=594) included in the heart rate change meta-analysis. The pooled effect showed a statistically significant greater reduction in HR with beta-blockers drugs as compared to placebo or no treatment during the first 24 hours of a cardiovascular event (WMD -9.68, 95%CI [-11.99,-7.37], p<0.00001; I²=4%).
3.6.3.3.4 Calcium channel blocker (CCB)

Systolic blood pressure change:
There were 7 trials (N=755) included in the systolic meta-analysis. The pooled effect showed statistically significant difference in SBP between calcium channel blocker drugs and placebo or no treatment during the first 24 hours of a cardiovascular event (WMD -5.49, 95%CI [-8.42,-2.56];p=0.0002; I²=80%). The effect was no longer statistically significant when a random effects model was applied.

Diastolic blood pressure change:
There were 6 trials (N=565) included in the diastolic meta-analysis. The pooled effect showed a statistically significant greater reduction in DBP with calcium channel blocker drugs as compared to placebo or no treatment during the first 24 hours of a cardiovascular event (WMD -5.08, 95%CI [-7.00,-3.15], p<0.0001; I²=64%). The statistical significant difference between groups remained when a random effects model was applied.

Heart rate change:
There were 5 trials (N=410) included in the heart rate change meta-analysis. There was no significant difference in heart rate change between calcium channel blocker drugs and placebo or no treatment during the first 24 hours of a cardiovascular event (WMD -1.10, 95%CI [-4.60,2.40];p=0.54; I²=54%).
3.7 Discussion

3.7.1 Summary of main results

Randomized controlled trials (RCT) comparing an intervention with no treatment or placebo is the method of choice for determining efficacy and effectiveness. The optimal measure of net health effectiveness is the total number of patients with at least one serious adverse event (SAE)\(^\text{20}\). However, in acute life-threatening cardiovascular events (CVEs) where the patient is hospitalized, total SAEs are particularly difficult to be documented and thus rarely measure it. In this review this was proven to be true as no trial reported this outcome. One possible reason is the subjectivity when physician must make a judgment as to whether a particular event led to prolongation of hospitalization as compared to the underlying life-threatening disease. Therefore, in acute clinical settings total all-cause mortality has been considered the best measure of net health effect\(^\text{21}\). All-cause mortality is an outcome measure that is not subject to physician judgment and which is usually reported in trials. This is the reason why we have focused primarily on total all-cause mortality in this systematic review.

The primary objective of this review was whether 24 to 48 hour (immediate) administration of blood pressure lowering drugs used within the first 24 hours of an acute cardiovascular event reduced mortality at three different time periods, 2 days, 10 days and \(\geq 30\) days. Our initial plan to pool the effects of all blood pressure lowering drugs proved to be inappropriate as the effects of the different classes of drugs was clearly heterogeneous. We have therefore presented the outcome data separately for each of the drug classes.
In studying the immediate intervention, the 2-day mortality provides a measure of the immediate benefits or harms and the 10 day and ≥30 day time periods provides a measure of delayed beneficial or harmful effects that only become manifest later. The principle here has been amply demonstrated by the fibrinolysis trials where early treatment leading to preservation of myocardium leads to reductions in mortality that are not manifest at 2 days, but which increase over time. For example, in the ISIS-2 1988\textsuperscript{5} where 17,187 patients within 24 hours of the onset of a suspected acute myocardial infarction were randomized to receive immediate treatment with a thrombolytic drug or placebo resulted in having no effect on mortality at 48 hours (RR=1.04, 95\%CI[0.89,1.21]), but reduced mortality at 10 days (RR= 0.82, 95\%CI[0.74,0.91]) and at 35 days (RR=0.77, 95\%CI[0.70,0.84]). Unfortunately, in this blood pressure-lowering systematic review the number of trials that reported mortality at 10 days and ≥30 days after immediate treatment was insufficient to ascertain whether there were delayed benefits or harms. The data that are available suggest that the benefits at 10 days and ≥30 days are less than at 2 days, if anything.

The most important conclusion of this review comes from the mortality data at two days after immediate blood pressure lowering. At 2 days there was a highly significant reduction in mortality for nitrates (RR 0.81, 95\%CI [0.74, 0.89], \textit{p}<0.0001) and no significant reduction in mortality for the other classes of drugs. Since the data is incomplete, we cannot be very confident whether the hemodynamic effect among the different drug classes during the first 24 hours contributed to mortality differences. However, by indirectly comparing the two classes of drugs where statistically significant effects were seen (compared to placebo or no treatment) in these early hemodynamic
changes, this review showed that the weighted mean systolic blood pressure lowering effect for beta-blockers (-12.54 mm Hg) and for nitrates (-12.67 mm Hg) was very similar, whereas the heart rate change was significantly different between the two classes (-9.68 vs. -0.83 bpm, respectively). Despite these similarities and differences in these hemodynamic changes, the day-2 mortality effect was favorable for nitrates (RR 0.81, 95%CI [0.74, 0.89]) but not for beta-blockers (RR 0.95, 95%CI [0.85, 1.07]).

Unfortunately, we do not have hemodynamic data for ACE-inhibitors; and the data for CCB was too heterogeneous to yield statistical significance versus control.

This significant mortality benefit at 2 days for nitrates is based predominantly on the two largest trials (ISIS-4\textsuperscript{103}, GISSI-3\textsuperscript{125}), but the authors of those trials have dismissed the finding, as the effect was no longer significant at 35 days. It is thus worth examining these two trials in more detail. The ISIS-4 1995\textsuperscript{103} trial (N=58,050) was a factorial-design trial with three independent interventions: isosorbide mononitrate vs. placebo; captopril versus placebo and magnesium versus open control. The nitrate used was control-released isosorbide starting with 30 mg every 12 hours for the first day and followed by a maintenance dose of 60 mg daily for 28 days. However, during the first few days, all patients were allowed to receive non-study intravenous (IV) nitrates (approximately 47% of patients in each group ultimately received these). The other large study (N=19,394) was an open-label, factorial design trial, GISSI-3 1994\textsuperscript{125}, with two independent comparisons: lisinopril versus control; and glyceryl trinitrate versus control. In the nitrate group patients were initiated with IV infusion of nitroglycerin at 5 - 20 µg/min (to achieve at least 10% of SBP reduction) during the first 24 hours. After that, the IV
infusion was replaced by a transdermal patch providing 10 mg of nitrate per day for 6 weeks. Also in this trial patients were allowed to receive non-study nitrates. The percentage of patients who received these in the control group was 57.1%, but the corresponding percentage for those allocated to the nitrate group was not reported. In general, these two trials (ISIS-4 1995\textsuperscript{103} and GISSI-3 1994\textsuperscript{125}) were similar in terms of population studied but dissimilar in design and drugs used. Despite the differences, the benefit for the nitrates at 2 days, was the same for both trials (RR 0.82, 95%CI [0.73, 0.92]) and (RR 0.82, 95%CI [0.68, 0.99]), respectively. Furthermore, the fact that the control group also received non-study nitrates makes it likely that this significant mortality benefit is underestimated. Based on this RCT evidence it is concluded that nitrates should be used routinely within 24 hours of the onset of an acute myocardial infarction as per baseline characteristics outlined in the RCTs.

Unfortunately, since treatment in these trials continued for more than 2 days, these two trials cannot be used to measure the delayed effect of the immediate use of nitrates on mortality at 10 days and ≥ 30 days. In the available trials the immediate use of nitrates had no significant delayed mortality reduction at 10 days, (RR 0.84, 95%CI [0.69, 1.01],\textit{p}=0.07) or ≥30 days(RR 0.92, 95%CI[0.82,1.04],\textit{p}=0.20) . The lack of a statistically significant effect is partly due to less data, but also due to the fact that the effect estimate appears to be diminishing over time. This opposes the effect seen with fibrinolytic agents and it some evidence against a delayed benefit of immediate nitrate administration.

On the other hand these large trials, because they continued nitrates for 35 days, can be used to assess the mortality benefit of nitrates given from 3 to 10 days and from 11 to ≥30
days. The effect of nitrates administered from 3 to 10 days is shown in the sensitivity analysis (Figure 3-8) RR 0.98 [0.91 to 1.06]. This provides evidence for no benefit or harm, when nitrates are administered during this time period after an acute myocardial infarction. Furthermore, when the effect of nitrates on mortality was assessed for the period from 11 to \( \geq 30 \) days it is clear that nitrates are not beneficial (RR 1.10, 95%CI [1.00 to 1.22]). This provides relatively robust evidence for the lack of benefit from nitrates administered beyond day 2 after an acute myocardial infarction. This does not preclude the use of nitrates if other appropriate indications exist, such as angina post-infarction.
The present systematic review did not find statistical evidence that immediate treatment with ACE inhibitors reduces mortality at 2 days after a myocardial infarction. Although most of the evidence comes from the same two large trials where the nitrates were studied, the evidence is of borderline significance (RR 0.91, 95%CI [0.82, 1.00], \( p=0.05 \)), so it remains possible that a real benefit has been missed. Other possible explanation is that ACE inhibitors could increase other serious adverse events in this early period.

Evidence in favor of this possibility in ISIS-4 1995\(^{103} \) is that cardiogenic shock or
profound hypotension requiring termination of study treatment was significantly higher in
the ACE-inhibitor group as compared to placebo (p<0.01 and p<0.001, respectively)
during the first 24-48 hours. It is also possible that the beneficial effect from ACE-
inhibitors is specific to a certain sub-group(s) of patients (such as those patients with
anterior infarction\textsuperscript{103}. If that was the case the significant beneficial effect would be
dilated in the overall effect. The best way to resolve this uncertainty is to do an individual
patient meta-analysis of the available trials to try to identify subgroups of patients who
benefit from routine use of ACE-inhibitors in this early phase of an MI.

Unfortunately, there were only two small trials in which a delayed effect of the
immediate treatment with ACE-inhibitors could be assessed. Therefore, there was
insufficient RCT evidence to ascertain the delayed effects of these drugs when given as
immediate treatment (within 24 hours and lasting for up to 48 hours) following an acute
myocardial infarction.

The present systematic review demonstrated that the immediate treatment with beta-
blockers was not associated with significant mortality benefit at 2 days (RR 0.95, 95%CI
[0.85, 1.07], p=0.39), 10 days (RR 1.12, 95%CI [0.60, 2.07], p=0.73) or ≥30 days.
However, there was very little data to assess the delayed effect of immediate treatment
with beta-blockers. In addition, there was significant heterogeneity for the day-2
mortality outcome (I\textsuperscript{2}=67%): the heterogeneity was not explained by the type of beta-
blocker. However, when a pre-planned sensitivity analysis was performed according to
trial design (double-blind; open-label), beta-blockers were not associated with a
significant reduction in mortality as compared with placebo or no treatment among
51,814 patients in double-blind trials (RR 1.04, 95%CI [0.91,1.19]; I\textsuperscript{2}=30%); but were
associated with a significant reduction in mortality among 16,193 patients in open-label trials (RR 0.73, 99%CI [0.58,0.91]; p=0.006; I²=69%). Given the clear lack of benefit in the double-blind trials, the most likely explanation for the benefit of beta blockers in the open label trials is that the two groups had other treatment differences than the planned intervention (performance bias). In keeping with that possibility, significantly more patients in the control group as compared to the beta-blocker group received calcium channel blockers drugs (RR 1.89 [1.74,2.06]; p<0.00001) in the largest trial of this meta-analysis, the ISIS-1 trial. If calcium channel blockers increase mortality this would lead to false evidence of a mortality benefit for beta-blockers. The evidence of a clear lack of mortality benefit in the more robust double-blind trials makes us confident that routine use of beta-blockers early after an MI is not useful.

The present systematic review also showed that immediate treatment with CCB was not associated with a statistically significant reduction in all-cause mortality at 2 days, 10 or ≥30 days. This conclusion is weak due to the fact that the included trials do not report mortality at all of these times and because there were many CCB trials excluded from this meta-analysis, due to lack of reporting or improperly reported mortality data. The reason for this lack or improper reporting of mortality is not known; however, we feel that it is unlikely that trials demonstrating a mortality benefit would not have reported their results in full. We suspect that publication bias exists as we excluded 84% of the calcium channel blocker trials due to a lack of or insufficiency mortality reporting. Therefore, if anything, we think that the data showing no benefit or harm from CCB’s in this review is likely biased and that the full mortality data would show a statistically significant harm from CCBs.
The effects of short-term treatment provide additional information to what we have learned from the immediate treatment. Nitrates were again associated with a significant reduction in mortality at 10 days; however, as discussed above, this reduction was entirely accounted for by the immediate treatment reduction in mortality at 2 days. In contrast, ACE inhibitors after short-term treatment now show significant effect at 10 days (RR 0.93, 95%CI [0.87, 0.98]). The reason for the significant mortality benefit at 10 days is that, in contrast to the nitrates, in the two large trials (GISSI-3, ISIS-4), the effect of the continued administration of ACE inhibitors was similar from 0 to 2 days (RR 0.91), from 3 to 10 days (RR 0.93, 95%CI [0.86 to 1.01]); and from day 11 to day 35 or 42 (RR 0.93, 95%CI [0.85 to 1.03]) (See Figure 3-9). This resulted in a significant mortality benefit for ACE inhibitors continued for 35-42 days (RR 0.93, 95%CI [0.88 to 0.97]) as compared to a non-significant mortality effect of nitrates continued for 35-42 days (RR 0.97, 95%CI [0.92 to 1.02]). However, it is emphasized that in a trial where it was possible to compare nitrates vs. ACE inhibitors in a head to head comparisons, GISSI-3, there was no differences in mortality at 42 days (7% vs. 6.6%). This led us to conclude that the routine use of ACE inhibitors post MI reduces mortality to a modest degree. However, it remains uncertain as to the optimal time of starting these drugs, and whether ACE inhibitors should be targeted at a subgroup of patients where the mortality benefit is larger.

The data to assess the effects of short-term treatment (start within 24 hour of the onset and lasting maximum 10 days) on mortality at ≥ 30 days was sparse for nitrates (7 trials) and nil for the ACE-inhibitors.
Figure 3-9 Sensitivity analysis: effect of ACE-I continuation on all-cause mortality at different times.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
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<td>Events</td>
<td>Total</td>
<td>Total</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td><strong>2.6.1 mortality up to day 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GISSI-3 1994</td>
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<td>9646</td>
<td>234</td>
<td>9672</td>
</tr>
<tr>
<td>ISIS-4 1995</td>
<td>549</td>
<td>29028</td>
<td>593</td>
<td>29022</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>38674</td>
<td>38694</td>
<td>100.0%</td>
<td>0.91 [0.82, 1.00]</td>
</tr>
<tr>
<td>Total events</td>
<td>749</td>
<td>827</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.47, df = 1 (P = 0.49); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2.6.2 mortality from 3 to 10 days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GISSI-3 1994</td>
<td>235</td>
<td>9446</td>
<td>252</td>
<td>9438</td>
</tr>
<tr>
<td>ISIS-4 1995</td>
<td>945</td>
<td>28479</td>
<td>1015</td>
<td>28429</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>37925</td>
<td>37867</td>
<td>100.0%</td>
<td>0.93 [0.86, 1.01]</td>
</tr>
<tr>
<td>Total events</td>
<td>1180</td>
<td>1267</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2.6.3 mortality from 11 to 35–42 days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GISSI-3 1994</td>
<td>184</td>
<td>9211</td>
<td>207</td>
<td>9186</td>
</tr>
<tr>
<td>ISIS-4 1995</td>
<td>594</td>
<td>27534</td>
<td>623</td>
<td>27414</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>36745</td>
<td>36600</td>
<td>100.0%</td>
<td>0.93 [0.85, 1.03]</td>
</tr>
<tr>
<td>Total events</td>
<td>778</td>
<td>830</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the present systematic review, **short-term** treatment with beta-blockers showed no statistically significant effect on mortality at 10 days (RR 0.96, 95%CI [0.91, 1.02]; 14 trials, N=71,457), but a statistically significant effect at ≥ 30 days (RR 0.91, 95%CI [0.84, 0.99], p=0.03; 5 trials, N=18,373). Although the effect at ≥ 30 days is statistically significant, suggesting a delayed benefit with beta-blockers, we believe this is a chance effect and probably not real. When mortality was analyzed separately for the periods 0-10 days and 11 to ≥ 30 for these 5 trials, a significant benefit is seen only during the first 10 days, contradicting the "suggested delayed benefit" shown above. Furthermore, these results contradict the lack of significant mortality effect, during the first 10 days, when all
14 trials with available data are considered. A potential explanation of these contradictions is publication bias from the 5 trials that reported data at $\geq 30$ days. In addition, the apparent exaggerated benefit in two trials (ISIS-1 1986$^{132}$ and Yusuf 1983$^{165}$) is possible due to performance bias as in both trials significantly more patients received calcium channel blockers (CCBs) in the control group. This could potentially increase mortality in the control group and exaggerate the benefit from the beta-blocker. The adverse effect of CCBs is in accordance with the findings of this review (see below).

Our systematic review showed that short-term treatment with CCB was not associated with a statistically significant reduction in all-cause mortality at 10 or $\geq 30$ days. Similar to the effect of the immediate treatment, this conclusion is not robust because only a small percentage of CCB trials could be included in this review. In our sensitivity analysis, there was a trend towards a greater mortality among MI patients treated short-term with calcium channel blockers as compared to placebo (RR 1.60 95%CI [0.90, 2.86]); particularly in those receiving dihydropyridine CCBs (RR 1.91, 95%CI [0.98, 3.72]).

Only 5 acute stroke RCT’s were included in the present systematic review and all of these studied calcium channel blocker (CCB) drugs. CCBs were not associated with significant effect on mortality at 10 days (RR 0.81, 95%CI [0.54, 1.21]) in this setting. This evidence is clearly insufficient to show whether CCBs are beneficial or harmful in acute stroke patients.
3.7.2 *Summary of findings tables*

The following tables represent key findings for the immediate and short-term treatment of the four classes of blood pressure-lowering drugs.

**Table 3-4 Summary of findings table for nitrates**

Immediate and short term administration of nitrates in patients with acute cardiovascular events

- **Patient or population:** patients with acute myocardial infarction
- **Settings:** hospitalized within 24 hours of the symptom onset
- **Intervention:** Nitrates
- **Comparison:** Placebo or no treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality at 2 days - immediate treatment</strong></td>
<td>Low risk population (^2)</td>
<td>RR 0.81 (0.74 to 0.89)</td>
<td>82624 (6 studies)</td>
<td>high</td>
<td>Highly significant benefit was achieved. 125 or 250 patients, with high or low risk, need to be treated to prevent 1 death</td>
</tr>
<tr>
<td></td>
<td>Placebo or no treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 per 16 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000 (15 to 18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk population (^2)</td>
<td>RR 0.91 (0.86 to 0.97)</td>
<td>78178 (6 studies)</td>
<td>high</td>
<td>Significant benefit is demonstrated, but this is the same absolute magnitude as day 2. Thus, likely reflects the mortality benefit at day 2.</td>
</tr>
<tr>
<td></td>
<td>Placebo or no treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40 per 32 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000 (30 to 36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality at 10 days - short-term treatment</strong></td>
<td>Low risk population (^2)</td>
<td>RR 0.91 (0.86 to 0.97)</td>
<td>78178 (6 studies)</td>
<td>high</td>
<td>Significant benefit is demonstrated, but this is the same absolute magnitude as day 2. Thus, likely reflects the mortality benefit at day 2.</td>
</tr>
<tr>
<td></td>
<td>Placebo or no treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 per 46 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000 (43 to 49)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk population (^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>80 per 73 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000 (69 to 78)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^*\)The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADD Working Group grades of evidence

- **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low quality:** We are very uncertain about the estimate.

\(^1\) Mortality results for this clinical condition, at the different times, and according to the different modalities of treatment (immediate and short term) displayed here, are considered the key points for this summary of findings table. The other results can be found in text.

\(^2\) These low and high risk values were chosen based on the second lowest, and second highest risks in the control group of the included studies.
### Table 3-5 Summary of findings table for ACE-inhibitors

Immediate and short term administration of ACE inhibitors in patients with acute cardiovascular events

**Patient or population:** acute myocardial infarction

**Settings:** hospitalized within 24 hours of the symptom onset

**Intervention:** ACE-inhibitors

**Comparison:** Placebo or no treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality at 2 days - immediate treatment</strong></td>
<td>Low risk population&lt;sup&gt;2&lt;/sup&gt;</td>
<td>RR &lt;sup&gt;0.91&lt;/sup&gt; (0.82 to 1)</td>
<td>77414 (3 studies)</td>
<td>high</td>
<td>No statistically significant effect, but possible benefit.</td>
</tr>
<tr>
<td></td>
<td>20 per 1000 (16 to 20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk population&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40 per 1000 (33 to 40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up: 0-48 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality at 10 days - short-term treatment</strong></td>
<td>Low risk population&lt;sup&gt;3&lt;/sup&gt;</td>
<td>RR &lt;sup&gt;0.93&lt;/sup&gt; (0.87 to 0.98)</td>
<td>84311 (10 studies)</td>
<td>high</td>
<td>Significant benefit was achieved. 200 or 333 patients, with high or low risk, need to be treated for 10 days to prevent 1 death</td>
</tr>
<tr>
<td></td>
<td>40 per 1000 (35 to 39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk population&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70 per 1000 (61 to 69)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). |

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> Mortality results for this clinical condition, at the different times, and according to the different modalities of treatment (immediate and short term) displayed here, are considered the key points for this summary of findings table. The other results can be found in text.

<sup>2</sup> These low and high risk values were chosen based on the lowest and highest risks in the control group of these 3 included studies.

<sup>3</sup> These low and high risk values were chosen based on the second lowest, and second highest risks in the control group of the included studies.
Table 3-6. Summary of findings table for beta-blockers.

Immediate and short term administration of Beta-blockers in patients with acute cardiovascular events

**Patient or population:** patients with acute myocardial infarction\(^1\)

**Settings:** hospitalized within 24 hours of symptom onset

**Intervention:** Beta-blockers

**Comparison:** Placebo or no treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks(^a) (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo or no treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality at 2 days - immediate treatment</td>
<td>Medium risk population(^2)</td>
<td>RR 0.95 (0.85 to 1.07)</td>
<td>68007 (6 studies)</td>
<td>low(^3,4)</td>
<td>No statistically significant effect.</td>
</tr>
<tr>
<td></td>
<td>15 per 1000 (13 to 16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality at 10 days - short-term treatment</td>
<td>Medium risk population(^5)</td>
<td>RR 0.96 (0.91 to 1.02)</td>
<td>71457 (14 studies)</td>
<td>high</td>
<td>No statistically significant effect.</td>
</tr>
<tr>
<td></td>
<td>42 per 1000 (38 to 43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

1. Mortality results for this clinical condition, at the different times, and according to the different modalities of treatment (immediate and short term) displayed here, are considered the key points for this summary of findings table. The other results can be found in text.

2. Medium risk was chosen as there was little variation in the control group risk across included trials.

3. Performance bias was highly suspected in a large open label-trial.

4. There was significant variability in the effect estimate.

5. This is the medium control group risk from the included studies.
Table 3-7. Summary of findings table for calcium channel blockers

Immediate and short term administration of calcium channel blockers (CCB) in patients with acute cardiovascular events

**Patient or population:** patients with acute myocardial infarction or stroke

**Settings:** hospitalized within 24 hours of the onset

**Intervention:** CCB

**Comparison:** Placebo or no treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo or no treatment</td>
<td>Medium risk population² 13 per 1000 30 per 1000 (8 to 114)</td>
<td>RR 2.33 (0.62 to 8.78)</td>
<td>242 (3 studies)</td>
<td>⊝⊝⊝ very low³,⁴,⁵</td>
<td>No statistically significant effect. Not enough trials/patients or events.</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality at 2 days - immediate treatment Follow-up: 0-48 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality at 10 days - short-term treatment Follow-up: 0-10 days</td>
<td>Medium risk population⁶ 70 per 1000 71 per 1000 (51 to 97)</td>
<td>RR 1.01 (0.73 to 1.38)</td>
<td>1900 (15 studies)</td>
<td>⊝⊝⊝ very low³,⁴,⁵</td>
<td>No statistically significant effect. Not enough trials/patients or events.</td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

1 Mortality results for these clinical conditions, at the different times, and according to the different modalities of treatment (immediate and short term) displayed here, are considered the key points for this summary of findings table. The other results can be found in text

2 Only the medium risk was chosen as there was little variation in the control group risk across included trials

3 These were very small open-label trials

4 The 95% confidence intervals of the effect estimate goes in opposite direction across trials reaching the threshold for clear benefit (RR=0.75) and clear harm (RR=1.25)

5 Probably there are many missing reports

6 This is the median control group risk from the included studies

125
3.7.3 Overall completeness and applicability of evidence

Out of 135 potentially appropriate randomized controlled trials we excluded 65 studies in which mortality data was non-extractable or non usable for our review. Thus this data, if made available by the authors, it could be added to our review. Of these 65 excluded trials, 14 involved an ACE inhibitor (N=4,407); 21 trials involved a B-adrenergic Blocker (N=2,524); 8 trials involved a nitrate (N=1,475) and 20 trials involved a CCB (N=10,958). These excluded patients make up a small proportion of the available included patients: for the ACE inhibitors, 5.0%; beta-blockers 3.4%; and nitrates 1.7%; but a large proportion to the calcium channel blocker population, 84%. Due to the relatively small number of excluded patients and trials for the ACE inhibitor, beta-blocker and nitrate groups, we are pretty confident that the effect sizes calculated in these meta-analyses are a good estimate of the true effect. However, that is not the case for the calcium channel blockers, where it is more likely that the non-significant increase in short-term mortality among those patients with acute myocardial infarction found in this review (RR 1.60 95%CI[0.90, 2.86]) would become statistically significant.

We have no information about the effects on mortality of other blood pressure lowering drugs (such as clonidine, prazosin and hydralazine, etc) used within 24 hours of the onset of an acute myocardial infarction or stroke. Likewise, we have no information regarding the effects on mortality produced by drugs embraced in this review started within 24 hours of the onset of other cardiovascular events such as acute aortic dissection, acute pulmonary edema, sub-arachnoid hemorrhage or unstable angina because mortality data was not assessed or reported in these conditions. To the best of our knowledge, only the randomized controlled trial by Yoshida (1998)\textsuperscript{42} included only patients with acute aortic
dissection and randomizing the patients within 24 hour of the onset. This trial compared two active treatments.

Thus, this systematic review evidence is primarily applicable to patients with acute myocardial infarction receiving blood pressure lowering treatment within 24 hours of the onset of the event and having a level of risk similar to those participants from the randomized trials included in this review. Since the evidence for effectiveness of nitrates and ACE-inhibitors mostly comes from two large trials [ISIS-4 1995\textsuperscript{103}; GISSI-3 1994\textsuperscript{125}], the practical recommendations primarily apply to patients having the following characteristics:

**ISIS-4 1995\textsuperscript{103}:**

Patients with suggestive of suspected or definite acute MI (with or without electrocardiographic changes) within 24 hours of symptom onset and with no clear indications for, or clear contraindications to any of the trial treatments.

In this trial the contraindications were not set by the protocol, but by the responsible physician and might include: negligibly low risk of MI death (e.g. normal electrocardiogram), major life-threatening disease other than acute MI, or a high risk of adverse effects of trial treatment such as: decreased blood pressure-cardiogenic shock or severe hypotension (eg., SBP persistently <90-100 mm Hg, especially with right ventricular infarction or poor peripheral perfusion); severely decreased plasma volume-clinical evidence of severe fluid depletion, perhaps due to chronic diuretic use.

Overall, 74% were male; 28% were 70 years of age or older; 92% were ultimately confirmed to have an AMI; 86% had Killip class I (no signs or symptoms of heart failure) and 17% had previous MI.
The co-interventions given in the overall trial were: non-study intravenous nitrates (~47%); anti-platelets (~93%); fibrinolytic agents (~68%) and intravenous beta-blockers (~9%).

**GISSI-3 trial**125.

Inclusion criteria: patients with chest pain accompanied by ST elevation or depression of at least 1 mm in one or more peripheral leads of the electrocardiogram (ECG), or at least 2 mm in one or more precordial leads; within 24 hours of symptoms onset; and having no contraindications to the study treatments. Exclusion criteria: severe heart failure requiring any of the study treatments; Killip class 4; high risk of further serious hemodynamic deterioration after treatment with vasodilators (SBP ≤ 100 mm Hg), contraindications to study drugs -namely a history of clinically relevant renal failure (serum creatinine ≥ 177 mol/L, proteinuria > 500 mg per 24 hours or both), history of bilateral stenosis of the renal arteries, allergies to one of the study drugs, other life threatening disorders (eg., tumors or serious respiratory diseases).

Overall, 78% were male; 27% were 70 years of age or older; 93% were ultimately confirmed to have an AMI; 83% had Killip class I and 14% had previous MI.

The co-interventions given in the overall trial were: non-study intravenous nitrates (~57%- only reported for the control group); aspirin (~84%); fibrinolytic agents (~72%) and intravenous beta-blockers (~30%).

### 3.7.4 Quality of the evidence

Forty trials (60%) out of 65 included studies were double-blind, involving 75% (N=125,487) of the entire studied population. Although the number of trials reporting adequate concealment of allocation was relatively small [13/40 (32%) in double-blind
and 10/25 (40%) in open-label design trials], the number of patients randomized with concealment of allocation was very high (121,618 in double-blind trials out of a total 125,487 and 37,055 in open-label trials out of a total 40,719). Similarly, although more than 75% of trials had an incomplete or not reported all-cause mortality at 2 days, the studies that indeed reported it were large enough (N=131,603) to decrease this risk of incomplete outcome to a minimum. That was not the case for ≥30 day mortality, which was reported by less than 25% of trials, and the trials were not large enough (24,918) to dismiss the possibility of bias for this outcome.

### 3.7.5 Potential biases in the review process

One limitation of the present review is that we did not consider many trials that claimed enrolling their patient in the early period of an acute cardiovascular event, (i.e., within 48 to 72 hours). Evidently, in these types of studies it is anticipated that some patients could be enrolled and have started their study treatment within 24 hours; therefore, data from these patients are missing from our review. Including such patients would require obtaining individual patient data from these studies, which was not possible. We have tried to get information from some recent trials of this type (for example from the ACCESS 2003 trial\(^94\)), with no success. Even though we accept this as a limitation, we feel that adding these trials would create a more unacceptable limitation as we are interested in determining the specific effects of early treatment and we do not want to contaminate that with patients enrolled after the early or acute vulnerable period. Another limitation of this review is that we assessed blood pressure and heart rate changes for only the first 24 hours of the initiation of treatment. The objective was to assess whether these early changes can be related to mortality at 2, 10 or ≥30 days.
Expanding the time window for these measures would likely have made more data available; however, we believe that the effects during the first 24 hours are the most important. An additional problem encountered in acute life-threatening settings is the significant number of patients censored in terms of blood pressure and heart rate data due to death, withdrawal or losses to follow-up. It is difficult, therefore, to have BP data in the same population that is contributing to the mortality data. We are aware that due to the fact that BP and heart rate data were only available from a small number of trials that we do not have a high degree of confidence in the magnitude of these measures.

3.7.6 Agreements and disagreements with other studies or reviews

3.7.6.1 Nitrates

There is a previous overview and meta-analysis that assessed the effects of nitrates in patients with acute myocardial infarction, Yusuf 1988\textsuperscript{26} et al. With only 2,000 patients they found a significant effect (OR 0.55, 95%CI [0.39, 0.76]) on early (first week or in hospital) mortality. These authors did not distinguish between immediate treatment or short-term treatment. Our overall results at 10 days (or in hospital) including both immediate and short-term treatment are not in accordance with their effect estimate: OR 0.90, 95%CI [0.85, 0.96] \(p=0.0008\). Our result with the inclusion of more recent larger trials in 84,185 patients is clearly a better estimate of the true treatment effect.

Our results are also in disagreement with the guidelines from the American College of Cardiology and the American Heart Association ACC/AHA, 2004\textsuperscript{2}. In chapter VI regarding the initial management of MI in the emergency department these guidelines
have relegated the use of nitrates (nitroglycerin exclusively) to patients with ongoing ischemic discomfort or control of hypertension or management of pulmonary congestion. The present systematic review demonstrates that the use of nitrates within 24 hours significantly reduces all-cause mortality (RR 0.81, 95%CI [0.74, 0.89], p<0.0001) at 2 days. This is consistent with 4 or 8 deaths prevented for 1000 low or high risk patients treated, respectively (See summary of findings Table 3-4). Therefore, routine nitrates should be administered to all patients with suspected acute myocardial infarction, who do not have the specific contraindications outlined above. Due to its proven effectiveness in the ISIS-4 trial\textsuperscript{103} and ease of administration, controlled-release oral isosorbide-5-mononitrate 30 mg twice a day the first day and 60 mg the second day is the best choice. However, the use of routine nitrates should be restricted to the first 48 hours as there was no further reduction in mortality associated with their use beyond day 2.

The mechanism whereby nitrates reduce mortality in the immediate period after an acute MI and not after that is not known. Since it appears from this review that blood pressure reduction is not the explanation, there must be another mechanism. Nitrates have been used for more than a century to relieve myocardial ischemia and chest pain. This has been thought to be due to their vasodilatory effects: venous, arterial and coronary vessels and on the redistribution of blood flow towards the ischemic sub-endocardium. These mechanisms may explain the early mortality benefit.

A second possible mechanism is that nitric oxide donors such as nitrates and nitroprusside inhibit platelet adhesion and aggregation. In the late 1980's in vivo animal experiments demonstrated that an infusion of nitroglycerin reduced platelet deposition on damaged arteries\textsuperscript{168}. These findings were confirmed in the early 1990's in vivo by De
Caterina 1990\textsuperscript{169} et al, showing that isosorbide mono-nitrates produced, a dose-dependent, inhibition of platelet aggregation and thromboxane production induced by adenosine diphosphate and adrenaline in patients with objectively proven coronary artery disease. A controlled study by Butterworth 1998\textsuperscript{170} et al, demonstrated that nitroprusside given at dose which reduced MAP by 10 mm Hg, significantly inhibited platelet aggregation and improved regional cerebral blood flow. Furthermore, the results from ISIS-4 1995\textsuperscript{103} and ESPRIM 1994\textsuperscript{120} trials support this theory, as they showed a greater mortality benefit with nitrates in patients who never received anti-platelets drugs. For example, in the former trial, the difference in mortality between the nitrate group and placebo group in patients who never received anti-platelets was 15.7\% versus 17.7\%, respectively (RR 0.89). In contrast, this difference was negligible in patients who did receive anti-platelet drugs, 6.9\% versus 7.0\%, respectively (RR 0.99). An explanation for the early and not late nitrate benefit is that the activation of the sympathetic nervous system (outflow of catecholamines: epinephrine and norepinephrine) is increased in the immediate period of myocardial infarction\textsuperscript{171}. At this early time catecholamines would be the most prominent inductive mechanism for platelet aggregation. It has been shown that nitric oxide donors such as nitrates exert a platelet aggregation inhibitory response only induced by ADP and catecholamines\textsuperscript{169}. That is, nitrates do not interfere with the ongoing thrombotic stimulus induced by thrombin, collagen or other stronger inducers of thromboxane generation and platelet aggregation.

A third potential explanation for the early mortality benefit conferred by nitrates is that in addition to their hemodynamic and cardiac work-load benefits, they might interfere with the heart excitability and/or conduction system in the early hours following the
myocardial infarction. Before the identification of the endothelium-derived relaxing factor as nitric oxide in the late 80's there were some reports showing that nitrates have anti-arrhythmic effects in acute myocardial ischemia animal models\textsuperscript{172,173}. At that time the theory that nitrates work through the release of nitric oxide (NO), increasing guanosine 3':5'- cyclic monophosphate (cGMP), was presented\textsuperscript{174,175}. More recently, others have reported the effects of nitric oxide on the excitability of the autonomic cells (sinoatrial node or atrioventricular node\textsuperscript{176-178} or directly on myocytes\textsuperscript{179}). The fact that neural nitric oxide synthase (nNOS) has now been identified in the nerve fibers of the heart\textsuperscript{180,181}, suggest a broader role of NO in the heart's electrophysiology. An augmented expression on nNOS during acute myocardial infarction in animal models has been demonstrated\textsuperscript{182}. Thus, an anti-arrhythmic effect from nitrates/nitric oxide remains a possibility\textsuperscript{183-186}.

\textbf{3.7.6.2 Angiotensin converting enzyme inhibitors (ACEi)}

The effects of ACE inhibitors on AMI patients have been reported in two systematic reviews (AMICG 1998\textsuperscript{27} and Rodrigues 2003\textsuperscript{28} et al). In the former, 98,496 patients were included from trials comparing ACE inhibitors to placebo or no treatment. The authors demonstrated a mortality reduction with ACEi obtained at 7 days and 30 days (RR 0.92, 95\%CI [0.86, 0.97]; and RR 0.93, 95\%CI [0.89, 0.98], respectively. Thus, these 7-day findings are very similar to our 10-day results. The other ACEi systematic review (Rodrigues et al 2003\textsuperscript{28}), had the objective to assess the effect of long-term treatments as they did not limited the length of treatment in the trials and quantified mortality at 30 days, 6 months and 1 year. Thus, the Rodrigues 2003\textsuperscript{28} review cannot be compared to ours.
The American College of Cardiology and the American Heart Association have recommended that an angiotensin converting enzyme (ACE) inhibitor should be administered orally within the first 24 hours of STEMI (ST-elevation myocardial infarction) to patients with anterior infarction, pulmonary congestion or LVEF less than 0.40 in the absence of hypotension or known contraindications to that class of medications. However, in a second paragraph they further state that ACE inhibitor administered within the first 24 hours of STEMI can be useful without the above characteristics.

In our ACE inhibitors analysis the effect estimates for open-label trials and double-blind trials differ, at 2 days RR 0.86, 95%CI [0.71,1.03]) and RR 0.93, 95%CI [0.83,1.04]), respectively, calling into question the borderline overall mortality benefit at 2 days (RR 0.91, 95%CI [0.82,1.00]), p=0.05. Furthermore, nitrates confer a superior relative 0.81 versus 0.91, and absolute mortality benefit 4 - 8 per 1000 versus 2 to 4 per 1000, respectively. Thus, we feel that the optimal time of administration of ACE inhibitors post-acute MI is presently unknown and that further research is required.

3.7.6.3 Beta-adrenergic antagonists or beta-blockers (BB)

Other systematic reviews (SRs) have evaluated the effect of beta-blockers (BB) in AMI (Yusuf 198523 et al, Freemantle 199924 et al, and Al-Reesi 200825 et al). All of these reviews have accepted trials where treatment was started later than 24 hours after the onset of AMI. Yusuf et al (198523) concluded that reliable estimation of the effects of early beta blockade on mortality has not yet been achieved. Freemantle et al (199924) also concluded that there were no mortality benefits from BB in "short-term" trials. The most
recent review (Al-Reesi et al 200825) inexplicably excluded 11 trials that we included in our review. Despite that, their conclusion stating that "acute intervention with B-blockers does not result in statistical significant short-term survival benefit following AMI" is in agreement with ours.

Despite these systematic reviews, the ACC/AHA 20042 recommended that oral beta-blocker therapy should be administered promptly to those suspected MI patients without a contraindication irrespective of concomitant fibrinolytic therapy or performance of primary PCI.

Based on our systematic review we do not recommend routine BB for the immediate or short-term treatment of patients with suspected MI. However, it should be emphasized that these findings and recommendations are not contradictory to the long-term mortality benefits for BB post MI when these drugs are started a few days or weeks after myocardial infarction and continued for some months (Yusuf 198523 and Freemantle 199924).

3.7.6.4 Calcium channel blockers (CCB)

In Acute Myocardial Infarction

The one other systematic review that has assessed CCB drug in patients with acute myocardial infarction or unstable angina, Held et al (198922) also included trials in which treatment was started after 24 hours or trials where the time of entry was not specified. However, they also concluded that "CCBs do not reduce the risk of initial or recurrent infarction or death when given routinely to patients with acute myocardial infarction or unstable angina".
The ACC/AHA, 2004² have restricted the use of CCB by stating that it is reasonable to give verapamil or diltiazem to patients in whom beta-blockers are ineffective or contraindicated for relief of ongoing ischemia or control of a rapid ventricular response with atrial fibrillation of flutter after STEMI in the absence of CHF, LV dysfunction or atrioventricular (AV) block.

**In Stroke**

There is one Cochrane systematic review already published that assessed CCB drugs in acute stroke (Horn et al, 2000²⁹) but with a different research question from ours. Their focus was not limited to the immediate initiation of treatment and for short term treatment. They included 28 studies. Of those, 12 trials had required their patients to start treatment within 24 hours of the onset. Of those, we have excluded one trial because it compared IV infusion vs. oral treatment, rather than CCB vs. placebo; and 5 trials because mortality data was not reported or usable in our review. Despite the differences their conclusion "No evidence is available to justify the use of calcium antagonists in patients with acute ischemic stroke" agrees with ours.

Two Cochrane systematic reviews involving patients with acute stroke and blood pressure lowering drugs have been published: Bath 2002¹⁸⁷ et al; Geeganage 2008³¹ et al. The former assessed nitrates for acute stroke with different methodology and objectives than ours. Studies were not limited to truly randomized trials or to the immediate initiation of treatment and for short term treatment. Since only two studies were included, the authors concluded that there was insufficient evidence to recommend the use of nitrates. We did not include those two trials because treatment started days after the onset of the stroke. The Geeganage et al (2008³¹) review also had a different approach to ours,
as it was not limited to RCTs studying blood pressure reducing drugs. In addition, in this review RCTs are not limited to a certain time of starting treatment after the stroke (for example, it included trials where treatment started even 7 days after the onset). Out of their 12 included studies, 3 trials started the treatment within 24 hours. We excluded all these 3 for the following reasons. In the INTERACT (2008\textsuperscript{188}) trial, patients were not allocated to a class of drug vs. placebo or no treatment. Instead, patients were allocated to two different BP targets (140 vs. 180 mm Hg) to be achieved in 1 hour and maintained for 7 days. The ACCESS (2003\textsuperscript{94}) trial included patients within 24 and 36 hours but without separating their results according to these times. And the third trial, Eveson et al (2007\textsuperscript{33}), results were not based on ITT principles. Patients first were randomized and then withdrawn if diagnosis was wrong. Analysis was not performed based on all randomized patients.

3.8 Authors’ conclusions

3.8.1 Implications for practice

3.8.1.1 Acute myocardial infarction.

Nitrates administered within 24 hours of symptom onset significantly decrease day-2 all-cause mortality (4 to 8 deaths prevented per 1000).

The evidence shows that continuation of nitrates beyond day 2 does not reduce mortality. ACE inhibitors administered within 24 hours of symptom onset have not been shown to significantly reduce mortality at 2 days.

ACE inhibitors administered within 24 hours of symptom onset and continued for 10 days significantly reduce day 10 all-cause mortality (3 to 5 deaths prevented per 1000).
The optimal time of starting ACE inhibitor therapy post myocardial infarction is not known.

Beta-blockers started within 24 hours of symptom onset do not reduce all-cause mortality at 2 days or after short-term use at 10 days.

Calcium channel blockers started within 24 hours of symptom onset do not decrease mortality and a trend towards increased mortality was seen after short-term use of these drugs at 10 days (RR 1.60 95%CI [0.90, 2.86]).

3.8.1.2 Other acute cardiovascular conditions

Calcium channel blockers administered after acute stroke have not been shown to affect mortality but the data is insufficient.

There is no RCT information regarding the effects on mortality produced by blood pressure lowering drugs started within 24 hours of the onset of other cardiovascular events such as acute aortic dissection, acute pulmonary edema, unstable angina, intracranial or sub-arachnoid hemorrhage.

3.8.2 Implications for research

3.8.2.1 In patients with acute myocardial infarction

Future RCTs of early treatment should report mortality at standard times 2 days, 10 days, 30 days and 6 months.

Mortality data at the times from all RCTs should be made available. This is particularly important for the existing calcium channel blocker RCTs.
Future trials in this condition need to be cognizant of the possibility that treatment effects may be different during the first 2 days as compared with after 2 days as demonstrated in this review.

An individual patient meta-analysis of immediate treatment ACE inhibitor trials is needed to ascertain whether there is a subgroup of immediate post MI patients with a mortality benefit.

More RCTs are needed to better define the optimal time to start ACE inhibitor therapy.

3.8.2.2 In patients with acute stroke, unstable angina, acute pulmonary edema, cerebral hemorrhage or acute aortic dissection:

Because blood pressure-lowering drugs are frequently used in these settings there is a need for more large RCTs assessing different aspects of these interventions: eg., different drug classes, different drugs within a class, dosing regimens, timing of onset of treatment, blood pressure threshold for treatment etc.

Regardless of the design of these RCTs, such trials must report total all-cause mortality at standard different times of follow-up: 2 days, 10 days, 1 month and 6 months.

An international organization should standardize and mandate the documentation and reporting of total serious adverse events in hospitalized and critically-ill patients.

3.9 Acknowledgements

We have deep gratitude for the trialists who provided us with additional information from their studies; for Eugenio Santoro especially, from the GISSI-3 trial, who kindly responded to all of our requests. We acknowledge the collaboration of Cochrane hypertension review group, particularly to Stephen Adams for his unconditional help in
retrieving all studies. We are grateful to Dr. Ken Basset, Dr. Thomas Perry, Benji Heran, Jenny Chang and Gavin Wong for their comments on a draft.
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4 FAILURE OF PSYCHOLOGICAL INTERVENTIONS TO LOWER BLOOD PRESSURE: RANDOMIZED CONTROLLED TRIAL

4.1 Introduction

Patients with mild primary hypertension have a number of options to help lower their blood pressure. Non-pharmacological options include the DASH (Dietary Approaches to Stop Hypertension) diet, a low-sodium diet, exercise, weight loss, and relaxation therapies. Relaxation therapies are based on the supposition that psychological stress may contribute to the elevation of blood pressure in some patients. Others have suggested possible links between stress and hypertension are elevated sympathetic tone or vagal dysregulation. Several systematic reviews have evaluated the efficacy of diverse psychological and relaxation therapies in reducing blood pressure in patients with primary hypertension as compared to no therapy or sham therapy. However, these studies have yielded conflicting results.

It remains important to determine whether psychological interventions lower blood pressure and the magnitude of the effect, if any, as many patients might prefer this form of therapy over drug therapy if both were equally efficacious. We were therefore interested in evaluating the efficacy of two psychological interventions in lowering blood pressure.

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3 A version of this chapter has been published. Marco I Perez, Wolfgang Linden, Thomas Perry Jr., Lorri J Puil, James M Wright. Failure of psychological interventions to lower blood pressure: a randomized controlled trial. Open Medicine 2009;3[2]:62-70.
pressure: an individualized program of behavioural therapy and a self-help program of psychological therapy.

With the objective of rigorously assessing the effects of these two psychological interventions, we compared them with pharmacotherapy using a thiazide, a first-line drug commonly used in the treatment of mild primary hypertension. A large body of evidence from randomized controlled trials (RCTs) shows that thiazides reduce blood pressure and quantifies the magnitude of their short-term effect on systolic and diastolic blood pressure as about 9/4 mm Hg. There is considerable value in using a drug with a known effect as a positive control for a study such as this one. As far as we know, no previous RCTs have directly compared psychological interventions with a drug therapy control.

4.2 Methods

4.2.1 Design

Prospective, open-label randomized controlled trial.

4.2.2 Setting and participants

Adult patients (aged 18 years or older) from the community, with mild hypertension defined as resting systolic blood pressure of 140 mm Hg or above and/or diastolic blood pressure of 90 mm Hg or above, were eligible. Patients were excluded if they had cardiovascular complications or any suspected medical condition that might lead to an unacceptable risk of complications resulting from uncontrolled hypertension during the study period. Patients whose hypertension was uncontrolled while they were taking medication (systolic blood pressure ≥ 170 mm Hg or diastolic blood pressure ≥ 100 mm Hg) or who had excessively high blood pressure while they were not taking any
medication (≥ 180/110 mm Hg) were also excluded. Patients with suspected secondary hypertension were excluded, as were those who were pregnant or anticipated being pregnant and those with a history of allergy to, hypersensitivity to, or intolerance of thiazides. Participants were encouraged not to adopt any other changes in lifestyle, diet or exercise during the trial.

4.2.3 Protocol

Patients who were taking medication at the time of initial screening underwent a washout period of 3–5 weeks. Patients who met the inclusion criteria and whose off-treatment baseline resting systolic blood pressure in clinic was 140 mm Hg or above or whose resting diastolic blood pressure was 90 mm Hg or above were randomly assigned to receive 1 of the following interventions for 12 weeks: hydrochlorothiazide 12.5 mg/d initially and then 25 mg/d if systolic blood pressure was 140 mm Hg or above or diastolic blood pressure was 90 mm Hg or above after 4 weeks of treatment; individualized behavioural psychotherapy consisting of ten 1-hour sessions with a psychologist; self-help psychological therapy, consisting of an initial 1.5-hour meeting with a psychologist and then daily sessions that involved reading a self-help manual and listening to an audiotape. Both of the psychological treatments entailed learning relaxation, biofeedback and stress management. Details of these psychological forms of management can be seen in a section below (section 4.7). Concealment of allocation was achieved by centralized randomization conducted via telephone by the Cochrane Hypertension Review Group coordinator at the University of British Columbia. This person was blinded to patients’ identification and to characteristics other than gender and previous use of antihypertensive drugs. Information about these two characteristics was needed to allow
block randomization. The study protocol was reviewed and approved by the institutional ethical review board at the University of British Columbia (UBC). Written informed consent was obtained from all patients.

4.2.4 Recruitment, clinical evaluation and follow-up

Participants were recruited by means of newspaper advertising and/or referral by health care practitioners or friends. This recruitment was coordinated by UBC’s Behavioural Cardiology Laboratory (BCL). Patients who had not previously been receiving antihypertensive drugs but who exhibited elevated blood pressure at the BCL were sent to the hypertension medical clinic for confirmation of eligibility. Patients who were already taking antihypertensive drugs were seen at the laboratory and were then sent to the clinic, where blood pressure was measured before and after washout, with the possibility of a third post-washout check in the event of borderline blood pressure readings. All of these potential participants provided a medical history and underwent a physical examination. A specific laboratory assessment was ordered if considered necessary. After enrolment, the patients attended the clinic every four weeks. At each visit, resting blood pressure was measured. All resting blood pressure measurements were reported as the average of five readings, separated by one-minute intervals, with the first reading after five minutes of rest. The patient was in a seated position and the examiner was out of the room during the readings, which were obtained with an automatic device that concealed the measurements from the patient (oscillometric VSM-100 automated blood pressure machine-VSM MedTech Ltd., Vancouver, BC, Canada\textsuperscript{15}). This rigorous methodology was intended to prevent any bias in the blood pressure measurements. True blinding of the patients and investigators was not feasible in view of the type of interventions in this study. At week
seven, serum levels of potassium were checked for all of the patients who had been randomly assigned to receive hydrochlorothiazide, to detect hypokalemia, if present, and to allow the prescription of a potassium-sparing diuretic if required. Patients were instructed to report to the clinic immediately if they experienced any unusual symptoms during the study.

Before treatment of any kind, each patient underwent 24-hour monitoring of ambulatory blood pressure, by means of the Spacelabs Medical ambulatory blood pressure monitor (model 90207, Spacelabs Inc, Redmond, Washington, USA). For this monitoring, blood pressure was recorded at 20-minute intervals between 8:00 a.m. and 8:00 p.m. (for daytime measurements) and at 1-hour intervals between 8:00 p.m. and 8:00 a.m. (for nighttime measurements). The monitoring was repeated 12 weeks later (at the end of the study).

4.2.5 Outcome measures

The primary outcome measure was the mean change in ambulatory blood pressure from baseline to week 12. The secondary outcome measure was the mean change in resting clinic blood pressure, over 12 weeks of treatment. All adverse events, regardless of their nature, were documented, reviewed and reported to the ethics committee.

4.2.6 Statistical analysis

The calculation of the sample size was based on a previous study\textsuperscript{16} in which there was a 7 mm Hg (standard deviation 11 mm Hg) difference in systolic pressure between individualized behavioural psychotherapy and no treatment. We calculated that a sample size of 40 patients per treatment arm would provide 80% power at $\alpha = 0.05$ level for detection of the above-mentioned difference in blood pressure. However, because of the
potential for dropouts, the desired sample size was increased to 50 patients per treatment arm. The efficacy end-points were analyzed according to the intention-to-treat principle. All statistical analyses were performed using the statistical package NCSS 2007 (LLC, Kaysville, Utah, USA). Paired Student’s t-test was used to compare variables with continuous data before and after treatment within each group. Treatment groups were compared by analysis of variance using the general linear model approach for repeated measurements and Tukey’s test for multiple comparisons. Using baseline values as covariates analysis of covariance (ANCOVA) was also performed. A p-value less than 0.05 was considered statistically significant.

4.3 Results

4.3.1 Study population

Recruitment for this single-centre study began in March 2002 and ended in May 2006. Unfortunately, because of recruitment difficulties, the desired sample size of 50 per group was not achieved. Of the 516 patients with suspected hypertension who were screened, 337 were not eligible because they did not meet the study’s inclusion criteria at the initial screening (Figure 4-1). The reasons for not qualifying varied: past medical history, desire to choose a particular treatment, required commitment of time too great, inability to come to our centre (e.g., living far away), lack of interest in stress management or in the drug. The remaining 179 patients were sent to the medical hypertension clinic for evaluation. Of these, 13 patients decided not to participate after undergoing the evaluation. An additional 101 patients were ineligible for the following reasons: 65 patients did not meet the minimum blood pressure inclusion criteria after the washout process, 8 patients had
excessively high blood pressure (≥180/110 mm Hg), and 28 had a medical history (such as coronary artery disease) that precluded their participation.

**Figure 4-1 Flow Diagram for Patients in the Study.**

A total of 65 patients (with baseline characteristics as listed in Table 4-1) were randomly assigned to 1 of the 3 groups: 21 to receive hydrochlorothiazide, 23 to undergo individualized behavioural psychotherapy, and 21 to perform self-help psychotherapy. Two patients in each group acknowledged that they had sought psychological or psychiatric help in the past. One of these patients (assigned to the hydrochlorothiazide
group) had received self-help psychological therapy (in the form of a booklet). There was no statistically significant difference in the number of patients who had previously received hydrochlorothiazide or any other antihypertensive drug. Except for systolic blood pressure as recorded during 24-hour ambulatory monitoring, which was higher for those in the self-help psychotherapy group, the groups were similar with respect to all variables. Six patients in the hydrochlorothiazide group, 6 in the individualized behavioural psychotherapy group, and 9 in the self-help psychotherapy group withdrew from the study or did not undergo the second 24-hour monitoring of ambulatory blood pressure (at 12 weeks).

Table 4-1 Patients Characteristics at Baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HCTZ n = 21</th>
<th>IBP n = 23</th>
<th>SHT n = 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean (SE)</td>
<td>58 (1.8)</td>
<td>54 (1.9)</td>
<td>60 (1.9)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>11 (52)</td>
<td>12 (52)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Taking antihypertensives at screening*, n (%)</td>
<td>15 (71)</td>
<td>12 (52)</td>
<td>13 (62)</td>
</tr>
<tr>
<td>CCB</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>BB</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>ACE-I</td>
<td>7</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>ARBs</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Thiazides</td>
<td>11</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Duration of hypertension, yr (SE)</td>
<td>7.6 (1.3)</td>
<td>5.5 (0.8)</td>
<td>8.2 (1.9)</td>
</tr>
<tr>
<td>Resting baseline BP, mm Hg, mean (SE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>154 (2.4)</td>
<td>147 (2.2)</td>
<td>154 (2.9)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>89 (1.6)</td>
<td>89 (2.0)</td>
<td>89 (2.1)</td>
</tr>
<tr>
<td>24-h ABPM, mm Hg, mean (SE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>146 (2.8)</td>
<td>143 (2.3)</td>
<td>153* (2.1)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>88 (2.0)</td>
<td>89 (2.0)</td>
<td>92 (2.1)</td>
</tr>
</tbody>
</table>

* Some patients were taking more than one antihypertensive

ABPM = ambulatory blood pressure monitoring, ACE-I = angiotensin converting enzyme inhibitors, ARBs = angiotensin II receptor blockers, BB = beta-adrenergic receptor blockers, CCB = calcium channel blockers, HCTZ = hydrochlorothiazide therapy, IBT = individualized behavioural therapy, SHT = self-help psychotherapy, BP = blood pressure, SE = standard error

* p < 0.05 for SHT v. IBT.

Continuous data (age, duration of hypertension, 24-h ABPM, resting blood pressure) are expressed as mean (SE); all other data are expressed as number (%).
4.3.2 Primary outcome: change in ambulatory blood pressure (24-h monitoring)

Hydrochlorothiazide produced a statistically significant reduction in both systolic and diastolic blood pressure during 24-hour monitoring of ambulatory blood pressure, and this change was greater than the changes observed with either individualized behavioural or self-help psychological therapy (systolic mean reduction ± standard error: −11.03 ± 2.53 v. −0.08 ± 2.38 v. −1.23 ± 2.83 mm Hg, respectively, p = 0.006; diastolic: −6.06 ± 1.56 v. 0.29 ± 1.47 v. −0.71 ± 1.75 mm Hg, respectively, p = 0.01. Neither form of psychological therapy reduced ambulatory blood pressure, as measured by 24-hour monitoring, relative to baseline (Table 4-2).

Table 4-2 Twenty-four-hour ambulatory blood pressure measurements at baseline and change from baseline at week 12.

<table>
<thead>
<tr>
<th>24-hour ambulatory blood pressure measurements</th>
<th>HCTZ</th>
<th>IBT</th>
<th>SHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n = 21)</td>
<td>Change from baseline (n = 15)</td>
<td>Baseline (n = 23)</td>
<td>Change from baseline (n = 17)</td>
</tr>
<tr>
<td>Systolic, mm Hg, mean (SE)</td>
<td>146.66 (2.79)</td>
<td>−11.03* (2.53)</td>
<td>143.08 (2.28)</td>
</tr>
<tr>
<td>Diastolic, mm Hg, mean (SE)</td>
<td>88.48 (2.05)</td>
<td>−6.06* (1.56)</td>
<td>89.18 (2.06)</td>
</tr>
</tbody>
</table>

HCTZ = hydrochlorothiazide therapy, IBT = individualized behavioural therapy, SHT = self-help psychotherapy, SBP = systolic blood pressure, DBP = diastolic blood pressure, SE = standard error.
* p ≤ 0.01 v. baseline v. either psychological therapy

4.3.3 Secondary outcome: change in resting clinic blood pressure

For this outcome, we included data from all patients with at least one blood pressure measurement after treatment and used the weighted average from all post-treatment blood pressure measurements for the analysis. As such, data were available for more participants: 19 in the hydrochlorothiazide group, 18 in the individualized behavioural therapy group, and 16 in the self-help therapy group. In this analysis, both
hydrochlorothiazide therapy and individualized behavioural psychotherapy were associated with a statistically significant reduction (relative to baseline) in systolic and diastolic blood pressure. The extent of reduction in blood pressure was numerically greater in the group receiving hydrochlorothiazide than in the other 2 groups, but the mean change in resting clinic systolic or diastolic blood pressure over 12 weeks showed no statistically significant difference among the 3 groups (Table 4-3).

Table 4-3 Resting Clinic Blood pressure Measurements at baseline and change from baseline over 12 weeks

<table>
<thead>
<tr>
<th>Resting blood pressure measurements</th>
<th>Baseline</th>
<th>Change from baseline</th>
<th>Baseline</th>
<th>Change from baseline</th>
<th>Baseline</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCTZ</td>
<td>IBT</td>
<td>SHT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic, mm Hg, mean (SE)</td>
<td>154.42 (2.39)</td>
<td>-15.13*(2.64)</td>
<td>147.22 (2.21)</td>
<td>-10.79* (2.91)</td>
<td>154.38 (2.86)</td>
<td>-8.54 (4.71)</td>
</tr>
<tr>
<td>Diastolic, mm Hg, mean (SE)</td>
<td>89.23 (1.61)</td>
<td>-6.00*(1.18)</td>
<td>89.43 (1.99)</td>
<td>-5.02* (1.50)</td>
<td>88.62 (2.09)</td>
<td>-0.23 (2.06)</td>
</tr>
</tbody>
</table>

BP = blood pressure, HCTZ = hydrochlorothiazide therapy, IBT = individualized behavioural therapy, SHT = self-help psychotherapy, SBP = systolic blood pressure, DBP = diastolic blood pressure, SE = standard error
* p < 0.01 v. baseline

4.3.4 Adverse events

A total of five patients withdrew because of adverse events. Three participants experienced intractable headache (one patient in the hydrochlorothiazide group and two in the self-help therapy group). In all three cases, the headache subsided after withdrawal from the study. One patient who was receiving hydrochlorothiazide withdrew because of a suspected allergic reaction to the study medication (the patient stopped taking the drug at day 21 because of soreness in the tongue and lips). One patient in the self-help therapy group withdrew because of palpitations. In addition to these five withdrawals, one patient who was receiving 25mg of hydrochlorothiazide experienced hypokalemia, which was
corrected by the addition of spironolactone. There were no serious adverse events during
the trial.

4.4 Discussion

It has been hypothesized that psychological stress may contribute to the elevation of
blood pressure in patients with primary hypertension, and that psychological therapy may
lower blood pressure. However, these hypotheses have been called into question by the
results of a recent Cochrane systematic review, in particular the results obtained when the
analysis was limited to studies that used blinded outcome assessment\(^5\). In that review of
relaxation therapies, 25 RCTs (\(n = 1198\) patients) were evaluated. The authors concluded
that the effect of these therapies in lowering blood pressure was questionable because of
the poor quality of the studies. In fact, when only trials using blinded outcome assessment
were included (9 RCTs, \(n = 498\) patients), there was no significant reduction in either
systolic or diastolic blood pressure.

The current study is the first RCT to directly compare psychological therapy with a
standard pharmacological antihypertensive treatment. The use of hydrochlorothiazide as a
control worked well in this study. The drug lowered ambulatory blood pressure, as
measured by 24-hour monitoring, by about 11/6 mm Hg, which is similar to the reduction
reported in a meta-analysis of other studies of standard-dose thiazide given for a similar
duration of therapy, 9/4 mm Hg\(^{14}\). This result shows that the patients in this trial were
representative of patients in other trials studying mild to moderate hypertension.

This study has shown that in a clinical setting where thiazide therapy lowered blood
pressure by a magnitude similar to that expected, two psychological therapies did not
have this effect. This difference in outcome was particularly evident from the blood
pressure data obtained with 24-hour monitoring. In particular, the individualized
behavioural therapy and self-help psychotherapy had no effect on 24-hour ambulatory
systolic or diastolic blood pressure.

Hydrochlorothiazide also significantly lowered resting clinic blood pressure relative to
baseline. In addition, individualized behavioural psychotherapy but not self-help
psychotherapy produced a statistically significant change in resting clinic blood pressure
from baseline. For this outcome, however, there was no statistically significant difference
among the groups. This lack of difference may have been due in part to the “placebo
effect” commonly observed in studies that used in-clinic measurements of blood pressure.
The causes of this phenomenon are unknown, but participating in a study may offer the
patient some reassurance (e.g., by having the doctor’s full attention, by meeting a
psychological need), which could be enough to reduce anxiety and stress or to provoke
changes in attitudes, which in turn might improve blood pressure readings in the clinic
setting. It is also possible that the individualized behavioural psychotherapy helped
patients to learn to relax in the clinic setting, which would have offset the “white-coat
effect.” If so, this would be unlikely to have any clinical value, as there was no reduction
in ambulatory blood pressure as measured by 24-hour monitoring. This study was a good
demonstration of the value of such 24-hour monitoring. A previous study provided
evidence for the lack of a placebo effect in patients with mild to moderate hypertension
when blood pressure was measured by 24-hour monitoring17. The combination of a lack
of the placebo effect and the large number of blood pressure measurements obtained
increases the power of 24-hour monitoring to identify a treatment effect, as occurred in
this trial.
One of the strengths of this study was the proper randomization as well as the foolproof method of concealing treatment allocation from the patients and the investigators. Two additional strengths were the use of an automated device for recording both ambulatory and clinic blood pressure, and the absence of the investigators at the time of measurement. The objective of this was to reduce subjective bias when measuring blood pressure. A further strength of this study was that all of the available results were used in the analysis, which prevented any reporting bias.

One limitation of this study was the small sample size, which was caused by difficulties in recruiting patients with newly diagnosed hypertension and by excluding a large number of previously treated patients who did not meet the blood pressure criteria after the washout period (65 [58%] of the 112 patients who underwent washout). A second, related limitation was the high rate of patients unavailable for the primary outcome analysis (6/21 [29%] from the hydrochlorothiazide group, 6/23 [26%] from the individualized behavioural psychotherapy group and 9/21 [43%] from the self-help therapy group). Because we did not achieve the desired sample size and because many patients withdrew after randomization, the study’s power was lower than planned, and the probability of incorrectly accepting the null hypothesis when it is not true (i.e., type II or beta error) was increased. Our inability to find differences when we compared the three groups of clinic blood pressure measurements is an example of this type II error. This loss of power, however, did not prevent detection of a difference between hydrochlorothiazide and either psychological intervention by 24-hour ambulatory measurements. A third limitation was the chance finding that baseline blood pressure in the self-help psychotherapy group was higher than that in the individualized behavioural
psychotherapy group. This might have reduced the opportunity for the individualized behavioural psychotherapy intervention to lower blood pressure in that group. However, when we performed the post-hoc ANCOVA analysis using baseline values as a covariate, the p-values changed minimally for both ambulatory and resting clinic blood pressure outcomes; we therefore believe that the initial difference in blood pressure between these two groups probably had little effect. Nonetheless, caution is warranted in interpreting these results, as the trial had limited power to prove a lack of effect of the psychological interventions on the 24-hour blood pressure measurements. When we planned our study, no information was available on the effect of psychological therapy in lowering blood pressure relative to a pharmacological treatment. We chose hydrochlorothiazide because, in addition to the well-known ability of this drug to lower blood pressure, the thiazides in general have the most evidence for reductions in mortality and morbidity when used as first-line drugs\textsuperscript{18}. The key finding of this study is that compared with hydrochlorothiazide, psychological therapies appeared to have no clinically important effect in lowering blood pressure over a 12-week period, as assessed by 24-hour ambulatory monitoring. These results apply to patients with mild uncomplicated hypertension (systolic $\geq$ 140 and/or diastolic $\geq$ 90 mm Hg).

This new information needs to be put into context with other available RCT data. The best available evidence of the effect of relaxation therapies on blood pressure was provided by a recent Cochrane systematic review. In that review, Dickinson and colleagues\textsuperscript{5} found that when only RCTs with blinded blood pressure measurement were included, the psychological or relaxation techniques had no statistically significant effect in reducing blood pressure. This led the authors to conclude, “In view of the poor quality
of included trials and unexplained variation between trials, the evidence in favor of causal association between relaxation therapy and blood pressure reduction is weak. Some of the apparent benefit of relaxation was probably due to aspects of treatment unrelated to relaxation\textsuperscript{5}. The results of the RCT presented here are in agreement with that conclusion. If future trials of psychological interventions and other relaxation therapies are conducted, they must have rigorous designs to minimize bias.

4.5 Funding source

The Canadian Institutes of Health Research (CIHR) was the funding source. The authors’ work was independent of CIHR. The funding source had no financial or other interest in the study outcome and had no role in the design of the study or the collection, analysis, interpretation or reporting of the data.

4.6 Trial registration

Clinical trials.gov identifier: NCT00247910.

4.7 Additional information: Details of psychological interventions.

4.7.1 Individualized behavioural therapy

The individualized behavioural therapy intervention was first developed for and used by patients with cardiac disease (in unpublished clinical work) and was then used in a randomized controlled trial involving hypertensive patients\textsuperscript{16}. The intervention consisted of 10 1-hour psychological therapy sessions over a 10-week period. To guarantee a high level of quality and maximal treatment benefit, the intervention was delivered by experienced PhD-level psychotherapists with specific training in cognitive behavioural interventions. In this study, 2 therapists provided these sessions, each treating a similar
number of patients (13 and 10, respectively). The first session consisted of an assessment
of risk factors (work stress, home stress, time urgency, hostility, absence of pleasurable
activities, coping styles, depression and anxiety). On the basis of this assessment, the
therapist and client together set the targets for the psychological intervention. To apply
the psychological interventions, each therapist used a set of manual-based techniques
(stress management, cognitive behavioural therapy, autogenic training, anxiety
management training)\textsuperscript{19-22}. The most frequent psychological therapies offered were
anxiety reduction, treatment of depression, management of anger and hostility, and
relaxation training. When more than one psychological treatment area was identified, the
therapist might have used a combination of these techniques. The results of pretreatment
24-hour monitoring of blood pressure were available to the psychotherapists to allow
them to tailor the techniques to individual clients. More details about this approach are
described elsewhere\textsuperscript{23}.

4.7.2 Self-help therapy

The self-help therapy involved an initial 1.5-hour session with a Master’s-level
psychotherapist. The patient was then instructed to follow a self-help manual over a 10-
week period to be used on a daily basis. The manual consisted of material derived from
Linden’s review of the scientific basis for stress management\textsuperscript{24}, which was being
prepared for publication at the time of the study. Topics covered in the self-help manual
included: recognition of stressors; behavioural coping skills; cognitive restructuring;
building a healthy, balanced lifestyle; strengthening social support; and adding enjoyable
activities to one’s life. In the first session, the therapist instructed each participant on how
to use the self-help manual and to record their relaxation practices. Patients were also
given an audiotape to assist with training and practice in breathing and relaxation

techniques.

Each patient was contacted by his or her therapist at the midpoint of the self-help
intervention (five weeks) to discuss any problems that might have arisen. Each patient
met with his or her therapist for one hour at the end of the treatment period to review
progress and to determine whether the patient wanted to receive individualized

psychological therapy in the future.

4.7.3 **Assessment tools for all treatment arms:**

The following psychological scales were used: the Cook–Medley Hostility Inventory\textsuperscript{25},
the State–Trait Anxiety Inventory\textsuperscript{26}, the Behavioral Anger Response Questionnaire\textsuperscript{27}, the
Perceived Stress Scale\textsuperscript{28}, the Beck Depression Inventory\textsuperscript{29} and the Balanced Inventory of
Desirable Responding\textsuperscript{30}. 
4.8 References


(15) Mattu GS, Perry TL, Jr., Wright JM. Comparison of the oscillometric blood pressure monitor (BPM-100(Beta) ) with the auscultatory mercury sphygmomanometer. Blood Pressure Monitoring 2001; 6(3):153-159.


5 CONCLUDING CHAPTER

5.1 Clinical and research focus

5.1.1 Acute-phase therapy

Chapter 2 and 3 of this thesis establish the scientific evidence for antihypertensive drug therapy when given in the acute phase (within 24 hours of the onset) of a myocardial infarction, other acute cardiovascular event, or a hypertensive emergency (acute end organ damage with marked hypertension). Acute cardiovascular events are characterized by high mortality during the first few hours or days, and this is particularly true for acute myocardial infarction\(^1\). Therefore, determining which drugs to administer, and when is key to patient outcome. Other systematic reviews of antihypertensive therapy have focused very little attention on acute phase therapy\(^2\text{-}^6\).

This thesis research distinguished two acute phase anti-hypertensive treatment strategies. In the first strategy, anti-hypertensive therapy was started within the first 24 hours of an acute cardiovascular event and given for a maximum of 48 hours. In the second, the anti-hypertensive drug was started within 24 hours and continued for up to 10 days. These are referred to herein as “immediate intervention” when given for 1-48 hours and “short-term intervention” when started within the first 24 hours and continued up to 10 days. The outcome sought for both strategies was all-cause mortality at 48 hours, 10 days and \(\geq 30\) days.
The immediate intervention, which sets a limit of 48 hours to the duration of therapy, is a novel question to ask for anti-hypertensive therapy. Typically, questions are raised about the time of initiation, not the duration of therapy. Few investigators have considered that anti-hypertensive therapy could have a “critical” early period in which benefit occurs; after which further therapy offers no benefit, and perhaps results in harm.

The rationale for including an “immediate intervention” (starting < 24 hours and maximum therapy 48 hours) follows what is found with other therapies that have been proven mortality benefits. For example, a meta-analysis of randomized controlled trials of fibrinolytic therapy in acute myocardial infarction found that there was significant mortality benefit at 35 days despite the fact that fibrinolytic therapies are only administered for a few hours in the early period after the event.

Although the anti-hypertensive drugs are started early (<24 hours) and the duration is short (maximum 48 hours) mortality outcome is measured at 48 hours, 10 and ≥30 days. This approach also follows from fibrinolytics. Consider the example of a large double-blind placebo controlled trial [ISIS-2 1988\(^8\)] where 17,187 patients within 24 hours of the onset of a suspected acute myocardial infarction were randomized to receive a one-hour streptokinase IV infusion or placebo infusion. Streptokinase had no effect on mortality at 48 hours (RR= 1.04, 95%CI [0.89, 1.21] but reduced mortality at 10 days (RR= 0.82, 95%CI [0.74, 0.91] and at 35 days (RR= 0.77, 95%CI [0.70, 0.84]).
5.1.1.1 Findings for the immediate intervention (start < 24 h, maximum therapy 48 hours)

The immediate use of nitrates in patients with suspected or definite acute myocardial infarction (N= 82,624) is the only class of drugs associated with reduction of mortality during the first 48 hours (RR=0.81, 95%CI [0.74, 0.89]). This represents 4 lives saved per 1000 treated (Chapter 3; see also table 5.1). Unfortunately, there were not enough trials that reported mortality at 10 days or at ≥30 days to draw any conclusions of the effect of this immediate intervention at those times.

Neither the immediate (start <24 h, maximum therapy 48 h) use of ACE-inhibitors (N= 77,414), nor beta blockers (N= 68,007) in patients with suspected or definite acute myocardial infarction were associated with statistically significant mortality benefit at 2 days (Chapter 3). In both cases there were insufficient trials to assess the immediate intervention on mortality at 10 days or at ≥30 days. The immediate use of calcium channel blockers (CCB) could not be appropriately assessed in most trials as they did not reported mortality data at any of these times.

In Table 5-1 the mortality benefit of immediate use of nitrates in patients with suspected or definite acute myocardial infarction is compared with the immediate use of fibrinolytics and aspirin in the same clinical setting.
Table 5-1 Effect of immediate drug therapies* on mortality at different times after acute myocardial infarction

<table>
<thead>
<tr>
<th>Drug therapy</th>
<th>Mortality, at 2 days</th>
<th>Mortality, at 10 days</th>
<th>Mortality, at ≥30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates (this review)</td>
<td>6 trials (N=82,624)</td>
<td>10 trials (N=6,007)</td>
<td>7 trials (N=5,771)</td>
</tr>
<tr>
<td></td>
<td>RR= 0.81</td>
<td>RR= 0.84</td>
<td>RR= 0.92</td>
</tr>
<tr>
<td></td>
<td>ARR= 0.43 %</td>
<td>ARR= NS</td>
<td>ARR= NS</td>
</tr>
<tr>
<td></td>
<td>NNT=233</td>
<td>NNT=NS</td>
<td>NNT=NS</td>
</tr>
<tr>
<td>Streptokinase³</td>
<td>1 trial (N=17,187)</td>
<td>1 trial (N=17,187)</td>
<td>1 trial (N=17,187)</td>
</tr>
<tr>
<td></td>
<td>RR= 1.04</td>
<td>RR= 0.82</td>
<td>RR= 0.77</td>
</tr>
<tr>
<td></td>
<td>ARR= NS</td>
<td>ARR= 1.5%</td>
<td>ARR= 2.8 %</td>
</tr>
<tr>
<td></td>
<td>NNH=NS</td>
<td>NNT= 66</td>
<td>NNT= 36</td>
</tr>
<tr>
<td>All Fibrinolytic⁷</td>
<td>9 trials(N=58,600)</td>
<td>9 trials (N=58,600)</td>
<td>9 trials(N=58,600)</td>
</tr>
<tr>
<td></td>
<td>RR= 1.06</td>
<td>RR= 0.91</td>
<td>RR= 0.82</td>
</tr>
<tr>
<td></td>
<td>ARR= NS</td>
<td>ARR= 0.6%</td>
<td>ARR= 1.8 %</td>
</tr>
<tr>
<td></td>
<td>NNH=NS</td>
<td>NNT= 166</td>
<td>NNT= 56</td>
</tr>
<tr>
<td>Aspirin⁸</td>
<td>1 trial (N=17,187)</td>
<td>Not applicable as treatment continued</td>
<td>Not applicable as treatment continued</td>
</tr>
<tr>
<td></td>
<td>RR= 0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARR= NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NNH=NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Only those BP lowering drugs that had shown beneficial effect at any time are displayed in this table.
RR=relative risk, ARR= absolute risk reduction, ARI=absolute risk increase, NNT=number needed to treat, NNH= number needed to harm, NS= not significant

³ According to the ATC 2002³ meta-analysis there are 15 trials (N=19,288) studying antiplatelets for patients with suspected acute myocardial infarction. This table shows the result of largest trial³ (N=17,187)
5.1.1.2 Findings for short-term intervention (start < 24 h, maximum therapy 10 days)

The second research question asked whether there was a mortality advantage of continuing therapy, started in the first 24 hours to 10 days. The 10-day time period was based on the fact that about 75% of deaths following an acute myocardial infarction occur within the first 10 days. It is thus an appropriate period to assess the effect of antihypertensive drugs on mortality.

Nitrates started within 24 hours and used for a maximum of 10 days, were associated with a statistically significant reduction in mortality at 10 days (RR=0.91, 95%CI [0.86,0.97] ARR=0.49%, NNT=204) (Chapter 3; See also table 5.2). However, the absolute mortality benefit at 10 days was almost entirely accounted for by the absolute mortality benefit at 2 days (RR = 0.81, 95%CI [0.74, 0.89], ARR=0.43%, NNT=233), (See Table 5-1and Table 5-2). This suggested that nitrates administered longer than 2 days had little or no effect on mortality. It was fortunately possible to confirm this with an analysis of the effect on mortality for the time period beyond 2 days (See Chapter 3, and Figure 5-1). Nitrates, administered from 3 to 10 days had no effect on mortality (RR=0.98, 95% CI [0.91, 1.06] and nitrates administered from 11 to ~30 days caused a trend toward an increase in mortality (RR=1.10, 95% CI [1.00, 1.22]).
Figure 5-1. Effects of Continuation of Nitrates on Mortality at Different Times.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>1.7.1 mortality up to day 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GISSI-3 1994</td>
<td>196</td>
<td>9663</td>
<td>238</td>
<td>9655</td>
</tr>
<tr>
<td>ISIS-4 1995</td>
<td>514</td>
<td>29018</td>
<td>628</td>
<td>29032</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>38681</td>
<td>38687</td>
<td>100.0%</td>
<td>0.82 [0.74, 0.90]</td>
</tr>
<tr>
<td>Total events</td>
<td>710</td>
<td>866</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.96 (P &lt; 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.7.2 mortality from day 3 to day 10

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>GISSI-3 1994</td>
<td>247</td>
<td>9467</td>
<td>240</td>
<td>9417</td>
</tr>
<tr>
<td>ISIS-4 1995</td>
<td>979</td>
<td>28504</td>
<td>1007</td>
<td>28404</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>37971</td>
<td>37821</td>
<td>100.0%</td>
<td>0.98 [0.91, 1.06]</td>
</tr>
<tr>
<td>Total events</td>
<td>1226</td>
<td>1247</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.53 (P = 0.60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.7.3 mortality from day 11 to 35-42 days

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>GISSI-3 1994</td>
<td>196</td>
<td>9220</td>
<td>195</td>
<td>9177</td>
</tr>
<tr>
<td>ISIS-4 1995</td>
<td>636</td>
<td>27525</td>
<td>555</td>
<td>27397</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>36745</td>
<td>36574</td>
<td>100.0%</td>
<td>1.10 [1.00, 1.22]</td>
</tr>
<tr>
<td>Total events</td>
<td>832</td>
<td>750</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² = 23%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.99 (P = 0.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACE-inhibitors started within 24 hours of the onset of a myocardial infarction and given for a maximum of 10 days were associated with a statistically significant reduction in mortality at 10 days (RR=0.93, 95%CI [0.87,0.98]); representing approximately 4 lives saved per 1000 treated (Chapter 3; See also table 5.2). However, whether this benefit was due to starting therapy within 24 hours or to effect occurring beyond 2 days could not be established, as there was no statistically significant benefit at 2 days. In fact, a mortality analysis of the different time period using trials where the ACE-I was continued for ~30
days revealed a similar effect mortality during all periods: 1-2 days, RR=0.91 (95% CI [0.82, 1.00]); 3-10 days, RR= 0.93 (95% CI [0.86, 1.01]; and 11 to ~30 days, RR= 0.93 (95% CI [0.85, 1.03]).

Beta-adrenergic antagonists and calcium channel blockers started within 24 hours and continued for a maximum of 10 days were both not associated with a statistically significant reduction in mortality at 10 days (RR=0.96, 95% CI [0.91,1.02] and RR=1.01 (95% CI [0.73,1.38]), respectively (Chapter 3).

Beta-adrenergic antagonist (BB), were the only class of drugs that had sufficient data to assess the effect of short-term therapy on mortality at ≥ 30 days. In 5 RCTs, (N=18,373) beta-blockers started within 24 hours and given for 10 days were associated with a statistically significant reduction in mortality during an average of 12 months of follow-up (RR=0.91, 95%CI[0.84,0.99], p=0.03 ). However, as explained in detail in chapter 3 this was a chance finding and publication as well as performance bias were likely present. Therefore, it is inferred that this does not represent a true delayed mortality benefit of beta-blockers administered for 1 to 10 days after an acute myocardial infarction.

Table 5-2 presents the findings of the present systematic reviews as compared to aspirin, which has a proven mortality benefit when started within 24 hours of the symptom onset. These indirect comparisons assume that the patients are similar. This is a reasonable assumption, as they are all studying patients with suspected or definite acute myocardial infarction.
Table 5-2. Effect of Short-term Drug Therapies* on Mortality in Patients with Acute Myocardial Infarction, at Different Times

<table>
<thead>
<tr>
<th>Trial or Meta-analysis of a Drug Therapy</th>
<th>Mortality, At 10 days</th>
<th>Mortality, at ≥ 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates (this review)</td>
<td>6 trials, N= 78,178</td>
<td>RR= 0.91</td>
</tr>
<tr>
<td></td>
<td>ARR= 0.49 %</td>
<td>NNT=204</td>
</tr>
<tr>
<td></td>
<td>3 trials, N=570</td>
<td>RR= 0.72</td>
</tr>
<tr>
<td></td>
<td>ARR= NS</td>
<td>NNT=NS</td>
</tr>
<tr>
<td>ACE-inhibitors (this review)</td>
<td>10 trials, N= 84,311</td>
<td>RR= 0.93</td>
</tr>
<tr>
<td></td>
<td>ARR= 0.37 %</td>
<td>NNT=270</td>
</tr>
<tr>
<td></td>
<td>Not applicable as treatment continued beyond day 10</td>
<td></td>
</tr>
<tr>
<td>Aspirin(^\text{\textsuperscript{1}})^ (^\text{\textsuperscript{2}})</td>
<td>1 trial, N= 17,187</td>
<td>RR= 0.80</td>
</tr>
<tr>
<td></td>
<td>ARR= 1.7%</td>
<td>NNT=60</td>
</tr>
<tr>
<td></td>
<td>Not applicable as treatment continued beyond day 10</td>
<td></td>
</tr>
</tbody>
</table>

* Only those BP lowering drugs that had shown beneficial effect at any time are displayed in this table. RR=relative risk, ARR= absolute risk reduction, ARI=absolute risk increase, NNT=number needed to treat, NNH= number needed to harm, NS= not significant
\(^\text{\textsuperscript{1}}\) According to the ATC 2002\(^\text{\textsuperscript{9}}\) meta-analysis there are 15 trials (N=19,288) studying antiplatelets for patients with suspected acute myocardial infarction. This table shows the result of largest trial\(^\text{\textsuperscript{8}}\) (N=17,187).

5.1.2 Discussion on timing and duration of therapy

The systematic review in Chapter 3 showed that nitrates, started within the first 24 hours of a myocardial infarction and continued for 48 hours, reduced mortality at 2 days, but that continuation of nitrates beyond 2 days resulted in no further mortality benefit (Table 5-1and Table 5-2). The review does not provide any indication as to when the best time is to administer nitrates within the first 24 hours. Fortunately, the largest trial in the meta-analysis (ISIS-4 study)\(^\text{\textsuperscript{10}}\) (N=58,050) provided subgroup data based on when the nitrates were started within the first 24-hour period. In this trial, patients suspected of having a myocardial infarction were randomized to receive 35 days of nitrates or placebo. The
overall effect of nitrates on mortality was not significant at 35 days (RR = 0.97, 95%CI [0.92-1.03]). However, the subgroup of patients who were given nitrates within the first 6 hours of the onset of symptoms (N=23,323) had a significant mortality benefit at 35 days (RR 0.89, 95%CI [0.82-0.98], ARR=0.88%; 9 lives saved per 1000 treated). (See figure 4 of page 675 in the original publication\textsuperscript{10}).

The findings from the ISIS-4 study\textsuperscript{10} suggest that the time-of-initiation of nitrate therapy is critical as it has been shown for thrombolitics\textsuperscript{7}. Unfortunately, the other RCTs in the present meta-analysis do not provide subgroup data according to the hour of onset of therapy. However, based on the ISIS-4 findings, the significant mortality benefit at 2 days reported in chapter 3 (RR=0.81) for patients who started therapy any time in the first 24 hours could be greater for the sub-group of patients starting nitrates within 6 hours.

The ISIS-4 study\textsuperscript{10} (N= 58,050; a factorial trial with 3 independent comparisons) also provided data according to hour of administration of ACE-inhibitor therapy. The overall effect on mortality was statistically significant at 35 days (RR 0.94, 95%CI [0.88-0.99]). However, in contrast to the nitrates, ACE-inhibitors administered within 6 hours of symptoms (N=23,323) had no effect on mortality at 35 days (RR 0.98, 95% CI [0.90-1.07]) suggesting that early treatment with ACE-inhibitors may not be a good idea. The effect of ACE inhibitors was better (RR 0.90, 95% CI [0.84-0.97]) if they were administered later.

In the case of beta-blockers, three small trials (N=840) studied therapy started within 6 hours and continued for up to 48 hours. Sample sizes were too small to assess mortality at 2, 10 or ≥ 30 days. There were 5 trials (N=2,785) that started beta-blockers within 6
hours and continued treatment for more than 3 days and showed no suggestion of a mortality benefit at 10 days (RR 1.15, 95% CI [0.78-1.70]. The timing of administration of calcium channel blockers could not be assessed due to lack of data.

5.1.3 Post-acute phase therapy

Chapter 3 focused on antihypertensive therapy that began within the first 24 hours. It showed that the therapeutic effects of anti-hypertensive drugs in stable clinical settings could not be extrapolated to the effects when these drugs are started in acute settings (eg, within 24 hours of an acute myocardial infarction). This thesis therefore challenges the approach and findings of other systematic reviews that pool anti-hypertensive therapy RCTs, regardless of time of initiation of therapy. Such an approach is simplistic and misses important therapeutic effects that are dependent on the time of initiation of therapy. For example, beta-blockers when started days or weeks after an MI and continued for months are known from other systematic reviews to have a significant mortality benefit\textsuperscript{3,6}. In contrast, this review and a systematic review by another group\textsuperscript{11} show that beta-blockers started within 24 hours and continued for 2 days or up to 10 days following a myocardial infarction does not affect mortality measured at 2 days or at 10 days.

5.2 The focus on all-cause mortality

All-cause mortality was chosen as the primary outcome in the systematic reviews because it is a measure of net health effect. Anti-hypertensive therapy in any setting, but particularly in acute settings, can cause both harm and benefit. Cause of death is often
difficult to ascertain. Thus, RCTs and systematic reviews measuring cardiovascular mortality are subject to inadvertent error and bias.

In the hypertensive emergency review (Chapter 2) mortality data was sparse with only 6 deaths reported in 15 trials (N=869). These trials had a short duration of follow-up (6-24 hours), but despite that the small number of deaths is strikingly low for patients with a hypertensive emergency who have a high risk of death during the first hours or days. It is likely that complete mortality data was not reported in these RCTs. Despite the lack of outcome data in the emergency review it accurately reflects the best available evidence and has been commended by others as an important basis for future research in this clinical setting\textsuperscript{12}.

In contrast, the second systematic review (Chapter 3) of acute cardiovascular events was large enough and included ample mortality data to make strong conclusions. The overall mortality rate in the placebo or control group vs. anti-hypertensive therapy group was 2 % (1525 / 75,449) and 1.8% (1362 / 75,463), respectively, at 2 days; and 5.6% (4602 / 82,766) and 5.2 % (4330 / 83,015), respectively, at 10 days.

The importance of using all-cause mortality as an outcome is shown by a recent systematic review that claims that beta-blockers given post MI decrease coronary heart disease (CHD) events, RR 0.69 (95% CI 0.62-0.76)\textsuperscript{13}. This certainly conveys a different message from our review, which showed no reduction in mortality with beta-blockers.

When the two reviews are compared it is clear that the differences in the results are explained by different methodology (including trials that start beta-blockers treatment days or weeks after the onset) as well as different outcomes (measuring CHD events and excluding “mortality in the period immediately after infarction”). However, we feel
confident that the outcome we have chosen has the lowest risk of bias (reporting, documenting, censoring), and is a measure of the net health effect (benefit minus harm). In fact, all-caused mortality is considered the optimal outcome to be measured in hospitalized critically ill patients where it is very difficult to identify and record all serious adverse events (total mortality and serious morbidity)\textsuperscript{14}.

This thesis shows the importance of determining all cause, as opposed to cardiovascular mortality or morbidity, when assessing the impact of drug therapy. This research also shows the importance of including all-cause mortality rates for the entire clinical period, particularly stressing inclusion of the first 24 hours. If data was not provided by the original publications this data was actively sought from the authors.

5.3 Hypertensive thresholds and anti-hypertensive therapy

In the first systematic review, the hypertensive emergency review required that all patients had a blood pressure that exceeded specific limits of blood pressure. The second review, acute cardiovascular events review, had no limitation in terms of BP.

In the first review that required patients to have a high blood pressure threshold for entry, only two placebo controlled trials (N=144 patients) met the inclusion criteria, while in the second review 65 placebo or no treatment controlled trials (N=166,206 patients) met the inclusion criteria. The first review had no mortality data versus placebo. As a result, most of the findings and conclusions derive from the second, larger review.
5.4 Do the findings of these systematic reviews support the currently approved indications for antihypertensive drugs in these acute settings?

In the following subsections the approved indications for different anti-hypertensive drugs, by Health Canada or by the U.S. Food & Drug Administration (FDA), for the acute cardiovascular events are compared with the findings of the present systematic reviews of randomized controlled trials in which all-cause mortality was used to assess the net health effect. Following this comparison, I present how I would personally use the antihypertensive drugs in the acute cardiovascular settings based on the evidence.

5.4.1 Nitrates (including nitroprusside)

Approved Indications:

Nitroglycerine is indicated for selected patients with **acute coronary syndromes**.

Nitroprusside is indicated for **hypertensive emergencies**.

The time that these drugs should be started is not specified for these indications.

Findings from the systematic reviews:

In the hypertensive emergencies review, nitrates (including nitroprusside) were the most studied class of drugs (9 out of 15 trials). However, there was no useful information with regard the effect of these drugs on mortality for nitrates or for any of the other classes of drugs. The differences in systolic and diastolic blood pressure reduction between these drugs and the active comparators were minor and are not considered to be clinically significant.

In the acute cardiovascular event review, nitrates were studied in 18 trials (N= 84,413) out of 65 included trials (N=166,206). Nitroprusside was studied in only 2 (N=1,140). All of these trials studied patients with acute myocardial infarction.
The overall effect of nitrates (including nitroprusside) administrated within 24 hours of the symptom onset was a significant mortality reduction at 2 days (RR 0.81, 95%CI [0.74-0.89]); 4 to 8 deaths prevented per 1000 patients treated. Nitrates were also associated with a statistically significant reduction in mortality when administered daily for 10 days (RR 0.91, 95%CI [0.86-0.97]). However, this benefit was entirely accounted for by the reduction in mortality at 2 days. No benefit was seen for nitrates administered from day 3 to 10.

When the effects of the different nitrates on mortality at 2 days were analyzed separately nitroprusside reduced mortality but not statistically significantly (RR 0.70, 95%CI [0.33-1.47]). Nitroglycerine significantly reduced mortality at 2 days (RR 0.82, 95%CI [0.68-0.99]). Oral isosorbide-5-mononitrate also significantly reduced mortality at 2 days (RR 0.82, 95%CI [0.73-0.92]). There is nothing to suggest that the effect is different for different nitrates.

**Conclusions:**

I would administer nitrates routinely and as soon as possible within the first 24 hours of a suspected or definite myocardial infarction (as per inclusion criteria of the trials involved) because they decrease mortality at day 2. Because of lack of effect on mortality when administered after day 2, I would not be continued nitrate therapy beyond day 2 unless there was a specific indication e.g., angina pectoris. Since the data is most robust for isosorbide mononitrate and it has the advantage of being administered orally, I would use isosorbide mononitrate in this setting. This approach represents a deviation from the current guidelines.
5.4.2 Angiotensin converting enzyme inhibitors (ACE-I)

Approved Indications:
Lisinopril is indicated for administration within 24 hours of acute myocardial infarction. Captopril is also indicated for post-myocardial infarction, but the time of starting is not specified.

Findings from the systematic reviews:
In patients with an acute myocardial infarction, ACE-inhibitors administrated within 24 hours of symptom onset were not associated with statistically significant reduction in mortality at 2 days (N=77,414; RR 0.91, 95%CI [0.82-1.0], but when these drugs were continued for 10 days there was a significant reduction in mortality (N=84,311; RR 0.93, 95%CI [0.87-0.98]) at day 10 (3 to 5 deaths prevented for 1000 treated).

When the different ACE-I drugs were analyzed individually captopril (6 trials, N=58,635) showed a significant reduction in mortality at 10 days (RR 0.92, 95%CI [0.86-0.99], but lisinopril (1 trial, N=19,318) did not (RR 0.90, 95%CI [0.79-1.02]. However, these results do not provide any suggestion of a different effect of these two ACE-I drugs in this setting.

Conclusion:
I would administer an ACE-inhibitor routinely to patients with suspected or definite myocardial infarction starting the day after admission and continue the drug daily after that. The optimal time of starting an ACE-inhibitor is unknown but the evidence suggests that in contrast to nitrates early administration is not beneficial.
5.4.3 Angiotensin II receptor blockers (ARBs)

Approved Indications:

Valsartan is indicated for patients within 12 hours of an acute myocardial infarction in clinically stable patients with signs or symptoms of left ventricular dysfunction. The other ARBs do not have this indication.

Findings from the systematic reviews:

No trial assessed the effect of any ARB versus placebo within 24 hours of an acute myocardial infarction or any other acute cardiovascular setting.

5.4.4 Beta-adrenergic receptor blockers (BBs)

Approved Indications:

Labetalol is the only BB indicated for hypertensive emergencies, whereas metoprolol is the only BB indicated for acute myocardial infarction. The time of administration of metoprolol is “as soon as possible”.

Findings from the systematic reviews: for labetalol

In the hypertensive emergencies systematic review there was no trial included that studied a beta-adrenergic blocker.

Conclusion:

The indication of labetalol for hypertensive emergencies is not supported by RCT evidence.

Findings for metoprolol:

The present systematic review shows that beta-blockers administrated to 72,600 patients within 24 hours of the onset of an acute myocardial infarction, and continued for 10 days,
do not reduce mortality at 2 days (RR 0.95, 95%CI [0.85-1.07]) or 10 days (RR 0.96, 95%CI [0.91-1.02]).

Limiting the analysis to the 5 trials\textsuperscript{15-19} (N=53,915) that studied metoprolol vs. placebo or no treatment in patients with acute myocardial infarction similarly showed no reduction in mortality at 2 days (RR 1.05, 95%CI [0.92-1.20] or at 10 days (RR 0.99, 95%CI [0.93-1.06]).

Conclusion:
I would not routinely administer metoprolol or any beta-blocking agent within 24 hours of the onset of an AMI and would only use a beta-blocker when there was a specific indication.

5.4.5 Calcium channel blockers (CCBs)

Approved Indications:
No CCB is officially indicated for a hypertensive emergency or an acute cardiovascular event.

Findings in the systematic reviews:
Although many large trials have been conducted assessing the use of CCB after acute myocardial infarction, there is very little mortality data because it was not reported in the majority of trials.

Conclusions:
I would not routinely administer a CCB within 24 hours of any acute cardiovascular event.
5.4.6 Diuretics

Approved Indications:
Furosemide and Ethacrynic acid are indicated for the treatment of acute pulmonary edema.

Findings in the systematic reviews:
In the hypertensive emergency review there were three included trials that involve diuretics\textsuperscript{20-22}. The three trials compared furosemide vs. nitrates. No mortality data was reported for any of these trials. There were no differences in systolic or diastolic blood pressure reduction between the two classes. No trial was found involving ethacrynic acid.

Conclusions
Despite the lack of RCT evidence, I would administer furosemide as part of the early overall management of patients with acute pulmonary edema.

5.5 Study bias and limitations of systematic reviews

5.5.1 Recruitment bias
Both systematic reviews excluded trials that had selected their patients on the basis of previous responsiveness to an anti-hypertensive drug. This type of exclusion was to avoid recruitment bias which can jeopardize the external validity of the trial’s results as the findings from these types of trials cannot be extrapolated to a broader population such as those with life-threatening conditions, e.g., hypertensive emergencies or acute cardiovascular events. There was one trial with this type of recruitment bias, Annane et al 1996\textsuperscript{23}, which was excluded from the hypertensive emergency review.
5.5.2 Randomization, concealment of allocation and blinding

Both reviews excluded trials with pseudo or quasi randomization (i.e., allocation of patients according to the date of birth or admission). In addition, since many trials did not provide sufficient details about how allocation concealment was achieved, trials were downgraded in their quality according to a Cochrane Collaboration risk of bias table (See Chapter 2 and 3 for details).

Blinding of treatment allocation was not required for study inclusion in these systematic reviews because the outcome all-cause mortality has the least risk of detection bias\textsuperscript{14}. However, in the larger systematic review of antihypertensive drugs on acute cardiovascular events without blood pressure thresholds (Chapter 3), there was a trend towards greater mortality benefit in open-label (OL) trials as compared to double-blind (DB) trials for nitrates, ACE-inhibitors and CCBs, but a significant difference for beta blockers.

- Nitrates OL RR \textbf{0.86} [0.76, 0.97] vs. DB RR \textbf{0.92} [0.86, 0.98]
- ACE inhibitors OL RR \textbf{0.89} [0.79,1.01] vs. DB RR \textbf{0.94} [0.88,1.0]
- CCB OL RR \textbf{0.47} [0.07, 3.02] vs. DB RR \textbf{1.76} [0.99, 3.14]
- BB OL RR \textbf{0.73} [0.58,0.91] vs. DB RR \textbf{1.04} [0.91,1.19]

For the beta-blockers, the confidence intervals do not overlap for the open-label (N=16,193) vs. double-blind (N=51,814) trials. This finding is discussed in detail in Chapter 3. The potential cause of these differences between open-label and double-blind trials is performance bias (See below section), which even hard outcomes, such as all-cause mortality, are subject to. Therefore, conclusions were based on the more conservative and methodologically stronger double-blind RCT evidence.
5.5.3 **Performance bias**

Although proper randomization would theoretically balance the co-variants that might influence the effect size, there are particular open-label trials where, in addition to the study interventions, co-interventions were administrated to significantly more patients in the experimental groups as compared to the control groups (or vice versa). This has the potential to lead to performance bias. The two open-label trials comparing a beta-blocker to control (ISIS-1 trial\textsuperscript{24} and Yusuf et al 1983 trial\textsuperscript{25}) were the only trials showing statistically significant benefit in mortality at 10 days post MI (RR 0.86, 95%CI[0.74,0.99] and RR 0.42, 95%CI[0.18, 0.99], respectively). These trials were also the only ones showing statistically significant difference in their co-interventions: i.e., significantly more patients in the control group received co-intervention with calcium channel blockers drugs (RR 1.89, 95%CI [1.74, 2.06]; and RR 2.56, 95%CI [1.20, 5.44], respectively). If calcium channel blockers tend to increase mortality this would bias the results toward a mortality benefit with beta-blockers as shown above.

5.5.4 **Funding bias**

The exact role of a drug manufacturer who is sponsoring a trial is usually unknown. One possible influence is through developing favorable stopping rules that might over estimate the effect size in favor of their drug\textsuperscript{26}. One example from Chapter 3 is for the comparison nitrates vs. placebo, in which the only trial that used an early stopping rule\textsuperscript{27} turned out to be an outlier in terms of effect size for this comparison (Figure 5-2).
Figure 5-2. Funnel plot of all-cause mortality at 10 days for the comparison nitrates vs. control

Outlier

Subgroups
- Immediate treatment
- Short-term treatment
5.6 Conducting an RCT as an additional tool for completing systematic reviews

The RCT reported in Chapter 4 provided an original contribution to knowledge but also an important opportunity for me to learn the inherent biases and problems associated with conducting a clinical trial. By designing, conducting, analyzing and reporting this study I learned a substantial amount about the strengths and potential bias in clinical trials. The experience considerably improved my ability to critically appraise RCTs, arguably the most important and often least emphasized task in performing a systematic review. The RCT is included in my thesis as it was a valuable learning tool for me, while I worked on both systematic reviews. My intention was to participate in a trial where I had the opportunity of experiencing all phases of a randomized control trial (i.e., from its design to its publication) in order to improve my skills as a systematic reviewer and to provide the experience I wanted to conduct RCTs in the future.

The problems that I encountered that I particularly learned from were difficulties with recruitment, losses to follow-up, the practicalities of blood pressure measurement as an outcome and reporting as well as recording serious adverse events. Recruitment in the clinical trial was particularly problematic, as is exemplified in the Quorum diagram of publication in Chapter 4. We had to screen a much larger number of patients to find patients who met all the inclusion criteria than we had anticipated. The problem in recruiting patients also led to a fairly select group of patients, which could potentially have an impact on the external validity of the findings. The recruitment in that trial taught me that many of the patients wanting to volunteer were interested in a
psychological intervention. Thus, the results of this trial are most relevant to patients who want to control their blood pressure with psychotherapy. Conducting this trial gave me an appreciation of the difficulties in recruitment of patients that is present in most trials being considered in a systematic review. In fact, in this clinical trial, because of the difficulty recruiting patients we did not achieve the planned sample size. In Chapter 4, this limitation of the study was discussed and the fact that because of the small sample size there was insufficient power (60% probability) to detect a difference in resting blood pressure. Fortunately, it did not prevent the study from being published as the trial will provide valuable information when it is pooled with other trials in systematic reviews in the future.

In addition, despite the relatively short duration of the clinical trial (3 months) and our attempts to maintain as complete a follow-up as possible, we lost 32 % of the patients for the primary outcome. This further decreased our power to detect a significant difference in at least one comparison for 24-hour ambulatory blood pressure measurements. However, the magnitude of the differences in the 24-hour blood pressure data was large enough that we were able to obtain a statistically significant greater blood pressure lowering effect with hydrochlorothiazide than with either of the psychological interventions. I did however learn that in most clinical trials loss of some patients to follow-up is inevitable helping me to appreciate why follow-up was often incomplete in the trials that I critically appraised. Fortunately, performing a systematic review and meta-analysis can compensate for the loss of power of individual trials by pooling the results. Indeed, the results of the present clinical trial was consistent with the conclusions
of the Cochrane systematic review of psychological interventions\textsuperscript{28} and with meta-
analyses of the magnitude of blood pressure lowering effect of low doses of thiazides\textsuperscript{29}.
While conducting the clinical trial I gained experience in dealing with serious adverse events. We were required to report all serious adverse events to the University of British Columbia’s Clinical Ethics Committee. Accurate recording and reporting of all serious adverse events in trials is essential. One patient in the trial experienced a transient severe headache that was thought by the patient to be related to the trial. This case was reported to the Ethics Committee who did not consider this event a serious adverse event in accordance to the international definition of serious adverse events (SAE): any untoward medical occurrence that results in death is life-threatening, requires hospitalization or prolongation of hospitalization, or results in persistent or significant disability\textsuperscript{30}. None of the patients experienced a serious adverse event during the trial.
Participating in the trial taught me the importance of concealment of allocation. While recruiting patients I encountered a patient who met all inclusion/exclusion criteria but had characteristics (previously treated with anti-hypertensive drugs and with relatively high levels of BP after the wash-out period) that caused me to wish that the patient would be randomized to drug therapy. Despite my bias, the randomization procedure prevented me from having any control over the allocation: the patient was allocated to the individualized psychotherapy group and completed the trial without any problems. I thereby learned that all investigators are subject to bias and why it is so important to ensure adequate concealment of allocation to prevent that bias in all RCTs.
The exposure to all the different components, facets and phases involved in conducting analyzing, interpreting and publishing a randomized clinical trial while performing two
systematic reviews of RCTs has provided me with the knowledge and confidence to
design, get funding for, conduct and report on a large high quality RCT in the future.

5.7 What are overall conclusions of this thesis?

5.7.1 Clinical implications

Nitrates (including nitroprusside) are the best therapeutic option to consider for initial
treatment of hypertensive emergencies (marked elevation of blood pressure associated
with acute end-organ damage) as they have been studied in most RCTs and showed a
similar blood pressure lowering effect and safety profile as other anti-hypertensive drug
classes.

For acute myocardial infarction, nitrates administered within 24 hours reduce all-cause
mortality at 2 days, RR 0.81, ARR 0.4%. Because of this, nitrates should be routinely
administered as early as possible within 24 hours and continued for 2 days to patients
with suspected or definite MI. Controlled-release oral isosorbide-5-mononitrate 30 mg
started within 6 hours and given twice a day the first day and 60 mg the second day is a
reasonable approach as it was used in the largest trial providing the evidence for this
recommendation.

ACE inhibitors, started within 24 hours of onset of a suspected or definite MI failed to
reduce all-cause mortality at 2 days but when continued for 10 days reduced mortality at
10 days. The optimal time of starting ACE-inhibitor therapy is unknown but early
administration did not appear beneficial.
Beta-blockers and calcium channel blockers should not be routinely prescribed within 24 hours of the onset of acute myocardial infarction.

5.7.2 Research implications

Future trials of antihypertensive drugs for myocardial infarction patients should randomize patients to different treatment strategies (both timing and duration) and report all-cause mortality at standard times, 2 days, 10 days, 30 days and 6 months. For nitrates, RCTs could be conducted to answer whether the benefit is achieved with the first dose of nitrate (started within 6 hours) or whether 2 days of administration are necessary. Secondary data analysis of individuals involved in ACE inhibitors trials could be used to answer whether these drugs have a timing or duration dependent mortality effect. It is particularly important to determine in post-MI patients whether the benefit is present in those without left-ventricular dysfunction. It is essential that mortality data should be made available from all existing RCTs involving calcium channel blockers in acute cardiovascular events. RCTs are needed in other acute cardiovascular events including stroke, acute aortic dissection acute pulmonary edema, unstable angina, intracranial or sub-arachnoid hemorrhage that examine the effect on mortality and permit assessment of optimal timing of onset and optimal duration of therapy of all classes of antihypertensive drugs.

5.7.3 Findings of the randomized controlled trial comparing HCTZ to two psychological interventions:

Hydrochlorothiazide (HCTZ) significantly reduced both systolic and diastolic 24-hour ambulatory blood pressure relative to baseline (mean reduction -11 / -6.1 mm Hg,
respectively) and this reduction was significantly greater than either individualized behavioral psychotherapy or self-help psychotherapy. Neither psychological therapy statistically significantly lowered 24-hour ambulatory blood pressure relative to baseline.

5.7.4 Clinical implications of the randomized controlled trial:

Low dose thiazides have a predictable blood pressure lowering effect that is greater than psychological interventions, which have not been proven to lower blood pressure or reduce adverse cardiovascular events in patients with primary hypertension.
5.8 References


(2) AMICG. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. Circulation 1998; 97(22):2202-2212.


APPENDIX I: UBC RESEARCH ETHICS BOARD

CERTIFICATE OF APPROVAL

The University of British Columbia
Office of Research Services,
Clinical Research Ethics Board – Room 210, 621 West 11th Avenue, Vancouver, BC V6Z 1L8

Certificate of Expedited Approval: Renewal
Clinical Research Ethics Board Official Notification

[Details redacted for privacy]

Linden, W.

UBC Campus

Perez, Marco, Medicine; Perry, Tom, Medicine; Wright, James, Pharmacology/Therapeutics

Canadian Institutes of Health Research

APPROVAL RECALLED

31 October 2005

[Details redacted for privacy]

In support of clinical trials:
1. The membership of the Research Ethics Board conformed with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board operates in accordance with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the trial of the Research Ethics Board have been documented in writing.

The Chair of the UBC Clinical Research Ethics Board has reviewed the documentation for the above named project. The research study, as presented in this documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved for renewal by the UBC Clinical Research Ethics Board.

The CREB approval for renewal of this study expires one year from the date of renewal.

Approval of the Clinical Research Ethics Board by one of:
Dr. Gail Bolward, Chair
Dr. James McConnell, Associate Chair

[Signature]
APPENDIX II: SEARCH STRATEGY, CHAPTER 2

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62 angiotensin converting enzyme inhibitor.mp.
or Angiotensin-Converting Enzyme Inhibitors/ 63 acebutolol.mp.
64 atenolol.mp.
65 Bisoprolol.mp.
66 esmolol.mp.
67 labetalol.mp.
68 metoprolol.mp.
69 nadolol.mp.
70 practolol.mp.
71 propranolol.mp.
72 sotalol.mp.
73 timolol.mp.
74 carvedilol.mp.
75 Adrenergic-beta-Antagonists.mp.
76 Amlodipine.mp.
77 Aranidipine.mp.
78 Azelnidipine.mp.
79 Barnidipine.mp.
80 Bencyclane.mp.
81 Benidipine.mp.
82 Bepridil.mp.
83 Cilnidipine.mp.
84 Cinnarizine.mp.
85 Clentiazem.mp.
86 Darodipine.mp.
87 Diltiazem.mp.
88 Efonidipine.mp.
89 Elgodipine.mp.
90 Etadefine.mp.
91 Fantofarone.mp.
92 Felodipine.mp.
93 Fendiline.mp.
94 Flunarizine.mp.
95 Gallopamil.mp.
96 Isradipine.mp.
97 Lacidipine.mp.
98 Lercanidipine.mp.
99 Lidoflazine.mp.
100 Lomerizine.mp.
101Manidipine.mp.
102Mibebradil.mp.
103Nicardipine.mp.
104Nifedipine.mp.
105Niguldipine.mp.
106Nilvadipine.mp.
107Nimodipine.mp.
108Nisoldipine.mp.
109Nitrendipine.mp.
110Perhexiline.mp.
111Prenylamine.mp.
112Semotiadil.mp.
113Terodiline.mp.
114Tiapamil.mp.
115Verapamil.mp.
116Calcium channel blocker.mp. or Calcium Channel Blockers/
117Nitroprusside.mp.
118Nitroglycerine.mp.
119Nitroglycerin/ or nitroglycerine.mp. or Isosorbide Dinitrate/
120Nitrates.mp. or Nitrates/
121Urapidil.mp.
122Trimethaphan/ or trimethaphan camysylate.mp.
123Reserpine.mp.
124Phentolamine.mp.
125Methyldopa.mp.
126Labetalol.mp.
127Ketanserine.mp.
128Hydralazine.mp.
129Guanethidine.mp.
130Fenoldopam.mp. or FENOLDOPAM/
131Diazoxide.mp.
132Clonidine.mp.
133Thiazide$.mp.
134Hydrochlorothiazide.mp.
135Chlorthalidone.mp. or Chlorthalidone/
136Furosemide.mp. or Furosemide/
137Or/41-136
13840 and 137
139Myocardial infarction.mp.
140Unstable angina.mp.
141Acute left ventricular failure.mp.
142Pulmonary Edema/ or pulmonary oedema.mp.
143Stroke.mp.
144Life-threatening bleeding.mp.
145Aneurysm, Dissecting/ or aortic dissection.mp.
146Intracranial Hemorrhages/ or Cerebral Hemorrhage/ or intracranial haemorrhage.mp.
147Intracranial Aneurysm/ or Subarachnoid Hemorrhage/ or subarachnoid haemorrhage.mp.
APPENDIX III: CHARACTERISTICS OF INCLUDED STUDIES, CHAPTER 2

Angeli 1999

Methods

Single-site study (Italy).
Single-blind
Method of randomization: reported as 1 to 1. No further details
Concealment of allocation: NR
Duration of treatment: single dose
Follow-up: 24 hrs

Participants

22 patients with high blood pressure associated with symptoms and signs of end organ damage
Note: There were two dropouts; one in each group
* Inclusion criteria:
Diastolic blood pressure of 140 mm Hg or greater after 20 minutes of bed rest associated with symptoms and signs of end-organ damage (angina, transient ischemic attack, hypertensive encephalopathy, and acute heart failure-based on gallop rhythm, tachypnea, orthopnea and fine basal rales)
* Exclusion criteria:
An overt pulmonary edema, valvular heart disease, serious disturbance of consciousness and history of myocardial infarction or stroke.
* Baseline characteristics for the two randomized groups:
Nifedipine (N): n=10
Captopril (C): n=10
Unless otherwise indicated, values are expressed as mean ± SD
age (years)
C: 61±12
N: 53 ± 12
Race: NR
BP: (mm Hg)
C:245/145
N:247/158
Patients previously receiving antihypertensive C:7/10 N:7/10
Secondary hypertension C:1/10 N:4/10
Diabetes C:1/10 N:0/10
Interventions

Nifedipine (N): n=10
Captopril (C): n=10
Dose regimen:
C: Single sublingual tablet of 25 mg under the patients' tongue and swallowed the saliva.
N: Single sublingual perforated capsule of 10 mg under the patients' tongue and swallowed the saliva.

Outcomes

Obtained from this trial for the two randomized groups:
Nifedipine (N): n=10
Captopril (C): n=10
Total SAE: NR
Mortality: nil during 24 hours of follow-up.
Total Non fatal CVE: NR
Withdrawals: N/A as is a single dose regimen
BP: reported as magnitude of lowering effect during the first 60 minutes (text on page 680 last paragraph):
Captopril= SBP-55 ± 24; DBP -29 ± 10
Nifedipine= -44 ± 20; DBP -39 ± 11
SD of change was reported on text, page 680, last paragraph.
Note: there is also report of BP ± SE over 60 minutes in graph (we did not use this graph for entering BP into Revman)
Heart rate:
Captopril= -5.25±15
Nifedipine= 1.17±14
Note: We used HR data reported in a graph, p.681.

Notes

Author successfully contacted.
Funding: Ministero dell Universita e della Ricerca Scientifica e tecnologica, progetto nazionale "Fisiopatologia del circolo"

Beltrame 1998¹⁰

Methods

Single-site study (Australia).
Open-label
Method of randomization: NR
Concealment of allocation : NR
Follow-up: until discharge from hospital
Duration of treatment 24 hours

Participants
69 patients with elevated blood pressure and cardiogenic pulmonary edema (within 6 hours of onset)

* Inclusion criteria:
Acute onset of dyspnea within the preceding 6 hours, clinical findings consistent with pulmonary edema (increased respiratory work, gallop rhythm, widespread crepitations in the absence of chest infection or aspiration); radiological evidence of pulmonary edema

* Exclusion criteria:
Non cardiogenic pulmonary edema, cardiogenic shock (SBP < 90). An overt AMI, valvular heart disease, obstructive airways disease, requiring immediate intubation, or cardioversion, or known in chronic renal failure

* Baseline characteristics for the two randomized groups
Furosemide/ morphine (F) (n=32)
Nitroglycerin/ N-acetylcysteine (N) (n=37)

Note: Screened 87, (18 excluded - 10 AMI, 3 chronic renal failure, 4 required immediate intubation, 1 unable to provide consent)
Of 69 randomized, 4 were subsequently shown not to have acute pulmonary edema, all were included ITT analysis

Unless otherwise indicated, values are expressed as mean ± SD

age (years)
F: 77 ± 6.6
N: 76 ± 9
Race: NR
SBP: (mm Hg)
F: 164 ± 34
N: 161 ± 32
HR (bpm)
F: 111 ± 21
N: 115 ± 21

Patients previously receiving antihypertensive
F: nitrates 11(34%), diuretics 18(56%), CCB 9(28%), BB 4(13%), digoxin 10(31%), ACEi 10(31%)
N: nitrates 12(32%), diuretics 21(57%), CCB 8(22%), BB 3(8%), digoxin 3(8%), ACEi 11(30%)

Past history
F: ischemic heart disease 11(34%), Chronic heart failure 17(53%),
Interventions

Furosemide/ morphine (F), (n=32)
Nitroglycerin/ N-acetylcysteine (N), (n=37)
Dose regimen:
F: iv furosemide bolus 40 mg, second dose at 60 min, 3 and 24 hours. Morphine 1-2 mg/5 min) to a maximum dose of 10 mg (median dose received 80mg of furosemide, and 3 mg of morphine).
N: intravenous nitroglycerin 2.5 mcg/min,( to max 10 mcg/min) at the same time patients receive N-acetylcysteine at 6.6 mcg/min over 24 hours (median dose received 2.5 mcg /min during first hour)
Assessment were performed at 30, 60, 3 hours, and 24 hours.
Cointerventions: On arrival, patients were given 50 % oxygen

Outcomes

Obtained from this trial for the two randomized groups:

Furosemide/ morphine (F) (n=32)
Nitroglycerin/ N-acetylcysteine (N) (n=37)
Total SAE: NR
Mortality: 3 patients died, but they were not reported according to group of allocation. Neither are reported the causes of death
Total Non-fatal CVE: NR
AMI:
Furosemide=4 /32
Nitroglycerin=6/37
Withdrawals due to adverse events: NR
Blood Pressure: obtained from a table, p275, over 24 hours
Calculated weighted mean BP change
Furosemide: SBP -21± 23; DBP -13.25±15
Nitroglycerin: SBP-23.75±22; DBP -16.25 ±19
Standard Deviation of change was not reported but Imputed from end point
Heart Rate: also obtained from table:
Calculated weighted mean HR change
Furosemide: -13.25± 15
Nitroglycerin -16.25±19
Standard Deviation of change was not reported but Imputed from end point

Notes
Funding: National Health and Medical Research Council of Australia

Mcnaire (DANISH II) 1986

Methods
Multi-centre study (Denmark).
Method of allocation / randomization: closed envelopes numbered consecutively, and statistical tables of randomized numbers were used.
Duration of treatment: 4 h
Follow-up: 24 hrs

Participants
52 patients with hypertensive encephalopathy
* Inclusion criteria:
Patients with diastolic blood pressure of 135 mm Hg or greater associated with cerebral symptoms (headache, consciousness disturbances, paresis, paresthesia, dizziness, blurred vision, nausea and vomits).
The distribution of patients with those symptoms was not reported according to randomized group
* Exclusion criteria:
Aged over 70 years, cerebral apoplexy with hemiparesis, subarachnoidal haemorrhage, ischemic heart disease, pulmonary oedema, uremia, creatinine > 500mcmol/l, pregnancy)
* Base-line characteristics for the two randomized groups:
Diazoxide (D) group: n= 28
Dihydralazine (H) group: n=24
Mean age in years (range)
D: 54 (33-69)
H: 52 (27-69)
Gender F/M
D: 6/22
H: 10/14
Hx of HTN
D: 14/28 (50%)
H: 9/24 (38%)
Note: Twelve out of 64 patients achieved DBP levels of <125
mmHg within one hour after 40 mg of IV furosemide. These patients were not randomized but followed. We did not include these patients in our review. As such: 64-12= 52

**Interventions**

Diazoxide (D): n=28
Dihydralazine (H): n=24

Dose regimen:
Diazoxide (D): two subgroups: A-initial dose 75 mg IV then 150 mg IV every 15 min to reach DBP 110 mm Hg or max dose of 600 mg (12 patients). B- initial dose 75 mg then 75 mg every 30 min to reach DBP 110 mm Hg or max dose of 375 mg (16 patients)
Dihydralazine (H): initial dose 6.25 mg I.M., then 12.5 mg I.M., every 30 min to reach DBP 110 mm Hg or max dose of 56.3 mg (24 patients)

**Outcomes**

Outcomes obtained from this trial for the two randomized groups:

Diazoxide (D): n=28
Dihydralazine (H): n=24
Total SAE: NR

Mortality
Two deaths: However, the group to which the dead patients were originally allocated was not reported. One died from stroke at day 12, the other died from rupture of aortic aneurism at day 10.

Total Non-fatal CVE:NR

Individual CVE:
AMI: Diazoxide =1/28 Hydralazine=1 /24

Withdrawals due to adverse events: NR

Blood pressure:
Except for the end point SBP/DBP values given in text (page 15 & 18; for dihydralazine, diazoxide groups, respectively), data was obtained from graphs, fig2, reported in page 18. The calculated weighted mean BP change was:
Diazoxide: SBP -29.63± NR; DBP -21.63±NR
Dihydralazine: SBP -43.40±NR; DBP -36.09±NR

Standard deviation of the change was not reported. In this case we imputed (according to our hierarchy) from other trials (any drug any dose) as there was no report whatsoever regarding SBP or DBP variability in this trial (including all publications).
However, on page 19 fig-3 there is a plot for MAP change according to groups. The calculated MAP variability (SD) for diazoxide group 19.46, and 22.25 for the dihydralazine group.

Heart rate:
There is no report on heart rate in the original or duplicate publications

Notes
Funding: Not reported

Elliott 1990

Methods
Single-site study (US).

Open Label
Method of randomization: not reported,
Concealment of allocation: not reported
Duration of treatment: 1 hour
Follow-up: 10 days.

Participants
28 patients with high blood pressure and acute end organ damage
* Inclusion criteria:
  All patients had supine diastolic blood pressure > 120 mm Hg in association with acute end organ damage. (decrease in creatinine, cardiomegaly, left ventricular hypertrophy on ECG, > grade II fundoscopic abnormality.
  * Exclusion criteria:
  congestive heart failure
  * Baseline characteristics for the two randomized groups:
    Nitroprusside (N): n= 15
    Fenoldopam (F): n = 13
    Unless otherwise indicated, values are expressed as mean ± SD age (years)
    N:42 ± 8
    F: 51 ± 5
    Race: black N:14/15 F:12/13,
    BP: (mm Hg)
    N:222/137
    F:214/136
    Presence previous of accelerated/ malignant HTN
    N:11/15 F:11/13

Interventions
Nitroprusside (N): n= 15
Fenoldopam (F): n = 13
Dose regimen:
IV Fenoldopam (dopamine1 receptor agonist) * Initial dose 0.1 mcg/kg/min and then increments of 0.05 -0.1 mcg/kg/min every 20 minutes to DBP 100-110 mm Hg and stable for 1 hour. Then an oral treatment (atenolol 100 mg and Furosemide 20 mg) was added. The IV drug was then taper down until stopping it.
IV Nitroprusside Initial dose 0.5 mcg/kg/min and then increments of 0.25 -0.5 mcg/kg/min every 20 minutes to DBP 100-110 mm Hg and stable for 1 hour. Then an oral treatment (atenolol 100 mg and Furosemide 20 mg) was added. The IV drug was then taper down until stopping it.

Outcomes

Obtained from this trial for the two randomized groups:

Nitroprusside (N): n= 15
Fenoldopam (F): n = 13
Total SAE: NR
Mortality: NR
Total non-fatal CVE: NR
Any CVE: NR
Withdrawals due to adverse events: NR
Blood Pressure: obtained from text, p.972, during treatment.
Calculated weighted mean BP change:
Fenoldopam: SBP-34±18, DBP -30 ± 14
Nitroprusside: SBP-48±19, DBP -32±12
Standard deviation of change was not reported but imputed from end point
Heart rate: obtained from text, p.972, during treatment.
Calculated weighted mean HR change:
Fenoldopam: 4 ± 19
Nitroprusside: 6±11
Standard deviation of change was not reported but imputed from end point

Notes

Funding: Not reported
Although it said that creatinine would be monitored for 48-72 hours and BP and clinical assessment would be done at day 7 to 10, no BP or clinical data was reported for 48-72 hrs or day 7-10.
Methods

Single-site study (US).

Double-blind placebo-controlled trial
Method of Randomization: NR
Method of Concealment of allocation: The investigators were given a numbered data collection instrument with a pre-packaged set of four unmarked capsules that had previously been randomized.
Duration of treatment: single dose (re-administered at minute 60)
Follow-up: 2 h

Participants

48 patients with high blood pressure* and acute pulmonary edema
* Based on values at baseline
Note: of the 110 patients screen for ape 57 were enrolled; 3 patients were disqualified because they were intubated upon arrival. Five patients were eliminated due to incomplete data collection. One was mistakenly enrolled in the study and later disqualified. The etiology of acute pulmonary edema was due to acute myocardial infarction (31%) or exacerbation of chronic CHF (69%)
Inclusion Criteria:
Clinical appearance of acute pulmonary edema (acute onset of dyspnea diaphoresis and rales>50% of posterior lung fields).
Exclusion Criteria:
systolic BP < 90 mmHg, pregnancy, known ace inhibitor allergy or age < 18 years. Patients who were intubated within 15 minutes of arrival were disqualified from the study.
* Baseline characteristics of the two randomized groups:
Captopril (C): n= 23
Placebo (P): n= 25
Age (years)
C: 71
P: 66
Gender-male
C: 11 (47%)
P: 15 (60%)
MAP: (mm Hg)
C: 132
P: 120
Assuming a standard difference of 60 mm Hg, the calculated SBP/DBP (mm Hg) would be:
C: 172/112
P: 160/100

Interventions

Captopril (C): n= 23
Placebo (P): n= 25
Dose Regimen:
2 capsules of (lactose plus 12.5 mg captopril) or 2 capsules of (lactose powder)
Were emptied sublingually for patients who had a systolic BP > 110 mmHg
Or
1 capsule (Captopril) or 1 capsule (Placebo) for those who had systolic BP 90-110 mmHg
The dose was re-administrated at minute 60
Co-interventions: standard treatment for all patients with oxygen, furosemide iv bolus ( 40 mg minimum , and nitroglycerin ( 0.4 mg -sublingually every 5 minutes for a total of three doses , morphine iv in 2 mg increments titrated against symptoms and BP .
Treatment was repeated at investigator discretion.
Treatment received at admission
C: furosemide 23 (100%), sl. nitroglycerin 23(100%), morphine 16 (69%), iv nitroglycerin 13(57%)
P: furosemide 25 (100%), sl. nitroglycerin 25(100%), morphine 18 (72%), iv nitroglycerin 18(72%)

Outcomes

Outcomes obtained from this trial for the two randomized groups:

Captopril (C): n= 23
Placebo (P): n= 25
Total SAE: NR
Mortality: NR
Total Non-fatal CVE: NR
Need for intubation:
C: 2/23 (9%)
P: 5/25(20%)
Blood pressure change in (mm Hg)
SBP: NR
DBP: NR
MAP: (obtained from table 1, page 207)
C: -43 mmHg,
P: -39 mm Hg
Standard deviation of the change was not reported
Heart Rate: NR

Notes
Funding: Not reported

Hirschl 1997

Methods
Single-site study (Austria).
Method of randomization/ allocation: not reported
Duration of treatment: until response or maximum allowed dose
Follow-up: 4 hrs

Participants
81 patients with elevated blood pressure and evidence of acute end organ damage
* Inclusion criteria:
  Patients with systolic blood pressure > 200 mmHg, and diastolic blood pressure > 110 mm Hg in association with clinical evidence of acute end organ damage (encephalopathy, stroke, acute heart failure, angina, aortic dissection)
* Exclusion Criteria:
  > 80 years old
  Acute or chronic renal failure
  Pheochromocytoma
  Organ transplant
  Pregnancy,
  Lactation
* Baseline characteristics for the two randomized groups:

Nitroprusside (N): n= 35
Urapidil (U): n= 46
Unless otherwise indicated, values are expressed as mean ± SD
Age (years)
N: 58 ±14.9
U: 62±12.9
Race: NR
BP: (mm Hg)
N: 211/109
Type of acute end organ damage on admission
Angina: 15 U: 11
Neurological emergencies: 15 U: 11
Acute heart failure: 2 U: 7
Aortic dissection: 3 U: 6

Interventions

Nitroprusside (N): n= 35
Urapidil (U): n= 46

Dose regimen:
IV Urapidil (peripheral alpha1 receptor blocker and central 5-HT1A receptor agonist). Initial dose 12.5 mg and then 12.5 mg every 15 minutes to a maximum of 75 mg or response.
IV nitroprussiate. Initial dose of 0.5 mcg /kg/ min and then 0.5 mcg /kg/ min every 15 minutes to a maximum of 3 mcg /kg/ min or response.

Outcomes

Obtained from this trial
Total SAE: NR
Mortality: NR
Total non-fatal CVE: NR
Individual CVE: NR
Withdrawals due to adverse events: not reported

Blood pressure:
Except for baseline values data was obtained from the graph in page 887 (fig.2). Weighted mean BP change was calculated as follow:
Nitroprusside: SBP -58.4 ± 17; DBP -28.4 ± 12
Urapidil: SBP -37.6 ± 17; DBP -17.6 ± 13
Standard deviation of the change was not reported but imputed from end point.

Heart rate:
Weighted mean HR change (at minute 90) was provided in the text (p.886) as follow:
Nitroprusside: -8.2 ± 14
Urapidil: -9.2 ± 21
Standard error of the change was provided. We converted it to SD.

Primary outcome stated by authors:
Percentage of responders within 90 min after start of therapy, the number of primary responders with a re-elevation of BP and the percentage of major adverse events in each group (Hypotension greater than 50% and heart rate >120 bpm and aggravation of clinical symptoms requiring immediate intervention) and minor adverse events (subjective symptoms).

Secondary outcome:
Extent of BP reduction, time to achieve BP control and the cumulative dose of each drug.

Notes
Funding: Not reported

Hirschl 1999 14

Methods
Single-site study (Austria)

Open label.
Method of randomization / allocation: Not reported
Duration of treatment: until response or maximum dose allowed
Follow-up: 24 hrs

Participants
46 patients with high blood pressure and evidence of pulmonary oedema
Inclusion Criteria:
Patients found with Pulmonary edema (rales over both lungs) plus SBP > 200 mmHg or DBP > 100 mm Hg.
Exclusion Criteria:
If the patient required intubation or had cardiopulmonary arrest before initiating therapy.
Baseline characteristics for the two randomized groups:
Nitroglycerine (NTG) n=23
Enalaprilat(ENA) n=23
age (years)
NTG=74
ENA=74
Male/female
NTG=12/11 vs. ENA=9/14
race: NR
BP (mm Hg):
NTG=206/116
ENA=211/115
Patients previously receiving antihypertensive NTG=9/23 vs. ENA= 8/23
Diabetes NTG=6/23 vs. ENA= 4/23
Previous myocardial infarction NTG=4/23 vs. ENA= 6/23

**Interventions**

Nitroglycerine (NTG) n=23  
Enalaprilat(ENA) n=23  
Dose regimen:  
NTG = Sublingual, initial dose 0.8 mg as: repetitive application of 0.8 mg every 10 min. until a cumulative dose of 3.2 mg.  
ENA = Initial dose: 2.5 mg IV; repetitive application of 2.5 mg every 30 min until a cumulative dose of 10 mg.  
The mean dose of drug given until admission was 1.6 ± 0.6mg of nitroglycerine and 3.7±1.5 mg of enalaprilat.  
Withdrawals due to adverse events were not reported.  
The number of patients requiring a second drug to reduce blood pressure was not reported.  
The time to achieve the target blood pressure was not reported.  
The mean time of drug infusion is not reported.

**Outcomes**

Obtained from this trial  
Total SAE: NR  
Mortality: nil at 24 hours of follow-up.  
Total non-fatal CVE: NR.  
Individual CVE  
Nitroglycerine (N)= 0/23  
Enalapril= 2/23; (1 asystole, 1 intubation).  
Withdrawals due to adverse events: NR  
Blood pressure:  
Data was obtained from text (p.211). Weighted mean BP change was calculated as follow:  
Nitroglycerine: SBP -52.3 ± 18; DBP -34.6 ± 12  
Enalapril : SBP -55.6 ± 19; DBP -34.3 ± 11  
Standard deviation of the change was not reported but imputed from end point.  
Heart rate:  
Weighted mean HR change was also calculated from data provided in the text (p.211) as follow:  
Nitroglycerine: -29 ± 7
Enalapril: -33.5 ± 12
Standard deviation of the change was not reported but imputed from end point.
Primary outcome of trial:
The aim of the antihypertensive treatment was Reduction of systolic blood pressure below 160 mm Hg and diastolic BP below 90 mm Hg at admission to the emergency department.
Secondary outcome: Chest x-ray congestion, adverse events, metabolic and respiratory parameters.

Notes
Funding: Not reported

Marigliano 1988 15
Methods
Single-site study (Italy).
Open-label
Method of randomization/allocation: NR
Duration of treatment: single dose
Follow-up: 2 hrs
Participants
44 patients with high blood pressure and acute symptoms
* Inclusion Criteria:
Elderly patients with systolic blood pressure of 210 mm Hg or greater associated with acute symptoms (dyspnoea, cephalgia, angina, mental aberration)
* Exclusion Criteria:
Not stated
Except for BP and HR, baseline characteristics were not reported according to randomization group

Interventions
Captopril (C): n=22
Nifedipine (N): n=22
Dose regimen:
C: Single sublingual tablet of 50 mg.
N: Single sublingual capsule of 10 mg.

Outcomes
Outcomes obtained from this trial
Total SAE: NR
Mortality: NR
Total non-fatal CVE: NR
Individual Cardiovascular events: NR
Withdraw due to adverse events= N/A (as single dose was given)

Blood Pressure:
Except for baseline BP values and standard deviation of the change provided on text of page S92, data was obtained from the graph fig.1&2 (p. S92). Weighted mean BP change calculated was:
Captopril: SBP-60.33 ±18; DBP-21±12
Nifedipine: SBP-60.6 ±18; DBP-37±14

Heart rate:
Except for baseline HR values and standard deviation of the change provided on text of page S92, data was obtained from the graph fig.1&2 (page. S92). Weighted mean HR change calculated was:
Captopril: -10.5±5
Nifedipine: +20.8±7

Notes
Funding : Not reported

Nelson 1983

Methods
Single-centre (US), randomized, single-blind, controlled trial

Method of randomization/ allocation: NR
Duration of treatment : 1.5 h
Follow-up: 48 h

Participants
28 patients with acute heart-failure blood pressure levels that met our threshold for this category of patients.
Base-line characteristics for the two randomized groups:
Isosorbide (N): n=14
Furosemide (F): n=14
Mean age in years

N: 56
F: 56
Mean SBP ± SE
N: 130±7
F: 119±4
Mean DBP ± SE
N: 75±3
F: 72±2

Interventions
Isosorbide (N): n=14
Furosemide (F): n=14
Dose regimen:
N: Intravenous infusion of isosorbide dinitrate at initial dose of 50 mcg/kg and max 200 mcg/kg/h
F: IV infusion of furosemide 1 mg/kg
Study treatment lasted 1.5 hours after randomization and the target was to reduce systemic BP by 10 mm Hg.
Treatment started between 5-14 h of AMI
Mean dose administrated:
Isosorbide dinitrate: mean cumulative dose 13.2 mg (146 mcg/min -considering 90 min of infusion).
Furosemide: mean dose 80 mg
Co-interventions: NR

Outcomes
Obtained from this trial for the two randomized groups:

Isosorbide (N) group: n=14
Furosemide (F) group: n=14
Total SAE: NR
Mortality : nil during 48 hours of follow-up
Total Non-fatal CVE: NR
Individual CVE: NR
Withdrawals due to adverse events: NR
Blood pressure:
Data was obtained from table II page 731. The calculated BP weighted mean change was:
Isosorbide: SBP: -6.6±22.4; DBP-1.6±18.7
Furosemide: SBP: 1.6±18.7; DBP 1±11.2
The standard deviation of the change was not reported but it was imputed from the end point.
Heart Rate:
Data was obtained from table II page 731. The calculated HR weighted mean change was:
Isosorbide: 3±18.7
Furosemide: 2±14.96
The standard deviation of the change was not reported but it was imputed from the end point.

Notes

Funding: Yorkshire Regional Hospital: West Riding Medical Research trust.

Pastorelli 1991

Methods

Single-site study (Italy).

Method of randomization/ allocation: NR
Duration of treatment: single dose
Follow-up: 1 h

Participants

96 patients with hypertensive emergencies*
Inclusion Criteria:
Patients with observed hypertensive emergencies (*defined as acute target organ damage and high blood pressure).
The different types of hypertensive emergencies were uniformly present in each group. No further details
Exclusion Criteria:
Not stated
Not reported

Interventions

Nifedipine sublingual (N): n=16,
Captopril sublingual (Cs): n=27,
Captopril oral (Co): n=14,
Ketanserine sublingual (K): n=15,
Placebo (P):20
Dose Regimen: single dose.

Outcomes

Obtained from this trial:

Total SAE: NR
Mortality: NR
Total non-fatal CVE: NR
Individual Cardiovascular events: NR
Withdraw due to adverse events: N/A (single dose)
Blood Pressure;
Data was obtained from graphs in page 861 and 862. The calculated weighted mean BP change was:
Nifedipine: SBP-26.66±12.45; DBP-18.16±9.13,
Placebo: SBP-7.2±13.5; DBP-7.8±9
Ketanserine: SBP-13.6±7; DBP-14.6±9
Captopril: SBP-22.56±9.32; DBP-14.74±9
It was not specified if SD or SE was reported on the text or graphs. It was assumed to be SD. Standard deviation of change was not reported but imputed from end point

Notes
Funding: Not reported

Rubio-Guerra 1999

Methods
Single-site study (Mexico)
Open label trial
Method of randomization /allocation: not reported
Duration of treatment: single dose
Follow-up: 6 hrs

Participants
60 patients with high blood pressure and evidence of end organ damage
Inclusion Criteria:
Mean arterial pressure > 130 mmHg and evidence of end organ damage.
Exclusion Criteria:
Liver failure, chronic renal failure, drug or ethanol abuse, pregnancy.
* Baseline characteristics for the two randomized groups:
Isosorbide dinitrate aerosol (I): n= 30
Nifedipine (N): n= 30
mean age ± SD (years)
I: 51±13
N: 51±11
Race: NR
BP: (mm Hg)
NR
Data was extracted from graphs and text based on ITT analysis
Distribution of patients according to the type of end organ damage at admission
Encephalopathy I:18 N:18
Intracranial Haemorrhage I:2 N:4
Stroke: I:5 N:4
Myocardial Ischaemia: I:2 N:0
Acute pulmonary edema: I:2 N:1
Retinal haemorrhage: I:0 N:2
Pulmonary congestion by CXR: I:0 N:1
Papilledema: I:1 N:0

**Interventions**

Isosorbide dinitrate aerosol (I): n=30
Nifedipine (N): n=30
I: Initial dose 1.25 mg through oral mucosa when admitted and a second dose given 15 min later when MAP decreased less than 15%.
N: 10 mg sublingually as a single dose.

**Outcomes**

Outcomes obtained from this trial

Total SAE: NR
Mortality: NR
Total non-cardiovascular events: NR
Individual Cardiovascular events:
Nifedipine = 2/30 (subepicardial ischemia)
Isosorbide = 0/30
Withdraw due to adverse events = NR
Blood pressure
Data was obtained from text (page 474). The calculated weighted mean BP change was:
Isosorbide: SBP -34±15, DBP -29±7
Nifedipine: SBP -37±26, DBP -29±6
Standard deviation of change was not reported but imputed from end point
Heart rate
Data was obtained from text (page 474) The calculated weighted mean HR change was:
Isosorbide: -13±14
Nifedipine: 10±23
Standard deviation of change was not reported but imputed from end point

**Notes**

Funding: Not reported
Methods

Single-site study (Austria).

Open label
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 6 hours
Follow-up: 6 hours

Participants

133 patients* with pulmonary oedema and high blood pressure.
* Note: not all randomized patients were included in the analysis of the original publication (please see below discussion)
The total number of patients included in the original analysis was: n=112
45 patients from the urapidil group
67 patients from the nitroglycerin group
This is because 20 (15%) patients withdrew or dropped out from the trial. However there is a discrepancy in the numbers as follows:
Of those 20, 13 were reported according to the randomization group and 7 not according to the randomization group.
"Withdrawals/dropouts reported according to randomization group: 13
Urapidil : 11 (3 due to AMI, 9 due to dose violation)
Nitroglycerin : 2 (due to AMI)
"Withdrawals/dropouts reported NOT according to randomization group: 7
So, 112 + 20 = 132 patients.
Thus, there is a discrepancy between the number of patients described in the text (total 132) with those described as total randomized patients (133).
Therefore, total randomized (133) minus those included in the analysis (112) equals 21(16%) not included in the original analysis
We tried to contact the authors to explain this discrepancy but they did not replied to our request.

Inclusion Criteria:
Patients with systolic blood pressure > 200 mmHg and diastolic blood pressure > 100 mm Hg in association with clinical evidence of pulmonary edema (rales over both lungs)
Exclusion Criteria:
Allergic reactions
Pregnancy,
Myocardial infarction
Respiratory insufficiency requiring intubation or coma at the time of the emergency physician arrived.

* Baseline characteristics for the two randomized groups:
Nitroglycerine (N): n= 67
Urapidil (U): n= 45
Mean age ± SD ( years)
N:74.9
U: 73±11
BP: (mm Hg)
N:216/116
U:218/118

Interventions
Nitroglycerine (N): n= 67
Urapidil (U): n= 45
Dose regimen:
Sublingual Nitroglycerine : Initial dose of 0.8 mg and then 0.8 mg every 10 minutes. If after hospital admission SBP was > 180 mm Hg and/or DBP 100 mm Hg the drug was still continued but changed to IV infusion on a rate of 0.5-5mg/ h to reach SBP < 160 mm Hg and DBP below 90 mmHg within 30 min after admission and no re-elevation of BP for 6 h.
IV Urapidil (peripheral alpha1 receptor blocker and central 5-HT1A -receptor agonist): Initial dose 12.5 mg and then 12.5 mg every 15 minutes. If after hospital admission SBP was > 180 mm Hg and/or DBP 100 mm Hg the drug was still continued but changed to IV infusion on a rate of 5-25mg/ h to reach SBP < 160 mm Hg and DBP below 90 mmHg within 30 min after admission and no re-elevation of BP for 6 h.

Outcomes
Obtained from this trial for the two randomized groups:
Nitroglycerine (N): n= 67
Urapidil (U): n= 45
Total SAE: not reported (NR)
Mortality = nil
Total non-fatal cardiovascular events: NR
Individual CVE:
Left ventricular failure requiring intubation:
Urapidil: 0
Nitroglycerin: 2
Blood pressure:
Data was obtained from table 1 page 560 (base-line values) and from text on page 559 & 560. It was not possible to follow full ITT principles due to inconsistencies in the report. (see notes above)
The calculated weighted mean BP change was:
Nitroglycerin: SBP -59.5 ±20; DBP-33.5±11
Urapidil: SBP -73.5 ±21; DBP-42±13
Standard deviation of change was not reported but imputed from end point.
Heart rate:
Data was obtained from table 1 page 560 (base-line values) and from text on page 559 & 560. It was not possible to follow full ITT principles due to inconsistencies in the report. (see notes above)
The calculated weighted mean HR change was:
Nitroglycerin: -17.5±9
Urapidil: SBP -15±7
Standard deviation of change was not reported but imputed from end point.

Notes
Funding: Not reported

Verma 1987

Methods
Single-site study (United Kingdom)
Single-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 90 minutes
Follow-up: Until hospitalization discharge

Participants
48 patients with acute left ventricular failure and blood pressure levels that met our threshold for this category of patients.
Inclusion criteria
ECG for transmural myocardial infarction
Radiographic changes consistent with diagnosis of left ventricular failure
Left ventricular filling pressure > 20
Systolic P >100 mmHg
Exclusion criteria
Sustained arrhythrias
Valvular disease requiring surgery

Base-line characteristics for the 4 randomized groups
Furosemide (F), n=12
Isosorbide dinitrate (I), n =12
Hydralazine (H), n =12
Prenalterol n=12 (this group is not considered any further, as this drug is not an anti-hypertensive drug. It is a beta-adrenergic agonist.
Mean age in years ± sd.
F= 57
I = 58
H = 56
Mean SBP ± sd
F=117±4
I =131±8
H =134±6
Mean DBP ± sd
F =73±4
I =75±3
H =77±3

Interventions
Furosemide 1 mg/kg IV bolus (N=12)
Isosorbide dinitrate 50-200 mcg/kg/h IV infusion (N=12)
Hydralazine 0.15 mg/kg IV over 5 minutes (N=12)
Target: to reduce mean arterial pressure 10 mm hg but not to reduce SBP < 100 mmHg.
Mean dose administrated:
Furosemide 84 mg
Isosorbide dinitrate 11.8 mg [8.3-15.6 ]
Hydralazine= 12.8 mg [10.2-16]
Co-interventions: all patients received 5 mg of intramuscular
diamorphine

Outcomes

Outcomes obtained from this trial

Total serious adverse events: not reported (NR)
Mortality
Isosorbide = 0/12
Furosemide=0/12
Hydralazine =1/12
Prenalterol=1/12
Total Non-fatal cardiovascular events: NR
Individual cardiovascular events: NR
Withdrawals due to adverse events: NR

Blood pressure:
All data was obtained from table 2 page 41. The calculated weighted mean BP change was:
Isosorbide: SBP-8±24, DBP-1.6±10.4
Furosemide: SBP 1±14, DBP1.3±10
Hydralazine: SBP-4.3±17.3, DBP-5±10
The standard deviation of the change was not reported but imputed from end point.

Heart rate:
All data was obtained from table 2 page 41. The calculated weighted mean HR change was:
Isosorbide: 2.6±17.3
Furosemide: 2±17.3
Hydralazine: 8±20.8
The standard deviation of the change was not reported but imputed from end point.

Notes

Funding: Yorkshire Regional Hospital: West Riding Medical Research trust.

Methods

Multi-centre study (Taiwan).

Open label
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: single dose
Follow-up: 2 h

Participants
64 patients with high blood pressure and cerebral signs or symptoms during haemodyalisis.
Inclusion Criteria:
Patients with SBP >190 or DBP >120 associated with symptoms during haemodyalisis.
Exclusion Criteria:
Patients with increasing BP less than 20 min after initiating haemodyalisis. Patients with drop of BP to level less than 170/110 within 20 min were also excluded.
* Except for BP and HR, baseline characteristics were not provided. The type of emergencies was not reported according to randomized group.

Interventions
Nifedipine (N): n=30
Captopril (C): n=35
Prazosin (P): n=27
Dose regimen: sublingual single dose
Nifedipine 10 mg, Captopril 25 mg, and Prazosin 10 mg

Outcomes
Outcomes obtained from this trial:

Total SAE: Not reported (NR)
Mortality: NR
Total non-fatal cardiovascular events: NR
Individual CVE: NR
Withdraw due to adverse events = N/A (single dose)

Blood pressure:
Data was obtained from tables 1,2 and 3 on page 285-286.
Standard deviation of change was not reported but imputed from end point. The calculated weighted mean BP change was:
Captopril: SBP-41±8, DBP-27.71±10
Nifedipine: SBP-42±10, DBP-35.85±8
Prazosin: SBP-14.6±6, DBP-21.57±8

Heart rate:
Data was obtained from tables 1,2 and 3 on page 285-286.
Standard deviation of change was not reported but imputed from end point. The calculated weighted mean HR change was:
Captopril: -1.28±9
Nifedipine: -4.28±17
Prazosin: -0.85±9

Notes
Source of Funding : NR

Yang 2004

Methods
Single-site study (Korea)
Open label
Method of randomization: NR
Concealment of allocation : NR
Duration of treatment: 1 hour
Follow-up: 1 hour

Participants
40 patients with acute pulmonary edema and high blood pressure (SBP >160)
Inclusion Criteria:
Systolic pressure > 160 and a diastolic pressure > 100 mmHg accompanied by cardiovascular abnormalities and acute pulmonary edema
Exclusion Criteria:
Not stated

* Baseline characteristics for the two randomized groups:
Nitroprusside:(NTP) n = 20
Nicardipine (NIC) n= 20
Age (years) ± sd
NTP:60 ± 14
NIC: 59±12
BP: (mm Hg)
NTP:195/115; ± 27/20
NIC:196/114 ± 14/13

Interventions
Nitroprusside infusion at a starting dose of 1 mcg /kg x min., for 1 hour
Nicardipine infusion at a starting dose of 3 mcg /kg per min for 1 hour
The dose regimen was titrated to maintain the BP at 80% of the initial mean arterial pressure.
-mean dose given of NTP was 1.5\textpm{}0.4 mcg/kg x min
-mean dose given of NIC was 3.5\textpm{}0.5 mcg/kg per min
Co-interventions: not reported
NR

Outcomes

Outcomes obtained from this trial:

Total SAE: Not reported (NR)
Mortality: NR
Total Non-fatal cardiovascular events: NR
Individual cardiovascular events: NR
Withdrawals due to adverse events: NR

Despite the author's statement that patients were to be remove from the study if they experience an excessive drop in BP, developed arrhythmia or respiratory difficulty, or became unresponsive or lost of consciousness, there is no report of these withdrawals.

Blood pressure:
Data was obtained from table 2 page 121. The calculated weighted mean BP change was:
Nitroprusside: SBP-41.25\textpm{} 24; : DBP-26.5\textpm{}12
Nicardipine: SBP-49\textpm{} 23; : DBP-30\textpm{}12
Standard deviation of the change was not reported but imputed from end point

Heart rate:
Data was obtained from table 2 page 121. The calculated weighted mean HR change was:
Nitroprusside: 2\textpm{}16
Nicardipine: -1.5\textpm{}20
Standard deviation of the change was not reported but imputed from end point

Notes

Funding: NR
APPENDIX IV: MEDLINE AND EMBASE SEARCHES,

CHAPTER 3

MEDLINE Search
controlled clinical trial.pt.
randomized.ab.
drug therapy.fs.
randomly.ab.
trial.ab.
groups.ab.
allocate$.ab.
or/1-7
animals.sh.
8 not 9
Alacepril.mp.
Benazepril.mp.
captopril.mp.
ceronapril.mp.
cilazapril.mp.
derapril.mp.
enalapril.mp.
enalaprilat.mp.
fosinopril.mp.
idapril.mp.
imidapril.mp.
Lisinopril.mp.
moexipril.mp.
movetopril.mp.
perindopril.mp.
quinapril.mp.
ramipril.mp.
spirapril.mp.
temocapril.mp.
trandolapril.mp.
zofenopril.mp.
angiotensin converting enzyme inhibitor.mp. or Angiotensin-Converting Enzyme Inhibitors/
acebutolol.mp.
atenolol.mp.
Bisoprolol.mp.
esmolol.mp.
labetalol.mp.
metoprolol.mp.
nadolol.mp.
propranolol.mp.
sotalol.mp.
timolol.mp.
carvedilol.mp.
Adrenergic beta-Antagonists.mp.
Amlodipine.mp.
Aranidipine.mp.
Azelnidipine.mp.
Barnidipine.mp.
Bencyclane.mp.
Benidipine.mp.
Bepridil.mp.
Cilnidipine.mp.
Cinnarizine.mp.
Clentiazem.mp.
Darodipine.mp.
Diltiazem.mp.
Efonidipine.mp.
Elgodipine.mp.
Etafenone.mp.
Fantafoxone.mp.
Felodipine.mp.
Fendiline.mp.
Flunarizine.mp.
Gallopamil.mp.
Isradipine.mp.
Lacidipine.mp.
Lercanidipine.mp.
Lidoflazine.mp.
Lomerizine.mp.
Manidipine.mp.
Mibefradil.mp.
Nicardipine.mp.
Nifedipine.mp.
Niguldipine.mp.
Nilvadipine.mp.
Nimodipine.mp.
Nitrendipine.mp.
Perhexiline.mp.
Premylamine.mp.
Semotiadil.mp.
Terodiline.mp.
Tiapamil.mp.
verapamil.mp.
calcium channel blocker.mp. or Calcium Channel Blockers/
nitroprusside.mp.
nitroglycerine.mp.
Nitroglycerin/ or nitroglycerine.mp.
or Isosorbide Dinitrate/
nitrates.mp. or Nitrates/
urapidil.mp.
Trimethaphan/ or trimethaphan camsylate.mp.
reserpine.mp.
phentolamine.mp.
methyldopa.mp.
labetalol.mp.
kentaserine.mp.
hydralazine.mp.
guanethidine.mp.
fenoldopam.mp. or FENOLDOPAM/
diazoxide.mp.
clonidine.mp.
thiazide$.mp.
hydrochlorothiazide .mp.
chlorothalidone.mp.
or Chlorthalidon/e/
furosemide.mp. or Furosemide/
or/11-106
10 and 107
unstable angina.mp.
acute left ventricular failure.mp.
Pulmonary Edema/ or pulmonary oedema.mp.
stroke.mp.
(acute adj2 stroke).ti,ab.
Aneurysm, Dissecting/ or aortic dissection.mp.
Intracranial Hemorrhages/ or Cerebral Hemorrhage/ or intracranial haemorrhage.mp.

**MEDLINE search continued...**

**EMBASE Search**
randomized controlled trial.mp.
randomized controlled trials.mp.
controlled clinical trial.mp.
controlled clinical trials.mp.
randomized.ab.
random$.ab.
allocat$.ab.
((sing$ or doubl$ or treb$ or tripl$) adj25 (blind$ or mask$)).mp.
trial.ab.
groups.ab.
or/1-10
exp animal/ 11 not 12
Alacepril.mp.
Benazepril.mp.
captopril.mp.
ceronapril.mp.
cilazapril.mp.
derapril.mp.
enapril.mp.
enaprilat.mp.
intracranial Aneurysm/ or Subarachnoid Hemorrhage/ or subarachnoid haemorrhage.mp.
acute myocardial infarction.mp.
or/109-117 myocardial infarction.ti,ab.
acute.ti,ab.
threatened.ti,ab.
suspected.ti,ab.
or/120-122 119 and 123 118 or 124 108 and 125 placebo$.mp.
(control$.adj2 treatment$).ti,ab.
(treatment$.adj2 control$).ti,ab.
(open adj2 control).ti,ab.
(served adj2 control).ti,ab.

Isradipine.mp.
Lacidipine.mp.
Lercanidipine.mp.
Lidofoflazine.mp.
Lomerizine.mp.
Manidipine.mp.
Mibepradil.mp.
Nicardipine.mp.
Nifedipine.mp.
Niguldipine.mp.
Nilvadipine.mp.
Nimodipine.mp.
Nisoldipine.mp.
Nitrendipine.mp.
Perhexiline.mp.
Prenylamine.mp.
Semothiadil.mp.
Terodiline.mp.
Tiaipamil.mp.
verapamil.mp.
calcium channel blocker.mp. or Calcium Channel Blockers/
nitroprusside.mp.
nitroglycerine.mp.

fosinopril.mp.
idapril.mp.
imidapril.mp.
Lisinopril.mp.
moexipril.mp.
movetopril.mp.
perindopril.mp.
quinapril.mp.
ramipril.mp.
spirapril.mp.
temocapril.mp.
trandolapril.mp.
zofenopril.mp.
angiotensin converting enzyme inhibitor.mp. or Angiotensin-Converting Enzyme Inhibitors/
acebutolol.mp.
atenolol.mp.
Bisoprolol.mp.
esmolol.mp.
labetalol.mp.
metoprolol.mp.
nadolol.mp.
practolol.mp.
propranolol.mp.
sotalol.mp.
timolol.mp.
carvedilol.mp.
Adrenergic beta-Antagonists.mp.
Amlodipine.mp.
Aranidipine.mp.Az elnidipine.mp.
Barnidipine.mp.
Bencyciane.mp.
Benidipine.mp.
Bepridil.mp.
Cilnidipine.mp.
Cinnarizine.mp.
Clentiazem.mp.
Darodipine.mp.
Diltiazem.mp.
Efondipine.mp.
Elgodipine.mp.
Fendiline.mp.
Flunarizine.mp.
Gallopamil.mp.

240
Nitroglycerin/ or nitroglycerine.mp. or Isosorbide Dinitrate/nitroglycerine.mp. or Isosorbide Dinitrate/ nitrates.mp. or Nitrates/ urapidil.mp. Trimethaphan/ or trimethaphan camsylate.mp. reserpine.mp. phentolamine.mp.

**EMBASE search continued...**
methyldopa.mp. labetalol.mp. ketanserine.mp. hydralazine.mp. guanethidine.mp. fenoldopam.mp. or FENOLDOPAM/ diazoxide.mp. clonidine.mp. thiazide$.mp. hydrochlorothiazide .mp. chlorthalidone.mp. or Chlorthalidone/ furosemide.mp. or Furosemide/ or/14-109 13 and 110 unstable angina.mp. acute left ventricular failure.mp. Pulmonary Edema/ or pulmonary oedema.mp. stroke.mp. (acute adj2 stroke).ti,ab.

Aneurysm, Dissecting/ or aortic dissection.mp. Intracranial Hemorrhages/ or Cerebral Hemorrhage/ or intracranial haemorrhage.mp. Intracranial Aneurysm/ or Subarachnoid Hemorrhage/ or subarachnoid haemorrhage.mp. acute myocardial infarction.mp. or/112-120 myocardial infarction.ti,ab. acute.ti,ab. threatened.ti,ab. suspected.ti,ab. or/123-125 122 and 126 121 or 127 111 and 128 placebo$.mp. (control$ adj2 treatment$).ti,ab. (treatment$ adj2 control$).ti,ab. (open adj2 control).ti,ab. (served adj2 control).ti,ab. (control adj2 group).ti,ab. (deferred adj2 group).ti,ab. (control$ adj2 subject$).ti,ab. (control$ adj2 patient$).ti,ab. or/130-138
APPENDIX V: CHARACTERISTICS OF INCLUDED STUDIES, CHAPTER 3

Beaufils 1988

Methods
Multi-centre (30-French)
Double-blind
Method of randomization: Not reported (NR)
Concealment of allocation: NR
Duration of treatment: 10 days
Follow-up: 10 days

Participants
303 patients within 6 hours after onset of symptoms of first AMI

Inclusion criteria: Involved two stages: Patients age less than 75 years, suffering from a first myocardial infarction* were pre-included and randomized. Confirmation of inclusion was with increase of CK-MB enzymes levels.
* Chest pain lasting more than 15 minutes, persistent abnormalities of repolarization.

Exclusion criteria: Patients with recurrent infarctions, in shock, un-interpretable ECG, or those who had received electrocardioversion, some form of nitrates, beta-blockers, CCB, or thrombolytic were excluded.

Attrition data: Screened: NR
Total randomized patients: 303 (270), Molsidomine: n= 152 (133), Placebo: n= 151 (137) Figures in brackets reflect the patients included in the mortality analysis. Not an intention to treat analysis.
Total withdrawals (discontinuation of drug): 24, Molsidomine 10, Placebo 14
Withdrawals due to adverse events: 22, Molsidomine 9, Placebo 13
Total lost to follow-up: Not included in the analysis 33/303 (10%) due to non-confirmation of AMI diagnosis 19, recurrent infarction 3, after 6 hour 7, used of nitroglycerin 4.
Molsidomine: 19
Placebo: 14

Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Age (years), molsidomine (M): 55.4±9.9, placebo (P): 57.1±10.3
Sex (M/F), M: 114/19, P: 124/13
Treatment time: M: 3.57±2, P: 3.45±1
Infarct location: anterior / inferior, M: (57 / 73), P: (55/80)
BP (mm Hg), M: 133/85, P: 129/83
Medical history: NR

Interventions
Molsidomine vs. Placebo:
Drug regimen:
Molsidomine: Initially 2 mg of an oral form and 2 mg of a sublingual form. Total 16 mg on the first day, 12 mg on the second day, (2 mg x 6 times a day), and 6 mg (2 mg tid) from third day to day 10
Placebo: identical form (no further details)
Other interventions: NR

Outcomes
Mortality: obtained from text, page 130
Molsidomine: 2day:NR; 10 day: 6/133 (eof)
Placebo: 2day:NR; 10 day: 11/137 (eof)
Total non-fatal SAE: NR
Blood Pressure data: NR
Heart rate data: NR

Notes
Funding: Hoechst Laboratories, Paris
Dates of conducting the trial: NR

Branagan 1986
Methods
Single-site study (Ireland)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 3 days
Follow-up: 1 month

Participants
121 patients with suspected AMI within 6 hr of onset
Inclusion criteria: Patients within 6 hours of suspected AMI (acute chest pain lasting more than fifteen minutes)
Exclusion criteria: Over 70 years of age, women capable of child-bearing, heart rate greater than 110 per min, or less than 60 per
min., complete heart block, heart failure requiring diuretic therapy or mechanical support. SBP less than 85 mm Hg, ventricular fibrillation, or were on nifedipine.

Attrition data: Screened: N = 1220, total randomized patients, Nifedipine (N ): =60, Placebo (P): n= 61

Total lost of follow-up (randomized but not considered for analysis in the original publication): Nifedipine: 6 (10%, because of non-ischemic chest pain), placebo: 7 (11%, because of erroneously entered 1, non-ischemic pain 6)

Thus, the total of patients analyzed (mortality) in the original publications was Nifedipine (N ): n=54, Placebo (P): n= 54

Total withdrawals (discontinuation of drug): N: 8 (15%), P: 7 (13%)

Withdrawals due to adverse events:
Nifedipine: 7 (13%, bradicardia 2, ventricular tachycardia 1, complete heart block 1, fatal cardiogenic shock 1, fatal heart failure 2)
Placebo: 7 (13%, bradicardia 3, CABG 2, fatal cardiogenic shock 2)

Baseline characteristics:
Note: continuous variables are expressed as mean ± SE
Male/female N: 37/9, P: 44/8
Age (years): N:55.6 ± 1.3, P: 56.6±1.25
Time to treatment (hours): N: 3.33±0.2, P: 3.28±0.18

Interventions
Nifedipine vs. Placebo
Drug regimen:
Nifedipine 10 mg sublingually, after 4 hours a second capsule was administrated, and then one capsule every 6 hours for 48 hours.
Placebo, no further details.
Other interventions: NR

Outcomes
Mortality: obtained it from text, page 863
N: at 2 day: NR; 10 day: NR; eof (1m): 7/54
P: at 2 day: NR; 10 day: NR; eof (1m): 5/54
Total Non-fatal SAE: NR
Blood Pressure change during first 24 hours: NR
Heart rate change during first 24 hours: NR

Notes
Funding: Bayer, UK.
Dates of conducting the trial: July 1982- September 1984

Bussmann 1981
Methods
Single-centre (West Germany).
Open label
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 48 hours
Follow-up: 18 months

Participants
60 patients with AMI within 24 hours
Inclusion criteria: Patients with acute myocardial infarction (prolonged chest pain, ST-segment elevation with development of q waves, and increase in CK and CK-MB activity), diastolic pulmonary arterial or pulmonary capillary pressure was over 15 mm Hg. Two subgroups: early < 8 hours; and late > 8 hours
Exclusion criteria: Not stated
Attrition data: Screened: NR, Total randomized patients: Total N= 60, Nitroglycerin (N): n=31, Control (C): n=29
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: 3 patients were Lost of follow-up during 1.5 years
Baseline characteristics:
Mean Age (years): N: 59±11, C: 63±11
Anterior/posterior infarct : N: 17/14, C:15/14
Time to intervention (hours): N: 10.0, C: 10.4
HR (bpm): N: 88±19, C:87±16
MAP (mm Hg): N: 108±19, C:109±15

Interventions
Nitroglycerin vs. No treatment (Control)
Drug regimens:
Nitroglycerin: Two subgroups:
Early: (NTG given within 8 h)= 0.75- 6 mg/ h (12.5-100 mcg/min) iv infusion according to DPAP and BP (mean dose reported was from 2.8 to 3.2 mg/h) (50 mcg/min) for 48 h
Late: (NTG given after 8 h) same dose regimen (mean dose reported was from 2.7 to 3.6 mg/h) for 48 h
Control (29)= not stated method
Other interventions:
Nitroglycerin group: Lidocaine 4, digitalis 8, furosemide 3, atropine 5, antihypertensive 2, morphine 12
Control group: Lidocaine 8, digitalis 11, furosemide 11, atropine 11, antihypertensive 5, morphine 19
Outcomes

Mortality obtained from text, page 418 & 419.[Klinische-Wochenschrift.1983;61(84):417-22]
Nitroglycerin: 2d:NR ; 10d:2/31 (6.45%) ; eof(3 m.):6/31 (19%)
Control: 2d: NR ; 10d:5/29 ( 17%) ; eof(3 m.): 12/29 (41%)
Non-fatal SAE : NR
Blood pressure data: NR
There was only a report for mean arterial pressure in graph on page 620.
Heart rate: obtained from graph & text on page 620 (Circulation 1981; vol 63)
The calculated weighted mean HR change at 24 h was:
Nitroglycerin: 1.76 ±16
Control:-2.2 ±16

Notes

Funding: NR
Dates of conducting the trial : NR

Bussmann 1992

Methods

Single-site study (West Germany)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 2 days
Follow-up: 2 days

Participants

46 patients within 18 hours after onset of symptoms of AMI
Inclusion criteria: Patients with acute myocardial infarction within 2-18 h
Exclusion criteria: Patients were excluded if Infarct was over 18 h, or decreasing CK concentrations, Systolic < 100 mmHg, cardiogenic shock
Attrition data:
Screened: NR (40 % of the screened people were not able to enter the trial due to technical or organizational reason)
Total randomized patients: 46 ; Captopril: n= 22, Placebo : n= 24
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: Captopril: 2, Placebo : 1
Total lost to follow-up: NR
Baseline characteristics:
Age (years) : captopril (C): 62, Placebo (P): 59.9
Male/female: C: 19/3, P:18/6
Anterior/posterior infarct: C: 11/11, P:12/12
HR (bpm): C: 83.1, P:77.6
MAP (mm Hg) C: 100.1, P:93.9

**Interventions**
Captopril vs. Placebo
Drug regimen:
Captopril: slow 2.5-5 mg IV bolus injections followed by a continuous infusion of 1.5-2.0 mg/ hour for 48 hours
Placebo: No further details
Other interventions:
Captopril: Thrombolysis 11, nitrates 21, morphine 19
Placebo: Thrombolysis 12, nitrates 23, morphine 15

**Outcomes**
Mortality: (obtained from text, page 653)
Captopril: (n= 22); at day 2: 0, at day 10: 1, at EOF: NR
Placebo: (n= 24), at day 2: 0 , at day 10: 2, at EOF: NR
Total non-fatal SAE: NR
Blood Pressure; Reported as change in MAP, page 654
Heart rate: NR

**Notes**
Funding: NR

Charvat 1990

**Methods**
Single-centre (Kuwait),
Open-label (placebo-controlled trial)
Method of randomization: NR
Method of allocation: NR
Duration of treatment: 48 hours
Follow-up: 72 hours

**Participants**
129 patients within 6 hours of onset of suspected AMI*
* Chest pain with 20 minutes or longer duration, ST elevation greater than 1 mm in 2 leads (40 ms after J point), cardiac enzymes.
Attrition data: Screened: NR,
Total randomized patients: Nitroglycerin (N): n=62, Placebo (P): n= 67
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: NR
Baseline characteristics:
Mean baseline of BP: (mm Hg): N:140/82 ± 29.27/26.16, P:136/91 ± 32.44/23.66
Localization of AMI
N: anterior 42, inferior 20
P: anterior 34, inferior 33

Previous Medical history:
Placebo: diabetes 14, smoking 43, hypercholesterolemia 16, prior angina 18, prior MI 10.

Interventions
Nitroglycerin vs. Placebo
Dose regimen
Nitroglycerin: two subsets:
a) if BP <160/105: Intravenous infusion of 10 mcg/min (to be increase 10 mcg/min every 5 minutes) until SBP reached 20 mm Hg reduction but not lower than 100 mm Hg.
b) If > 160/105: Intravenous infusion of 40 mcg/min (to be increase 10 mcg/min every 5 minutes) until SBP reached 20 mm Hg and DBP < 90 mm Hg.
Placebo; infusion of 5 % dextrose. (no further details)
Treatment started within 6 hours of onset of pain and lasted for 48 hours after randomization.
The mean dose of nitroglycerin to obtained target was 75 ± 44 mcg/min.

Other interventions:
Sublingual nitroglycerin, morphine 10-20 IV, nasal oxygen, iv morphine if pain not relieved, continuous lidocaine 1-4 mg/min. CCB and BB if new ECG changes, diuretics if CHF, iv heparin to all patients. No thrombolysis was mentioned.

Outcomes
Mortality: obtained from table II, page 51
N: 2d:NR ; 10d:5/62 ; eof:N/A (FU=72 hours)
Placebo: 2d: NR ; 10d:5/67 ; eof: N/A (FU=72 hours)
Total Non-fatal SAE: NR

Blood Pressure;
Data was obtained from text, page 51(single point in time after titration (2-6 h).
The calculated weighted mean BP change was:
Nitroglycerin: SBP-21±21.2; DBP-11±12.6
Placebo: SBP-1±25 ; DBP-4 ±19
Standard deviation of change was not reported but imputed from end point
Heart rate
The calculated weighted mean HR change was:
Nitroglycerin: 2±19
Placebo: -3 ±18.24

Notes
Funding: NR

Chiche 1979
Methods
Single-centre (France), open-label
Method of randomization/ allocation: NR
Duration of treatment: 7 days
Follow-up: 28 days

Participants
95 patients with signs & symptoms of myocardial infarction, within 12 h of the onset.

Interventions
Nitroglycerin (N): n= 50
Placebo (P; dextrose 5 %): n= 45
Dose regimen:
Nitroglycerin: Intravenous infusion at initial rate of 10-15 mg/min with progressive adjustments of 10-15 mg/min according to clinical observation (no more than 20 mm Hg drop of blood pressure); for 7 days
Placebo: glucose 5% (no further details)
Duration of treatment: seven days
Mean dose of nitroglycerin was :50 mcg/min

Outcomes
Mortality: obtained from text, page 686 & 699
Nitroglycerin: 2d:NR ; 10d:NR ; eof(1m): 3/50
Placebo: 2d:NR ; 10d:NR ; eof(3 m): 8/45
Non-fatal SAE: (page 693 )
LTA:
Nitroglycerin: 2d:NR ; 10d:1/50 ; eof(1m):NR
Placebo: 2d:NR ; 10d:3/45;eof(3 m):NR
Blood pressure: No data was reported
HR: NR

Notes
Funding: NR

Clausen 1966
Methods
Single-site study (Denmark)
Open-label
Method of randomization: NR
Concealment of allocation: selection was performed by one to the secretaries and no physician concerned took any part in the
selection.
Duration of treatment: 14 days
Follow-up: 22 days

Participants
130 patients within 24 hours after onset of symptoms of AMI
Inclusion criteria: Diagnosis of AMI was based on ECG and enzymes.

Exclusion criteria: History of asthma

Attrition data: screened: Total randomized patients: 130,
propranolol: n= 66
placebo: n= 64,
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: nil
Baseline characteristics: Not reported based on the total of randomized patients.
Medical history (%)
Propranolol (n=53): diabetes 6(11), previous infarction 13(25),
angina pectoris 35(66)
No treatment: (n=57): diabetes 3(5), previous infarction 7(12),
angina pectoris 34(60)

Interventions
Propranolol vs No treatment

Drug regimen:
Propranolol: 10 mg orally four times in twenty-four hours from
day 1 to day 14. Sometimes patients required propranolol IV 5 mg
instead of the initial 10 mg.
Other interventions:
All patients were given digitalis, diuretics metaraminol or
procainamide if necessary.

Outcomes
Mortality: obtained from table V, page 922.
Propranolol group: 2day:NR; 10day: 13/66 ; eof(21day,N/A ): 18/66
No treatment group: 2day:NR ; 10day: 13/64 ; eof(21 day,N/A ): 16/64
Total non-fatal SAE: NR
Blood Pressure change during first 24 hours: NR
Heart rate change during first 24 hours: NR

**Notes**
Funding: Danish League Against Heart Disease
Dates of conducting the trial: November 1965-1966

**Cohn 1982**

**Methods**
Multi-centre (11 in US).
Double blind,
Concealment of allocation: opaque code envelope
Method of randomization: Patients stratified within each hospital according to age (below or above 65), systolic BP (greater or lower than 150 mm Hg) and left ventricular filling pressure (greater or lower than 20 mmHg).
Duration of treatment: 48 hours
Length of follow-up: 13 weeks

**Participants**
812 men within 24 hours of the onset of acute myocardial infarction* and with LVFP > 12 mm Hg
Inclusion criteria: Patients with acute myocardial infarction in the past 24 hours (* chest pain, ST-segment elevation, q waves lasting at least 0.04 sec or a new conduction defect) plus left ventricular filling pressure > 12 and SBP > 100 mm Hg).
Exclusion criteria: Shock, hypertension likely to require specific anti-hypertensive therapy, severe bronchopulmonary disease or other medical illness likely to prevent survival for 13 weeks
Attrition data: Screened: 3,663, excluded on screening: 1577 the inclusion criteria were not met, 436 refused consent and 838 rejected the use of catheter.
Total withdrawals (discontinuation of drug): N: 1.2 %, P:2%
Withdrawals due to adverse events: NR
Total lost to follow-up: nil
Baseline characteristics:
Age - years: Nitroprusside (N): 58.3, Placebo (P): 58.7
SBP(mmHg): N: 133.1, P:132.3
Neither DBP nor standard deviation of SBP at baseline is reported
Time of infarction (h): N: 16.5, P:15.4
Anterior involvement (%): N: 50.4, P:48.1
Medical history (%):
Nitroprusside: previous AMI 39.7, angina 53.4, hypertension 41.0, CHF 19.2, cerebrovascular accident 9.6
Placebo: previous AMI 45.2, angina 61, hypertension 40.7, CHF 17.8, cerebrovascular accident 8.7
Medication in previous 2 months (%)
N: Diuretics 29.5, nitrates 33.3, digitalis 19.2, beta blockers 11.8
P: Diuretics 28.5, nitrates 40.2*, digitalis 19.3, beta blockers 16.3

**Interventions**
Nitroprusside vs. Placebo
Drug regimen:
Nitroprusside: IV infusion was started at a rate of six drops per minute (10 mcg) and increase 10 mcg/min q 5 min until maximum dose allowed or achievement of the target* or a side effect happen. The maintenance treatment was for 48 h
Placebo: (dextrose solution) same regimen as nitroprusside
*Target: to attain SBP reduction of 20% of BL +76 mm Hg
mean dose reported was 72.8 mcg/h at titration
mean dose reported was 92.3 mcg/h at 24 h
mean dose reported was 94.4 mcg/h) at 48 h
Other interventions:
Except for diuretics No antihypertensive was allowed. Nitrates were not allowed either.
Beta blockers were not given except in unusual circumstances and previous beta-blockers was usually discontinued before randomization. Analgesics, antiarrhythmic drugs, diuretics, digitalis and anticoagulants were used according to local policies.
During first 24 hours the use of diuretics was considerably higher in the placebo group. In the first 8 hours 45 % of patients given placebo received diuretics as compared with 11 % of patients given nitroprusside.

**Outcomes**
Mortality: (table 2-page 1132; graph fig. 2 page 1134; table 3-p. 1133)
Placebo: 2d:9/405; 10d: 22/405 ; eof(3m):77/405
Non-fatal SAE: NR
Blood pressure:
Data was obtained from graphs (fig 1 on page 1132).
The calculated weighted mean BP change was:
Nitroprusside: SBP -16.13± NR ; DBP: NR
Placebo: SBP-6.55± NR ; DBP: NR
Heart rate
Data was obtained from graphs (fig 1 on page 1132).
The calculated weighted mean HR change was:
Nitroprusside : 3.93 ± NR
Placebo: 1.86 ± NR

Notes
Funding: Cooperative Studies Program of the Medical Research Service, Veterans Administration Central Office, Washington, DC.
Dates of conducting the trial: 1975

COMMIT 2005

Methods
Multi-centre (1,250-China)
Double-blind
Method of randomization: NR
Concealment of allocation: Sequentially-numbered sealed treatment packs prepared centrally
Duration of treatment: 28 days
Follow-up: 28 days

Participants
45,852 patients within 24 hours after onset of AMI

Inclusion criteria: Patients who presented with ST elevation, left-bundle branch block or ST depression within 24 hours.

Exclusion criteria: Not to have a clear indication for or contraindication to any of the study treatments. Patients scheduled for primary percutaneous coronary intervention, other life-threatening disease, high risk of adverse effects with metoprolol (SBP < 100 mm Hg) or low heart rate (<50 bpm) heart block, or cardiogenic shock.
Note: evidence of moderate heart failure (Killip II or III) was not an exclusion criterion.

Attrition data: Screened: NR, Total randomized patients: 45,852, Metoprolol: n=22,929, Placebo: n=22,923
Total withdrawals (discontinuation of drug): Metoprolol: 3024 (13.2%), Placebo: 1836 (8.0%)
Total withdrawals due to adverse events: NR
Total lost to follow-up: 2 (1 in metoprolol group, 1 placebo group)
Baseline characteristics:
Confirmed MI: 95.8% (Metoprolol [M] 21,993; Placebo [P] 21,955)
Possible MI: 1.8% (M 405, P 409)
Unstable angina 1.3% (M 294, P 302)
Other 1.1% (M 236, P 256)
Note: continuous variables are expressed as mean ± SD
Age (years): Metoprolol (M): 61.4 ± 11.8, Placebo (P): 61.3 ± 11.8
Female: M: 6431 (28 %), P: 6328 (27.6 %)
Time since onset (h): M: 10.3 ± 6.7, P: 10.3 ± 6.7
SBP (mm Hg): M: 128.2 ± 22.6, P: 128.2 ± 22.5
Heart rate: M: 82 ± 17.3, P: 82.3 ± 17.1
ECG findings (%)
Metoprolol: ST elevation (86.7), bundle branch block (6.2), ST depression without ST elevation (7.1)
Placebo: ST elevation (86.8), bundle branch block (6.5), ST depression without ST elevation (6.7)
Killip class I; II; III (%): M: 75.3; 19.9; 4.7, P: 75.6; 19.8; 4.6
Medical history (%)
Metoprolol: Previous MI (8.4), hypertension (43.4),
Placebo: Previous MI (8.3), hypertension (43.1),

**Interventions**

Metoprolol vs. Placebo
Note: there was another comparison, aspirin plus clopidogrel vs. aspirin, as per a 2x2 factorial design. This comparison is not discuss in this review further

Drug regimen:
Metoprolol: Initially, 5 mg IV over 2-3 min, x 3 doses (every 2-3 minutes if the SBP > 90 mm Hg, and > 50 bpm). Then, 15 minutes after these IV doses, a 50 mg orally was given every 6 hours during days 0-1. From day 2 onwards a 200 mg controlled-release for up to 4 weeks
Placebo: Same regiment, No further details
The three injections were received by 90% of those allocated to metoprolol and 96% allocated to placebo. The oral treatment was completed in 86.2% for those in metoprolol group and 91.6% in the placebo group.
Other interventions:
Non-study b-blockers and anti-platelets were to be avoided.
Unless contraindicated thrombolysis was administrated to all patients before randomization
Metoprolol group: non-trial beta blocker (6.1%)*, fibrinolytic (54.3%), anticoagulant (74.4%) antiarrhythmic (22.0%), ACE inhibitor (67.2 %)*, nitrate (94.1%), diuretic (24.2 %), CCB (10.9%).
Placebo group: non-trial beta blocker (15.7%)*, fibrinolytic
(54.6%), anticoagulant (74.7%) antiarrhythmic (22.7%), ACE inhibitor (69.3%)*, nitrate (94.3%), diuretic (22.4%), CCB (12.6%).

* p < 0.0001

Outcomes
Mortality: obtained from figure 3, page 1626
Metoprolol: n=22,929
2day: 395 (1.7%);
10(7) day: 1441(6.28%); eof (4wk,N/A):1774 (7.7%)
Placebo : n= 22,923
2day: 364 (1.6%);
10(7) day: 1449 (6.32%); eof (4wk, N/A): 1797(7.8%)
Total non-fatal SAE: NR
Blood Pressure change during first 24 h: NR
Note:
Fatality rate according to baseline BP:

< 120; 120-139, 140-159, > 160

Metoprolol: 9.6, 6.8, 6.5, 7.2
Placebo: 8.8, 7.6, 7.0, 7.0

The above data was obtained from table 6, page 1628.

Heart rate change during first 24 h: NR

Fatality rate according to baseline BP:

< 70; 70-89, 90-109, > 110

Metoprolol: 4.3, 6.0, 11.0, 20.3
Placebo: 4.1, 6.6, 10.7, 18.3

Notes
Funding: By Sanofi-Aventis and Bristol-Myers Squibb (clopidogrel manufacturers) and by AstraZeneca (metoprolol manufacturers)
Dates of conducting the trial: August 1999- February 2005
COMMIT trial is also the Second Chinese Cardiac Study (CCS-2).

CONSENSUS-II 1992
Methods
Multi-centre (103 Scandinavian Countries)
Double-blind
Method of randomization: Patients were stratified in blocks of 2-10 according to whether they had had previous myocardial infarction and according to study centre. No further details
Concealment of allocation: Package of the study drugs were labeled with numbers assigned to the patients.
Duration of treatment: 6 months
Follow-up: 6 months

Participants
6,090 patients within 24 hours after onset of symptoms of AMI

Inclusion criteria: Presented within 24 of the onset of chest pain suspected of AMI (elevation of the ST segment in two or more contiguous ECG leads; new pathologic Q-waves or elevated plasma levels of enzymes)
Exclusion criteria: Blood pressure < 105/ 65 mm Hg (supine), need for vasopressor, severe valvular stenosis, untreated third-degree AV block, a history of angioedema, or sensitivity to ACE inhibitors, or the use of such drugs within one week before the infarction; severe renal, hepatic or hematologic disorders, history of cerebral transient ischemic attacks or other life-threatening condition, a clear indication for ACE inhibitors

Attrition data: Screened: 10,387, Excluded by screening: 4297 (41%)
Total randomized patients: 6090, Enalapril: n= 3044 , Placebo : n= 3046
Total withdrawals (discontinuation of drug): NR
Total withdrawals due to adverse events: NR
Total lost to follow-up: NIL
Baseline characteristics:
Mean age (years): Enalapril (E): 65.7, Placebo (P): 65.8,
No. of men (%): E: 2208 (73%), P: 2239 (74%)
Time to randomization (hours): E: 15, P: 15
Inferior infarction E: 1006 (33 %), P: 1023(34 %)
SBP/ DBP (mm Hg): E: 133 /80, P: 134/ 80
Heart rate (bpm): E: 75, P:75
Medical history (%)
Enalapril: previous AMI 709 (23), heart failure 203 (7), diabetes 355 (12), angina pectoris 1141 (37), smoking 1135 (37),
Placebo: previous AMI 723 (24), heart failure 171 (6), diabetes 330 (11), angina pectoris 1195 (39), smoking 1101 (36)

Interventions
Enalapril vs. placebo
Drug regimen:
Enalaprilat: 1 mg IV diluted in 100 ml of 0.9 percent saline over 2 hours*. Then, 6 hours after oral enalapril at dose of 2.5 mg bid titrated up to 20 mg /day on the fifth day and thereafter for month.

Placebo: No further details

* The infusion was discontinued if systolic/ diastolic blood pressure decrease to < 100 / 60 mm Hg.

Other interventions: according to study groups

Enalapril group: beta-blockers 2020 (66%), CCB 715(23%), nitrates 1607(53%), thrombolytics 1702 (56 %)

Placebo group: beta-blockers 2053 (67%), CCB 716(24%), nitrates 1611(53%), thrombolytics 1712 (56 %)

Outcomes

Mortality: obtained from text, page 679
Enalapril: 2day: NR; 10day: 140/3044(4.6%); end of trial: N/A; 312/ 3044 (10.2%); at 6 mo 334 (11%)
Placebo: 2day: NR; 10day: 131/3046 (4.3%) ; end or trial: N/A; 286/ 3046 (9.4%); at 6 mo 310 (10.2%)

Total non-fatal SAE: NR

Blood Pressure change during first 24 h: NR
Heart rate change during first 24 h: NR

Notes

Funding: Merck Sharp and Dohme

Dates of conducting the trial: March 1990- March 1991

Crea 1985

Methods

Single-site study (UK)
Single-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: during hospital stay
Follow-up: until discharge of hospital

Participants

17 patients with AMI within 12 hours of onset
Inclusion criteria:
Patients with prolonged chest pain typical of acute myocardial infarction and with ECG changes consistent with transmural ischemia.

Exclusion criteria:
Older than 75 years, SBP < 90 mm Hg, heart rate less than 55 beats/min, severe hypertension requiring intravenous vasodilators, PR interval > 0.3 second, second and third-degree AV block, QRS
interval longer than 0.1 second, severe heart failure, syncope or cardiac arrest before admission.

Attrition data:
Total randomized patients:
Verapamil (V): n=8
Placebo (P): n=9
Total withdrawals (discontinuation of drug): V=2; P=0
Withdrawals due to adverse events: V=2; P=0
Total lost of follow-up: NR

Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Age (years)
V: 59±7
P: 56±6
BP (mm Hg): V: 118/81, P:127/77
Previous AMI
V: 2(25%)
P: 1(11%)
Time to treatment (hours)
V: 6±3
P: 7±3
Anterior involvement
V: 4(50%)
P: 5(55%)

**Interventions**
Verapamil (V): n=8
Placebo (P): n=9
Drug regimen:
V: verapamil IV bolus of 10 mg at interval of 30 min up to a total dose of 40 mg, followed by oral administration of 80 mg 3 times daily until discharge*.
P: Saline solution and placebo tablets were administered in a manner similar to that of verapamil.
* medication was interrupted if decrease in systolic blood pressure to less than 90 mm Hg and second or third-degree AV block mean dose was not reported
Other interventions:
Nitroglycerin, and morphine were given for chest pain.

**Outcomes**
Mortality: obtained it from text, page 902
Verapamil: 2day: NR; 10day: 0/8; eof: N/A
Placebo: 2day: NR; 10 day: 2/9; eof: N/A
Total non-fatal SAE: NR
Individual SAE:
CHF: V=2/8; P=2/9
Second-degree AV block: V=2/8; P=0/9
Blood Pressure;
Data was obtained from graphs in figure 1, page 902.
The calculated weighted mean BP change was:
Verapamil (n=8): SBP-4.77±19; DBP-4.4±6.18
Placebo (n=9): SBP-7.5±16; DBP-4±6.6
Standard deviation of change was not reported but imputed from end point
Heart rate
Data was obtained from graphs in figure 1, page 902.
The calculated weighted mean HR change was:
Verapamil (n=8): -4±23.8
Placebo (n=9): -9±13.32
Standard deviation of change was not reported but imputed from end point

Notes
Funding: British Heart Foundation and by MRC Programme Grant PG

Di Pasquale 1994
Methods
Single-site study (Italy)
Single-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 3 days (comparison), then same active treatment in both study groups after discharge
Follow-up: 6 months

Participants
371 patients within 4 hours after onset of symptoms of AMI
Inclusion criteria: First AMI*, KK I-II, acceptable echocardiography.
* Diagnosis of AMI was based on ST elevation 1 mm in peripheral, 2 mm in precordial, blood CK-MB within normal range.
Exclusion criteria: Not suitable for thrombolysis, Left bundle branch block, cardiomyopathy, CHF, not satisfying reperfusion (relief of pain, peak of CPK within 12 h, early ventricular arrhythmias) unstable angina (not elevation of CPK)
Attrition data: Screened: 479, excluded at screening: 108 (78 not suitable for thrombolysis, 16 with KK > 3-4, 14 with CK greater than normal)
Total randomized patients: 371, Captopril: n= 188, No treatment : n= 183
Total withdrawals (discontinuation of drug): 112, Captopril: 57, No treatment: 55
Withdrawals due to adverse events: NR
Total lost to follow-up: NR
Baseline characteristics: not reported based on all randomized patients

**Interventions**

Captopril vs. No treatment
Drug regimen:
Captopril: 6.25 mg orally 15 min before thrombolysis; 6.25 mg every 8 hours for 2 days, 12.5 mg every 8 hours for 4 days, followed by 25 mg every 8 hours until after discharge.
No treatment (control group): received no captopril for first 3 days, and then started captopril on the 4 day as above
Other interventions:
All patients received thrombolysis (urokinase 1 million IU was administered)
Captopril group: 58 patients received IV metoprolol
No treatment group: 49 patients received IV metoprolol

**Outcomes**

Mortality: obtained from personal communication (email annexed in appendix 2)
Captopril: n= 188, at day 2: NR; at day 10 (in hospital): 2; at eof (6 mo): not based on intention to treat analysis
No treatment (control group): n= 183, at day 2: NR; at day 10 (in hospital): 5; at eof (6 mo): not based on intention to treat analysis
Total non-fatal SAE: NR
Blood Pressure: NR
Heart rate: NR

**Notes**

Funding: NR
Dates of conducting the trial: Nov 30 1988 to Dec 31 1992
Author successfully contacted
As confirmed by the author, there is another publication of the same trial (Int J cardiol: 46;107-112) See appendix 2

**Di Pasquale 1997**

**Methods**

Single-site study (Italy)
Double-blind
Method of randomization: NR
Concealment of allocation: it was carried out by sequentially numbered boxes and was decided before thrombolysis
Duration of treatment: 3 days (comparison), then same active treatment in both study groups for 10 days
Follow-up: 10 days

**Participants**
61 patients within 4 hours after onset of symptoms of suspected AMI
Inclusion criteria: First episode of anterior AMI*, killip class I-II, an acceptable echocardiographic window and admission to the hospital within 4 h of the onset of symptoms (pain).
* AMI was based on ECG ST elevation of 1 mm in the peripheral leads and 2 mm in precordial leads, with concomitant alteration of the segmentary kinetics in the echocardiogram performed at entry. The basal creatine kinase (CK, CK-MB before thrombolysis) had to be within the normal range. All the patients admitted into the study had to have successful reperfusion. There was no age limit
Exclusion criteria: Patients who were not suitable for thrombolysis, who had left bundle branch block on the admission ECG, a history of cardiomyopathy, or heart failure were excluded. Patients who did not satisfy the reperfusion criteria (first 4-6 h after thrombolysis), and those receiving ACE inhibitors and [beta]-blockers also were excluded from the study.
Attrition data: Screened: 123, excluded at screening (31- for no or late thrombolysis, 5-KK >3, 26-inferior AMI)
Total randomized patients: 61, captopril: n=31, Placebo: n= 30
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: captopril: 8/ 31 (26%) (4 patients with no reperfusion and 4 with unstable angina), Placebo: 8/30 (26%) (5 patients with no reperfusion and 3 with unstable angina)
These patients were not considered for the analysis of efficacy, it is not known if those were accounted for safety
Baseline characteristics: Not available for all randomized patients

**Interventions**
Captopril vs. Placebo
Drug regimen:
Captopril: 6.25 mg orally within 4 hours of starting thrombolysis, then up to 25 mg every 8 hour for 3 days. (The dose was increased
(to maintain SBP > 100 mm Hg)
Placebo: same regimen, No further details; although this group received captopril 72 hours after thrombolysis.

Other interventions:
All patients received standard treatment: nitrates, heparin, aspirin, and where possible, metoprolol i.v., 5 mg, 3 times. The thrombolytic drug used was recombinant tissue-type plasminogen activator (RTPA) (100 mg).

Outcomes
Mortality: obtained from page 206 in results section,
Captopril (n=31): at day 2 : NR; at day 10:2/31; at eof: NR
Placebo (n=30): at day 2: NR; at day 10:2/30; at eof: NR
Total non-fatal SAE: NR
Blood Pressure: NR
Heart rate: NR

Notes
Funding: NR
Dates of conducting the trial: June 1994 to June 1995

Durrer 1982
Methods
Single-centre (Netherlands),
Open-label
Duration of treatment: 24 hours
Follow-up: 1 month
Method of randomization: not reported
Method of allocation: Consecutive order a series of sealed envelopes containing randomized allocations. Separate batches of different-colored envelopes were used for early and late admissions. The envelopes were issued in balanced series of 20 to ensure that the number of patients in each group would be approximately equal. Each batch of envelopes was shuffled by two people to ensure proper randomization

Participants
328 patients within 4 or 12 hours from onset of AMI*
Inclusion criteria: Patients with acute myocardial infarction criteria (*precordial pain that lasted for at least for one hour accompanied by sweating and pallor and resistant to sublingual nitroglycerine; ECG- Q waves or QR or QS complexes, ST changes)
There were two subgroups: 1- admitted within four hours after the onset of symptoms of myocardial infarction and; 2- admitted between 4 and 12 hours
Exclusion criteria: If any doubt of AMI, cardiogenic shock with
SBP < 90 mm Hg, or urinary output <20 ml, pulmonary edema, SBP < 95 mm Hg, Heart rate >120 bpm, 2 or more previous MI
Attrition data: Screened: 906, excluded at screening 578.
Total randomized patients:328, nitroprusside (N): n = 163, and placebo n=165
Total withdrawals (discontinuation of drug): 7 (nitroprusside group)
Withdrawals due to adverse events: NR
Total lost to follow-up: NR
Baseline characteristics:
Age(yr) N:60.9±11.4, P:61.4±10.9
SBP(mmHg): N: 137±22.2, P:136.6±21.2
Male/female: N: 124/39, P:131/34
Anterior localization: N: 86 (53%), C:88(54%)
Medical history:
Nitroprusside: previos AMI 34, CHF 15
Placebo: previos AMI 28, CHF 23

Interventions
Nitroprusside vs. Placebo
Drug regimen:
Nitroprusside: iv continuous infusion (24 hours) to bring SBP to a target of 100 mmHg; the infusion started at 15 mcg/min, with increases of 5 mcg, - until maximum dose allowed of 500 mcg/min or a total of 720 mg. After 24 h infusion was tapered down and the drug was replace with oral isosorbide 5 mg q 4 hours for the next six days.
Total mean dose of nitroprusside was 183 ± 193 mg/h “(127 mcg /min)”
Placebo: 5% glucose, no further details were given. It is not mentioned if patients took isosorbide after placebo
Other interventions:
All patients received standard medical treatment which was identical in both groups of patients: sublingual NTG, 2.5 mg of droperidol and 0.05 of fentanyl were used to relieve the pain. Beta blockers were used in 33% of nitroprusside group and 26% in placebo group.

Outcomes
Mortality: obtained from table 2 and text on page 1124
Nitroprusside: 2d:0/163 ; 10d:5/163 ; eof(1m.):9/163
Placebo: 2d:7/165 ; 10d: 18/165 ; eof(1m.):20/165
Total Non-fatal SAE: NR
Blood pressure:
Data was obtained from table 1 and 2, page 1123, and was limited to one single point at hour 4 after starting treatment. The calculated mean change was:
Nitroprusside: SBP-34.1± 12.2; DBP-20.4±8.7
Placebo: SBP-14.6± 18.9; DBP-9.7±11.5
Standard deviation to change was not reported but imputed from end of treatment
Hear rate: NR

Notes
Funding: The Wijnand M Pon Foundation.
The trial used a particular method for closing-out. Patients in the treatment and control groups were paired on the basis of their entry numbers- for example the fifth patient allocated to nitroprusside was paired with the fifth patient who received placebo. Then, the outcomes were scored according to those pairs as a tie, in favour of nitroprusside or placebo, respectively.
However, they used a "closed" plan which meant that the trial had to end when a maximum of 62 pairs yielding preferences had been plotted.
The critic of this is that it is not clear how the pairs were chosen, i.e., consecutively, randomly, or by outcome. If a total of 62 pairs were chosen and there were a total of 328 randomized patients, then it seems that the pairs were not chosen in consecutive order or randomly.

Eichler 1985
Methods
Single-site study (South Africa)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 36 hours
Follow-up: 3 days

Participants
32 patients with AMI* within 12 hours of onset of chest pain.

Inclusion criteria:
* History and ECG changes characteristic of AMI admitted to CCU within 12 hours from onset of chest pain.

Exclusion criteria:
Second or third degree AV block
Sustain tachycardia
SBP < 90 mm Hg
Heart failure (wedge pressure > 25 mmHg
Patients on current anti-arrhythmic
B-blocker
Digitalis
Calcium antagonist therapy
Attrition data:
Total randomized patients:
Tiapamil (T) group n= 16
Placebo (P) group n= 16.
Total withdrawals (discontinuation of drug): 2
T: 1
P: 1
Withdrawals due to adverse events: 2
T: 1 (ventricular fibrillation)
P: 1 (chest pain)
Total lost of follow-up: NR
Baseline characteristics:
Age(yr)
T: 55.1±10.5
P: 51.6±11.6
SBP(mmHg)
T: 128±22
P: 135.6±24
Male/female
T: 11/4
P: 13/2
Anterior/ inferior localization
T: 9/6
P: 7/8
History of previous AMI: NR

**Interventions**
Tiapamil vs Placebo
Dose regimen:
Tiapamil as a load dose of 1 mg/kg over 3 min followed by an infusion of 25 mcg/kg/min over 36 hours.
Placebo (equivalent volumes of saline solution)
Mean dose was not reported
Other interventions: (number of patients)
Tiapamil group: Atropine 1, furosemide 4, nitrates 1, fibrinolytic
NR.
Placebo group: Atropine 1, furosemide 3, nitrates 10 *, fibrinolytic
NR.

Outcomes
Mortality: nil (text page 781)
Total non-fatal SAE: NR
Blood Pressure:
Data was obtained from table 2, page 783
The calculated weighted mean BP change was:
tiapamil (n=16 ): SBP-9.85 ±9 ; DBP-12.85 ±13
Placebo (n=16): SBP 0.42 14± ; DBP 2.28 ±13
Standard deviation of change was not reported but imputed from end point
Heart rate
Data was obtained from table 2, page 783
The calculated weighted mean HR change was:
tiapamil (n=16 ): -8.65±17.8
Placebo (n=16): -1.21±17.7
Standard deviation of change was not reported but imputed from end point

Notes
Funding: Hoffman La Roche (Switzerland) supplied drugs

Erbel 1988
Methods
Single-site study (West Germany)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: hospital stay (between 3-4 weeks)
Follow-up: hospital stay (between 3-4 weeks)

Participants
149 patients within 6 hours after onset of symptoms of AMI
Inclusion criteria: Diagnosis of AMI was based on acute chest pain lasting for more than 30 minutes and persistent ST segment elevation of more than 0.3 mV in leads V1-V5 or 0.2 mV in leads I-III, avl, avf,
Exclusion criteria: Long period of resuscitation, history of allergic reaction to streptokinase, previous cerebrovascular accident, surgery during the preceding 10 days, history of acute peptic ulcer, and history of bleeding.
Attrition data: total randomized patients: nifedipine (N): n= 74, placebo (P): n= 75
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost of follow-up: NR
Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Age: N:53±11, P:59±9
Gender (M/F): N:66/8, P: 59/16
Time to treatment (min): N:162±54, P:179±74
Medical history (number of patients)
Nifedipine: previous AMI NR, diabetes 6, hyperlipidemia 19, smokers 45,
Placebo: previous AMI NR, diabetes 14, hyperlipidemia 25, smokers 48

**Interventions**
Nifedipine vs. Placebo
Drug regimen
Nifedipine: Two 10 mg of nifedipine capsules sublingually in addition, nifedipine 0.2 mg intracoronarily was administrated before and after reperfusion of the vessel [after opacification of the infarct-related vessel]. During their hospital stay patients received nifedipine 20 mg orally three times a day
P: placebo; no further details.
Other interventions:
All patients received intravenous heparin 5000 IU (Overlapping acetylsalicylate 1 gm and streptokinase 250,000 IU [ 20 minutes before catheterization] plus 250,000 IU intracoronarily for a total dose of 500,000 IU.
After streptokinase, coronary angioplasty was attempted in patients with coronary lesion of more than 75%.
Nifedipine group: IV nitroglicerine 36, oral isosorbide 28, beta-blockers 15, diuretics 11,
Placebo group: IV nitroglicerine 33, oral isosorbide 29, beta-blockers 14, diuretics 12

**Outcomes**
Mortality: obtained from fig 9, page 534
Nifedipine (n=74) : 2day 5; at 10 days: 10; eof: N/A
Placebo (n=75) : 2day 1; at 10 days: 6; eof: N/A
Total non-fatal SAE: NR
Blood Pressure change during first 24 hours: NR
Heart rate change during first 24 hours: NR

**Notes**
Funding: NR
ESPRIM 1994

Methods
Multi-centre (international-117)
Double-blind
Method of randomization: stratified in blocks of 8 and by study centre.
Method of allocation: by a centralised computer system.
Duration of treatment: 14 days
Follow-up: 13 months

Participants
4,017 patients within 24 hours of the onset of a suspected AMI*,
*based on typical persisting chest pain (>30) or less than 30 min but with definite CAD history.
Exclusion Criteria: overt heart failure, definite indications or contraindications for intravenous vasodilators, pregnancy, or previously randomised in this RCT.
Attrition data: screened: NR
Total withdrawals (discontinuation of IV drug): N: 177/2007 (8.8%), P: 191/2010 (9.5%)
Total withdrawals due to adverse events (IV drug): NR
Hypotension: N: 1.9%, P:1.5%
Cardiogenic shock: N: 0.9%, P:0.9%
Death: N: 1.8%, P:2.4%
Total lost of follow-up: NR
Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Male/Female: Molsidomine (nitrate- N): 1470/537, Placebo (P):1473/537
Age-years: N=63.6±12.8, P=63.4±10
SBP: N=135±22, P=135±23
DBP: N=81±13, P=81±14
Medical history (%)
Molsidomine, nitrate- (N) group: previous AMI 14.9, previous angina 36.7, diabetes 13.4, hypertension 40.5.
Placebo (P): previous AMI 15.7, previous angina 37.6, diabetes 12.3, hypertension 40.4.

Interventions
Molsidomine vs. Placebo
Dose Regimen:
Molisolmedine: Intravenous linsidomine (molsidomine) 1 mg/ h for 48 hours (adjusted until from 0.2 mg to a maximum of 2 mg /h); followed by Oral therapy with molsidomine 4x4 mg tablets daily for 12 days
Placebo: patients received placebo under exactly the same conditions, IV and oral therapy (no further details).
Treatment started within 24 hours of onset of pain and lasted for 48 hours after randomization.
Mean duration of iv treatment: 44.8 h
Other interventions:
At investigator discretion: before randomisation about half of the patients had received thrombolytic therapy, aspirin, and heparin, 30% received iv nitrates. After randomisation 86% received aspirin, 61 subcutaneous heparin, 74% iv heparin, and 20% thrombolytic therapy. More than 15% received nitrates.

**Outcomes**
Mortality: (day 2- text on page 93; day 10-figure 1 page 93, month 13- text on page 94)
Total Non-fatal SAE: NR
Blood pressure data: NR
HR: NR

**Notes**
Funding: Hechst (France) Cassella (Germany)
Trial conducted on: June 1990- November 1992

**Fitzgerald 1990**

**Methods**
Multi-centre (9 in England).
Double-blind
Method of randomization: NR
Method of allocation: NR
Duration of treatment: 5 days
Follow-up: 6 months

**Participants**
360 patients within 8 hours of the onset of an AMI.
Inclusion criteria: Patients thought with acute myocardial infarction in the past 8 hours. (*clinical findings, and systolic blood pressure greater than 90 mm Hg
Exclusion criteria: Had received long-acting nitrates within 8 hours. Physician wishing to prescribe nitrates within 8 hours.
Attrition data: Screened: NR,
Total randomized patients: Isosorbide 5 mono-nitrate (N): n=184,
Placebo (P): n= 176
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: 7 in isosorbide group and 4 in the placebo group
Baseline characteristics:
Age, years: Isosorbide 5 mono-nitrate (N): 60 [33-74, Placebo (P): 60 [38-74
BP (mmHg): N: NR, P: NR
Site of infarct
N: anterior 77, inferior 82, posterior 1, unknown 11, not MI 13
P: anterior 79, inferior 79, posterior 0, unknown 5, not MI 13
Medical history
N: 1st MI 138, 2nd MI or more 22, unknown 24
P: 1st MI 136, 2nd MI or more 29, unknown 11

Interventions
Isosorbide 5 mono-nitrate vs Placebo
Drug regimen:
Isosorbide, Initial: oral 40 mg if SBP was >110 mmHg or 20 mg if SBP < 110 mm Hg. Maintenance: oral 20 mg qid x 48 hours, 20 tid x 24 hours and 20 bid x 48 hours (total duration of treatment 5 days). Medication was withheld if SBP was < 90 mm Hg or if HR was outside the 50-130 range. Medication was re-commenced if patient recuperated the allowed range.
Placebo: no details were given.
Other interventions:
Lignocaine: N: 23%, P: 21%
IV nitrates: N: 15%, P: 25%
Diamorphine: N: 42%, P: 36%

Outcomes
Mortality: (text [in percentage], on page 122)
Isosorbide: 2d:NR ; 10d: 9/184 ; eof (6 m): 26/184
Placebo: 2d: NR ; 10d:7/176 ; eof(6 m): 19/176
Total Non-fatal SAE: NR
Blood Pressure;
Data was obtained from graphs fig 1& 2, on page 122.
The calculated weighted mean BP change (at 24 h) was:
Isosorbide (n=184): SBP-19.25±29; DBP-8.75 ±17.56
Placebo (n=176): SBP-13.05±13.26; DBP-6.68±17.14
Standard deviation of change was not reported but imputed from end point
Heart rate
Data was obtained from graphs fig 3, on page 122.
The calculated weighted mean HR (at 24 h) change was:
Isosorbide (n=184): -0.22±12.76
Placebo (n=176): 3.25±12.48
Standard deviation of change was not reported but imputed from end point

Notes
Funding: Schwarz Pharma Limited

Flaherty 1983

Methods
Single-centre (US).
Single-blind
Method of randomization: A card was drew to randomized patients
Concealment of allocation: NR
Duration of treatment: 48 hours
Follow-up: 15 months (range 4-44)

Participants
104 patients with AMI within 12 hours from onset of chest pain.
Inclusion criteria: Patients with high probability of acute myocardial infarction (history and electrocardiographic changes) within 12 h from onset of chest pain.
Exclusion criteria:
Age >75 h
SBP < 90 mm Hg
Second or third degree AV block
Heart rate: < 55 beats/min
Severe hypertension (SBP>200 mmHg, DBP>120) after relief of pain
Attrition data: Screened: NR,
Total randomized patients: 104, Nitroglycerin (N): n=56, Placebo (P): n= 48
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: 3 patients at month 3
Baseline characteristics for the two randomized groups:
(mean values ± SD)
Age (years) Nitroglycerin (N): 60±11, Placebo (P): 57±9
SBP (mmHg): N: 142±27, P:150±29
DBP (mmHg): N: 90±18, P:96±18
Male (%): N: 64, P: 69
Anterior/ transmural localization (%): N: 44/84, P: 36/77
Medical history (%)
N: previous infarction 16, previous heart failure 38
P: previous infarction 27, previous heart failure 34

**Interventions**

Nitroglycerin vs. Placebo

Dose regimen:
Nitroglycerin: intravenous initial dose was begun at 5 mcg /min with stepwise increases at 3-5 min intervals, followed by an adjustment phase to lower MAP 10 % from baseline. The infusion continued x 48 hours
Placebo : equivalent volumes 20-30 ml/h of 0.9 ml of 95% ethanol added to 500 ml of 5% dextrose in water to match the composition of the vehicle in which nitroglycerin was dissolved. The infusions were terminated abruptly after 48 hours. Then patients received nitroglycerin ointment 2%, or placebo ointment every 4 hr for 72 h, to maintain BP levels previously attained with iv infusion.
The mean dose of NTG to obtain 10% lowering of MAP was 90±74 mcg/min
The mean duration of the Nitroglycerin titration period was 81±63 min (range 9 to 425)
The mean duration of placebo titration was 27±23 min (range 0 to 115).

Other interventions:
Patients with Killip class I-II received lidocaine 1 mg/kg bolus and 20 mcg/kg/min for at least 24 hours. Patients with Killip class III-received half of the above dose. Morphine, sublingual NTG, diuretics, digitalis and Antihypertensive were allowed. Heparin by constant infusion was given to all patients. Propranolol in case of a recurrent ischemia. The actual number of patients who receive the above co-interventions was not reported. Thrombolysis was no mentioned

**Outcomes**

Mortality: (based on text ?page 580)
Nitroglycerin: 2d: NR ; 10d:4/56 ; eof(3 m.):11/56
Placebo: 2d:NR ; 10d: 7/48 ; eof(3 m.):11/48
Total non-fatal SAE: NR
Total individual SAE:
Blood pressure:
Data obtained from text, page 579. The weighted mean BP change was calculated from a single point after baseline:
Nitroglycerin (n=56): SBP-19 ±21; DBP-9 ±15
Placebo (n=48): SBP-4 ±29; DBP-3 ± 19
Standard deviation of change was not reported but imputed from end point
Heart rate
Data obtained from text, page 579. The weighted mean HR change was calculated from a single point after baseline:
Nitroglycerin (n=56):-2 ±15
Placebo (n=):-2 ±15
Standard deviation of change was not reported but imputed from end point

Notes
Funding: National Institute of Health (NIH)
Dates of conducting the trial : NR

Galcera 1993
Methods
Single-site study (Spain)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 14 days*
Follow-up: 14 days
* The exact duration of treatment is not reported. It is assumed that it is 14 days as the primary objective of the trial was to determine short-term remodelling (by radionuclide ventriculograms at baseline and at weeks)

Participants
43 patients within 24 hours after onset of symptoms of first AMI.
Inclusion criteria: ST segment elevation in at least 3 precordial leads (anterio infarction), with retrospective documented development of Q waves and typical changes in enzymes levels. Under 70 years, availability for radionuclide ventriculography within the first 24 h.

Exclusion criteria: Patient refusal to participate, previous valvulaopathy, Killip class III or IV, and enzymatic evidence of infarct extension
Attrition data: Screened: 85, excluded at screening 13 (2 died on admission, 2 hemodynamic study not available, 9 not available for radionuclide); other 29 patients who had pulmonary capillary
wedge pressure less than 17 mm Hg were not randomized (the latter point was not pre-specified in the inclusion criteria)
Total randomized patients: Captopril: n= 22, Placebo : n= 21
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: NR
Baseline characteristics: NR based on all randomized patients

**Interventions**
Captopril vs. Placebo
Drug regimen:
Captopril : Oral 6.25 mg titrated to a target dose of 25 mg tid
Placebo: No further details
Other interventions:
All patients received conventional therapy including intravenous nitroglycerin, patients could received CCB, BB, diuretics digitalis at physician discretion. Thrombolysis: Captopril: 15 / 22 (68%), Placebo : 16 / 21(76%)

**Outcomes**
Mortality: obtained from text, page 260
Captopril : 2day:NR ; 10day (before day 14): 1/21 ; eof(14 d ): NR
Placebo : 2day:NR ; 10day (before day 14): 2/22 ; eof(14 d ): NR
Total non-fatal SAE: NR
Blood Pressure change; NR
Heart rate change: NR

**Notes**
Funding: NR
Dates of conducting the trial: February 1988- June 1990

**Gelmers 1988**

**Methods**
Multi-centre (4, Netherlands )
Double-blind
Method of randomization: Patients were randomly assigned (in block of six)
Concealment of allocation: NR
Duration of treatment: 28 days
Follow-up: 6 months

**Participants**
186 patients within 24 hours after onset of symptoms of stroke
Inclusion criteria: Patients over 45 years, completed acute ischemic stroke, admission to hospital within 24 after the onset of symptoms.
*Diagnosis of stroke was based on the sudden onset of persistent focal neurologic deficit with no subsequent progressive
deterioration. It was confirmed by a complete neurologic workup that included a CT scan.

Exclusion criteria: All patients with brain ischemia caused by factors other than atherothrombosis, such as subarachnoid haemorrhage, intracerebral haemorrhage, haematoma, and complicated migraine. Patients with overt, severe systemic disease (myocardial infarction, cardiogenic shock, severe renal or hepatic failure, severe systemic infection, non-stabilized mellitus).

Attrition data: Screened and excluded after screened: NR
Total randomized patients: 186, Nimodipine: 93, Placebo : 93
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost of follow-up: NR

Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Age (years): Nimodipine (N):69.3 ±11.9, Placebo (P): 69.6 ±10.7
Gender: N: female 44, male 49 , P: female 31, male 62
Localization of the stroke: N: left 55, right 38 ; P: left 61, right 32
Medical history:
N: hypertension 21, diabetes 16, cardiac disorders 32
P: hypertension 21, diabetes 16, cardiac disorders 31

Interventions
Nimodipine vs. Placebo
Drug regimen:
Nimodipine: 30 mg every 6 hours for 28 days
Placebo: tablets identical in appearance and taste to the drug and according to the same schedule.
Other interventions:
All patients received standard therapy of 10 percent depolymerised dextran of low molecular weight for 12 hours a day for five days. Low dose heparin sodium (10,000 IU in two divided doses) for prevention of deep venous thrombosis.
During the study, patients were not allowed to use vasodilators, steroids, antiplatelet agents, barbiturates, or hyperosmolar agents. Cardiotonic agents, anti-hypertensive medications and antibiotic were administrated as required. No calcium-channel blockers other than nimodipine were administrated

Outcomes
Mortality: obtained from graph figure 1, page 205
Nimodipine: 2day: NR; 10day (7day):4/93; eof (4w-N/A):8/93
Placebo: 2day: NR; 10day (7day):9/93; eof (4w-N/A ):19/93
Total non-fatal SAE: NR  
Blood Pressure data: NR  
Heart rate data: NR

Notes  
Funding: Unrestricted grant from Bayer AG, Wuppertal, Germany  
Dates of conducting the trial: September 1982-1984

GISSI-3 1994

Methods  
Multi-centre (200 centres, 2/3 in Italy).  
Open-label 2 x 2 factorial design  
Method of randomization: computer network system  
Method of allocation: Program based on biased coin algorithm  
Duration of treatment: 6 weeks  
Follow-up: 6 months

Participants  
19,318 patients within 24 h of onset of suspected AMI  
Note; the diagnosis of AMI was confirmed in 95% of randomized patients, acute coronary syndrome in 3.6%, other diagnosis in 1.4%  
Inclusion criteria: Patients with chest pain and ST elevation of 1 mm in peripheral leads, or 2 mm in precordial leads, within 24 hours of symptoms onset and having no contraindications.  
Exclusion criteria: Severe heart failure, Killip class 4; high risk of adverse effects, contraindications such as renal failure, bilateral renal artery stenosis, allergies, life threatening disorders, previous randomization.  
Attrition data: Screened: 43,047, excluded at screening: 23,653: 33.2%- admitted after 24 hours  
23.2% -contraindication to study drug  
15.4%- persistently unstable  
28.2%-had administrative reasons  
Total randomized patients: 19,394  
(76 (0.39%) were lost to follow-up, thus 19,318 were included in the mortality analysis; but 499 patients were not included in the original paper leaving a total 18,895, in 1994)  
Glyceryl trinitrate: n= 9,663 (9,453 included in the 1994-original paper)  
Control - no glyceryl trinitrate : n= 9,655 (9,442 included in the 1994-original paper)  
Lisinopril : n= 9,646 (9,435 included in the 1994-original paper)  
Control - no Lisinopril : n=9,672 (9,460 included in the 1994-original paper)
Total withdrawals (discontinuation of drug): 2,745 /18,895 (14.5 %)
Glyceryl trinitrate : 1089/ 9453 (11.5%)
Lisinopril : 1656/ 9,435 (17.56%)
Total withdrawals due to adverse events: NR
Glyceryl trinitrate : hypotension 2.6 %, headache 3.0 %
Lisinopril : hypotension (9.7%), renal function impairment (2 %),
coughing (0.5 %).
Total lost to follow-up: (from total randomized 19,394)
Up to 6 weeks: 76 (0.39%) [Reported in J Am Coll Cardiol 1996;
27:337-344] the distribution according to groups is not reported.
Baseline characteristics: Abbreviation: Glyceryl trinitrate (N ),
Control group -no glyceryl trinitrate (XN), Lisinopril (L), control
group- no Lisinopril (XL)
Age > 70 yr : L: 26.8, XL: 27.4, N: 26.9, XN: 27.3
Medical history (%): previous AMI, angina, treated hypertension, diabetes
L: 14, 34.4, 30.2, 15.5.
XL: 13.8, 34.4, 29.6, 15.7.
N: 13.7, 34.5, 30.6, 15.9.
XN: 14.1, 34.5, 29.2, 15.4.
Time from symptom onset: <6; >6-12; >12-24 hours
L: 34.9; 24.6; 40.5
XL: 34.8; 25.2; 40
N: 34.8; 25.3; 39.9
XN: 34.9; 24.5; 40.6

**Interventions**

Glyceryl trinitrate vs. open control and Lisinopril vs. open control
Drug regimens
Glyceryl trinitrate was initially started as IV infusion at a rate of 5 mcg x min with adjustments every 5 minutes of 5-20 mcg/min to achieve a target of systolic blood pressure reduction of at least 10 % but not lower than 90 mm Hg, during the first 24 hours. After that the IV infusion was replaced with a patch providing 10 mg of nitrate transdermally per day. The patch was removed at bedtime. The duration of study treatment was for 6 weeks. Note: if the patch was not tolerated a single oral dose of 50 mg isosorbide mononitrate was given daily.
Control group ( open control) was given no study treatment ( no
Lisinopril was also given for 6 weeks. Initially, 5 mg every 24 hours was given. After 48 hours, 10 mg/day was given until completion of 6 weeks. If systolic blood pressure was reduced (within the first 3 days) to less than 120 mm Hg a dose of 2.5 mg was given. If, at any time, systolic blood pressure was reduced to less or equal to 100 mm Hg, a maintenance dose of 5 mg daily could be adopted. If SBP was reduced to less than 90 the therapy was stopped.

Control group (open control) was given no study treatment (no further details)

Other interventions:
Lisinopril group: IV beta-blockers 30.1%, fibrinolytics 71.4%, aspirin 83.6%, other antiplatelets 3.6%.
Control - no Lisinopril group: IV beta-blockers 31.3%, fibrinolytics 71.9%, aspirin 84.2%, other antiplatelets 3.5%. non-study ACE-I 13.3%
Nitrate group: IV beta-blockers 30.4%, fibrinolytics 71.9%, aspirin 84.1%, other antiplatelets 3.4%. non-study nitrate not reported.
Control - no nitrate group: IV beta-blockers 30.9%, fibrinolytics 71.4%, aspirin 83.6, other antiplatelets 3.7%, non-study nitrate 57.1% (mainly for angina, reported in page 1119 in Lancet 1994;343)

Outcomes
Mortality: (data, at day 2 and 10, was obtained from personal communication-see email Appendix 2)
Lisinopril: 2d: 200; 10d: 435/9,646; end of treatment (42 days): N/A 619/9646
Control lisinopril: 2d: 234; 10d: 486/9,672; end of treatment (42 days): N/A 693/9672

Nitrate: 2d: 196; 10d: 443/9,663; end of treatment (42 days): N/A 639/9663
Control nitrate: 2d: 238; 10d: 478/9,655; end of treatment (42 days): N/A 673/9655
Total non-fatal SAE: NR
Blood Pressure change during first 24 hours: NR
Heart rate change during first 24 hours: NR
Notes
Funding: Zeneca Pharmaceutical (who supplied Lisinopril and Schwarz Pharma (who supplied intravenous and transdermal Glyceryl trinitrate).
Dates of conducting the trial: June 1991 and July 1993.

Hargreaves 1992

Methods
Single-site study (UK)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 28 days
Follow-up: 28 days

Participants
105 patients within 24 hours after onset of symptoms of AMI
Inclusion criteria: Suspected acute myocardial infarction within 24 hours of the start of chest pain and SBP > 90 mm Hg.
Exclusion criteria: Not reported
Attrition data: Screened: NR
Total randomized patients: 105, Captopril: n= 36, Isosorbide mononitrate: n=33, Placebo : n= 36
Total withdrawals (discontinuation of drug): 18 but distribution according to group not reported
Total withdrawals due to adverse events: NR
Total lost to follow-up: NR
Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Age (years): Captopril (C): 60.6±9.4, Isosorbide mononitrate (N): 60.6±11.2, Placebo (P): 60.8 ±8.4
Sex ( Men/women ): C: 30/6 ; N: 30/3 ; P: 31/5
Site of infarction (anterior / inferior): C: 12/23, N: 15/18, P: 14/21
Previous infarction: C: 0(0%), N: 4(12%) , P: 4(11%)
BP (mm Hg): NR

Interventions
Captopril vs. Isosorbide mononitrate vs. Placebo
Drug regimen:
Captopril: orally, initial 6.25 mg, then, 12.5 mg t.i.d. for 28 days
Isosorbide mononitrate: 20 mg, no further details
Placebo: no further details
Other interventions: Thrombolysis
Captopril: 32 (88%)
Isosorbide mononitrate: 30(91%)
Placebo: 30 (83%)
Outcomes
Mortality: obtained from text, page 370
Captopril: 2day:NR ; 10day: 0/36 ; eof(N/A, 28 days ): NR
Isosorbide: 2day:NR ; 10day: NR ; eof(N/A, 28 days ): 2/33
Placebo: 2day:NR ; 10day: 2/36 ; eof(N/A, 28 days ): NR
Total non-fatal SAE: NR
Blood Pressure change during first 24 h: NR
Heart rate change during first 24 h: NR

Notes
Funding: Bristol-Myer Squibb and Stuart Pharmaceutical
Date of conducting the trial : NR

Heber 1987
Methods
Single-site study (UK)
Open-label
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 5 day
Follow-up: 1 year

Participants
166 patients within 6 hours after onset of symptoms suggesting AMI

Inclusion criteria: Under 75 years of age, diagnosis of AMI was based on clinical ECG and CK-MB more than 15IU.

Exclusion criteria: Presentation more than 6 hours, left ventricular failure, persisting hypotension (SBP < 100 mmHg) or hypertension (SBP > 200 mmHg), or conduction disorders, tachyarrhythmias requiring treatment, haemodynamically valvular regurgitation, history of bronchospasm, hepatic or renal disease, recent treatment with verapamil.

Attrition data: Screened: 630, total randomized patients: 166, labetalol: n= 83
No treatment: n= 83,
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: NR

Baseline characteristics:
There were 137 men, 29 women, age 39-74 years.
Age (years): Labetalol (L): 61, No treatment (X): 58
Male/ female: L: 65/18, X: 72/ 11
SBP /DBP (mm Hg) : Labetalol: 144/83 , No treatment: 141/91
BP standard deviation at baseline: NR
Medical history (%)
Labetalol group: previous ischaemia 27(32.5), hypertension 18 (21.6), diabetes 3(3.6),
No treatment group: previous ischaemia 33 (39.7), hypertension 9(10.84), diabetes 4 (4.81),

**Interventions**

Labetalol vs. No treatment

Drug regimen:
Labetalol: 0.25-1 mg/ kg (according to SBP at baseline) initial IV bolus over 10 minutes, then 6 hour IV infusion 10 mcg /min. Then, oral treatment of 50-200 mg every 8 hours was started for five days.
The aim of was to maintain systolic blood pressure near but not below 100 mm Hg.
The mean dose during IV infusion of labetalol was 23 ± 14 mg (range 2 ? 78 mg)

Other interventions:
All patients were treated otherwise in a conventional manner: analgesics, diuretics, digoxin, atropine, antiarrhythmics, and inotropics. Nitrates and CCB were discourage during the acute phase.
Labetalol group: furosemide 18, thiazides 24, atropine 5, digoxin 5, lignocaine 5, inotropes 2.
No study treatment group: furosemide 14, thiazides 26, atropine 10, digoxin 4, lignocaine 4, inotropes 1.

**Outcomes**

Mortality: obtained from text, page 16
Labetalol: 2day: 5/83; 10day (in hospital):5/83; eof( one year): 12/83
Placebo: 2day: 1/83; 10day (in hospital): 1/83; eof (one year ): 7/83
Note: 6 patients died within the first six hours (text, page 14)

Total non-fatal SAE: NR

Blood Pressure:
Data was obtained from figure 1, page 14.
The mean BP change at 6 h was:
Labetalol (n= 83): SBP -30.9 ±NR; DBP -7.13 ± NR
Placebo (n= 83): SBP -13.48± NR; DBP -7.48 ± NR
Standard deviation was not reported
Heart rate:
Data was obtained from figure 2, page 15.
The mean HR change at 6 h was:
Labetalol (n= 83): -14.00 ± NR
Placebo (n= 83): -5.12 ± NR
Standard deviation was not reported

Notes
Funding: NR
Dates of conducting the trial: February 1982 -September 1983

Hildebrandt 1992

Methods
Single-site study (Denmark)
Double blind:
Method of randomization: blocks of four by computer
Concealment of allocation: consecutively numbered treatment packages
Duration of treatment: 48 hours
Follow-up: until hospital discharge

Participants
100 patients with suspected myocardial infarction (MI)* within 8 hours of onset.
* MI: severe chest pain and ECG ST segment elevation of depression.
Exclusion criteria: Cardiogenic shock, known bleeding disorders, contraindications to streptokinase; intolerance to study drugs, pregnancy, lactation.
Attrition data:
Total randomized patients:
Isosorbide dinitrate ( N ): n= 50
Placebo (P): n= 50
Total withdrawals (discontinuation of drug): %
N: 9
P: 16
Withdrawals due to adverse events: NR
Total lost of follow-up: 1 (excluded before initiation of treatment because of cardiogenic shock)
Baseline characteristics:
Mean age (years) Isosorbide dinitrate ( N ):64, Placebo (P):62
Male: (%): N: 78, P: 65
Blood pressure: NR
Medical History: (%)
Isosorbide: previous AMI 26, angina 36, hypertension 20, diabetes 6, hypercholesterolemia 12.
Placebo: previous AMI 22, angina 31, hypertension 12, diabetes 12, hypercholesterolemia 6

Interventions
Isosorbide dinitrate (N): n= 50
Placebo (P): n= 49
Dose regimen:
N: Intravenous infusion of isosorbide dinitrate at initial dose of 33 mcg /min to achieve 10 % reduction in SBP. Duration of treatment 48 hours or until adverse effect.
P: identical 50 ml bottles at same rate
Mean dose of isosorbide administrated was not reported
90% of patients completed 48 h of infusion
Co-interventions: previous to isosorbide patients received 1.5 million I.U. of streptokinase as bolus and 2 mg/h as infusion.
Aspirin 150 mg orally, was also given. Diuretics and digoxin were given at the discretion of the staff.

Outcomes
Obtained from this trial for the two randomized groups:
Isosorbide dinitrate (N): n= 50
Placebo (P): n= 49
Mortality: (from text on page 1141)
Isosorbide: 2d:0/50; 10d:2/50. eof (1m): NR
Placebo: 2d:2/49; 10d:6/49. eof (1m): NR
Non-fatal SAE: NR
Any individual SAE:
CHF:
Isosorbide: 2d:NR ; 10d:14/50 ; eof(3 m.): NR
Placebo: 2d:NR ; 10d:20/49 ; eof(3 m.): NR
SHOCK:
Isosorbide: 2d:NR; 10d:2/50 ; eof(3 m.): NR
Placebo: 2d:NR; 10d:5/49 ; eof(3 m.):NR
Blood Pressure:
SBP: NR
DBP: NR
Heart rate : NR

Notes
Funding: Schwarz-Pharma AG

ICSG 1984
### Methods

Multi-centre (8 countries - Europe)

Double-blind

Method of randomization: randomization was performed within each center and was balance in blocks of four patients.

Concealment of allocation: (double blind)

Duration of treatment: during hospital stay

Follow-up: during hospital stay

### Participants

144 patients within 4 hours after onset of suspected AMI

Inclusion criteria: Patients of either sex between 21 and 70 years of age; within four hours of the onset of symptoms of a suspected first myocardial infarction*.

* patients were classified as A: if they had chest pain > 30 minutes by without ECG abnormality; or B: if they had ST-elevation or depression of more than 0.5mm in standard inferior leads, or more than 1 mm in chest leads V3-V6 or new T-wave inversion in V3-V6 or II, III, and AVF.

Exclusion criteria: Bradycardia (<50 beats per minute); hypotension (SBP < 100 mm Hg), clinical evidence of severe left ventricular failure, any degree of heart block, or a history of previous myocardial infarction and a QRS duration longer than 0.11 second; contraindication to beta-blockade ( rales > 10 cm above the diaphragm), bronchial obstruction; current treatment with a beta-blocker, CCB, digitalis or another antiarrhythmic agent.

Attrition data: Screened: NR, Total randomized patients: 144, Timolol: n=73, Placebo: n=71

Total withdrawals (discontinuation of drug): NR

Total withdrawals due to adverse events: 24, Timolol (T): 14, Placebo (P): 10

Total lost to follow-up: NR

Baseline characteristics:

Note: continuous variables are expressed as mean ± SD

Age (years): Timolol (T): 57±19 (32-74), Placebo (P): 54±10 (33-72)

Gender: male/ female: T:62/11, P:61/10

Time to treatment (hours): T:3.4, P: 3.6
Infarct location: anterior; inferior; indeterminate
Timolol (T):34, 22, 5
Placebo (P):34, 28, 1
SBP (mm Hg): Timolol (T):156/90, Placebo (P): 156/93
Neither DBP nor standard deviation of SBP at baseline were reported

Interventions
Timolol vs. Placebo
Drug regimen:
Timolol: Therapy had to be initiated within 5 hours of the onset. Treatment began with a bolus injection of 1 mg timolol maleate and repeated 10 minutes later (if hemodynamic stable), and then 0.6 mg /hour infusion for 24 hours. Then oral therapy 10 mg bid during hospital stay
Placebo: normal saline same dose regiment. No further details
Other interventions: number of patients (milligrams of drug)
Timolol group: digitalis 6 (NR), diuretics 33 (furosemide 1280), analgesics 21 (morphine 630), beta-blockers 3 (NR), nitrates 7(NR).
Placebo group: digitalis 6 (NR), diuretics 37 (furosemide 1260), analgesics 33* (morphine 838*), beta-blockers 8 (NR), nitrates 11(NR).
* p< 0.05

Outcomes
Mortality: obtained from text, page 11
Timolol: 2day:1/73 ; 10day (hospital stay):3/73; eor( N/A):
Placebo: 2day: 3/71; 10day (hospital stay):4/71; eor( N/A):
Total non-fatal SAE: NR
Blood Pressure:
Data was obtained from figure 1, page 11.
The mean BP at end point (24 h) was:
Timolol (n=73 ): SBP 119±NR ; DBP 69.94±NR
Placebo (n= 71): SBP 132.41 ± NR ; DBP 78.26 ±NR
Heart rate:
Data was obtained from figure 1, page 11.
The mean HR at end point ( 24 h) was:
Timolol (n=73 ): 57.58±NR
Placebo (n=71): 69.80 ±NR

Notes
Funding: Merck, Sharp and Dohme Research Laboratories, Rahway NJ
Dates of conducting the trial: NR

Infeld 1999
Methods
Multi-centre (Australia)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 14 days
Follow-up: 3 months

Participants
50 patients within 12 hours after onset of symptoms of stroke
Inclusion criteria: Acute middle cerebral artery territory cortical infarction* and if it was possible to obtain acute CT and SPECT scans, commence of treatment within 12 hours of stroke onset.
* Diagnosis was made on the basis of either 1. presence of cortical neurological deficits such as dysphasia, anosognosia, visual or sensory inattention, dyspraxia, or parietal sensory deficit or 2. evidence of cortical infarction on the acute CT scan
Exclusion criteria: Presence of cerebral hemorrhage or noncerebrovascular pathology such as tumor, previous cerebral pathology, presence of other neurological systemic or psychiatric illness, concurrent use of other dihydropyridine, 1 or more contraindications to CCB (pregnancy, post-partum, hepatic, renal or cardiac disease, or drugs affecting hepatic metabolism)
Attrition data: screened/excluded during screened: NR
Total randomized patients: Nimodipine: n=25, Placebo: n=25
Total withdrawals (discontinuation of drug): Nimodipine: 3 (died)/25, Placebo: 3 (died)/25
Withdrawals due to adverse events: Nimodipine: 3 (died)/25, Placebo: 3 (died)/25
Total lost to follow-up: 4 (2 in each group) were excluded for any analysis.
Baseline characteristics:
Female/male: 26 men, 24 women
Age (years): Nimodipine (N): 69.8 ± 2.5, Placebo (P): 70.7 ± 2.3
Treatment delayed (hours) N: 8.2 ± 0.6, P: 8.7 ± 0.5
SBP/DBP (mm Hg): NR

Interventions
Nimodipine vs. Placebo
Drug regimen:
Nimodipine: 120 mg/day orally in 4 divided doses (30 mg every 6 hours) x 14 days
Placebo: similar in appearance (No further details) x 14 days

**Outcomes**

Mortality: obtained from text, page 1418 and 1419

Nimodipine: 2day: NR ; 10day (7 day):3/25 ; eof(3 mo-N/A): NR
Placebo: 2day: NR ; 10day (7 day):3/25 ; eof(3 mo-N/A): NR

Total non-fatal SAE: NR

Blood Pressure data : NR
Heart rate data : NR

**Notes**

Funding: National Health and Medical Research Council and the National Stroke Foundation. The investigators are grateful to Bayer Australia Limited for supplying nimodipine and placebo

Dates of conducting the trial : November 1993 - May 1996

**INWEST 1994**

**Methods**

Multi-centre (34-Europe )
Double-blind
Method of randomization: predetermined randomization list
Concealment of allocation: NR
Duration of treatment: 21 days
Follow-up: 6 months (24 weeks)

**Participants**

295 patients within 24 hours after onset of symptoms of stroke

Inclusion criteria: Clinical diagnosis of a recent (within 24 h) ischemic stroke in the carotid artery territory , 40 year or older and functionally independent before stroke, should be conscious with a stable marked hemiparesis, Mathew score of 65 or less or an Orgogozo score between 5 and 50.

Exclusion criteria: Recent or unstable cardiac disease, any disorder interfering with the neurological or functional assessment or other life-threatening concurrent illness.

Attrition data: Total screened: NR
Total randomized patients: 295 (7/295 other than ischemic stroke)
Nimodipine 1 mg: n= 101
Nimodipine 2 mg : n= 94
Placebo : n= 100

Total withdrawals (discontinuation of drug): 101
Nimodipine 1 mg: n= 36/101
Nimodipine 2 mg : n=38/ 94
Placebo : n= 27/100

Withdrawals due to adverse events: 16 (not reporting according to group)
Total lost of follow-up: 7
Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Age (years): Nimodipine 1 mg (N1): 71.9, Nimodipine 2 mg (N2): 72.1, Placebo (P): 71
Male sex (%) N1: 45, N2: 45, P: 49
Previous vascular events (%)
N1: TIA 12; RIND 2; stroke 17; myocardial infarction 9; atrial fibrillation 34
N2: TIA 12; RIND 2; stroke 13; myocardial infarction 13; atrial fibrillation 27
P: TIA 17; RIND 6; stroke 9; myocardial infarction 16; atrial fibrillation 32
SBP / DBP (mm Hg) N1: 158.6/87.1, N2: 161/89.4, P: 159.5/91.2

Interventions
Nimodipine vs. Placebo
Drug regimen:
Nimodipine: subdivided in two groups: 1 mg group and 2 mg group: received 1 or 2 mg / hour intravenous infusion for 5 days and then both groups receive 30 mg nimodipine orally 4 times a day (120 mg/day) for 16 days (total treatment 21 days)
Placebo: No further details
Other interventions: NR

Outcomes
Mortality: obtained from text, page 207, and table 3 page 208
Nimodipine: 2day:NR; 10day (5day):25/195 ; eof( 6 months-N/A):83/195
Placebo: 2day:NR ; 10day (5day):11/100 ; eof( 6 months-N/A): 33/100
Total non-fatal SAE: NR
Blood Pressure:
Data was obtained from graph in fig1-A, page 1252 (Ahmed 2000).
The mean BP change during first 24 hours (single point @ day 1; combining the 2 doses) was:
Placebo (n=92 ): SBP -4.8±25.7 ; DBP -3.6 ±13.7
SD of the change was not reported, it was imputed from end point
Heart rate data: NR

Notes
Funding: Bayer AG
Dates of conducting the trial: April 1989-January 1990

ISIS-1 1986
Methods
Multi-centre (245-International)
Open-label
Method of randomization: based on a computer generated randomization list
Concealment of allocation: by a 24 h direct line telephone service
Duration of treatment: 7 days
Follow-up: 12 Months

Participants
16,027 patients within 12 hours after onset of symptoms of suspected AMI

Inclusion criteria: Patients with suspected myocardial infarction* within 12 hour of the onset of symptoms, not already on beta-blockers or verapamil and with no clear indication for or contraindication to beta-blockade (heart rate persistently below 100 mm 50 bpm, SBP <100 mm Hg), severe heart failure of bronchospasm)

* AMI was coded according to ECG findings as “probable” when a total elevation of > 6 mm in leads V1-V3 or V4-V6 or of >2 mm in leads I and AVL or > 3 mm in leads II, III and aVF; or “possible” when less extreme ST elevation but with some other abnormality such as ST depression T-inversion, pathological q-waves; or normal.

Attrition data: Screened: Total randomized patients: 16,027, Atenolol:n= 8037, Control: n= 7990
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: 69 atenolol, 60 control
The completeness of follow-up was 99.3 in hospital and 97.7% to Jan 1 1985.
Baseline characteristics:
Age (years): Atenolol (A): 58.8± 8.96, Control (C): 58.9± 8.93
Females: A: 23%, C: 23%
Mean delay (hours): A: 5 ± 2.69, C: 5 ±2.68
Mean SBP (mm Hg): A: 145 ± 26.89, C: 144.9 ±26.82
Mean heart rate/min: A: 79.2 ± 17.93, C: 144.9 ±17.87
Medical history
Atenolol: Previous MI 1295 (16%), diabetes 6%
Control: Previous MI 1327(17%), diabetes 6%

**Interventions**

Atenolol vs. no treatment (control)

Drug regimen:
Atenolol: 5 mg IV injection over 5 minutes and a second dose after 10 minutes (if no contraindications developed). Then, 50 mg orally followed by other 50 mg 12 h later. Then, 100 mg/ day for 6 days or until discharge if earlier.

Control: beta-blockers were avoided in hospital unless clearly indicated (chest pain unresponsive to nitrates, control of hypertension)

Other interventions:
Physicians were free to use other treatments felt appropriate. The percentage of drug use during hospital is as followed:
Atenolol group: IV atenolol 94%, some oral beta-blocker 92%, diuretic 38%, iv nitrates 7%, calcium antagonists 9%, digitalis 11%, anti-arrhythmics 15%, inotropic agents 5%
Control group: IV beta-blocker 2%, some oral beta-blocker 7%, diuretic 37%, iv nitrates 8%, calcium antagonists 17%, digitalis 14%, anti-arrhythmics 17%, inotropic agents 3%

**Outcomes**

Mortality: obtained from figure 1, page 59, and table III page 60 (all-cause mortality)
Atenolol (n=8037): at 2 day: 121(0.015); at 10 day (7d): 317 (0.039); eof (1 year): 866 (0.107)
Control (n=7990): 2 day: 171(0.021); at 10 day (7d): 367(0.046); eof (1 year): 951(0.12)
Total non-fatal SAE: NR

Blood Pressure change during first 24 h: NR

Note: In this trial there is information about mortality according to baseline BP and age

Heart rate change during first 24 h: HR

**Notes**

Funding: ICI pharmaceuticals Ltd
Dates of conducting the trial: mid 1981- Jan 1985

**ISIS-4 1995**

**Methods**

Multi-centre (1,086; multinational).
Double-blind.
Method of randomization: computer generated list
Concealment of allocation: by central phone; baseline details were recorded onto computer generated list before a specific numbered trial treatment pack was to be allocated. The computer used a
“minimisation” algorithm which limited chance differences between treatment groups in these baseline features.

Duration of treatment: 28 days
Follow-up: 1 year

**Participants**
58,050 patients with definite or suspected AMI within 24 hours of onset

Inclusion criteria: Patients with definite or suspected AMI within 24 hours with no clear indications or contraindications for the study drugs.

Attrition data: Total randomized patients: 58,050
Captopril: n= 29,028
Placebo captopril: n= 29,022
Isosorbide mononitrate: n= 29,018
Placebo nitrate: n= 29,032
Total withdrawals (discontinuation of drug): NR
Total withdrawals due to adverse events: NR
Total lost of follow-up:
By discharge: the report on mortality was for 99% of the total randomized population
At day 35: Captopril: 1.8%, Placebo: 1.6%, Isosorbide mononitrate: 1.7% Placebo: 1.8%

Baseline characteristics: There were no differences in across the randomized groups. Overall of the randomized patients, at entry: 79% had ST elevation, 40 % were within 6 hours, 28% were 70 or older, 74% were male, 2% had SBP < 100 mm Hg, 17% had previous MI, 92% was confirmed to have an AMI

**Interventions**
Captopril vs Placebo vs. Isosorbide mononitrate

Drug regimens:
Captopril: oral captopril; initially, 6.25 mg, then after two hours 12.5 mg, after twelve hours 25 mg. Maintenance: 50 mg bid for 28 days.
Nitrate: control-release isosorbide mononitrate; Initially, 30 mg, then after twelve hours 30 mg. Maintenance: 60 mg for 28 days
Placebo: no further details.

Other interventions:
Captopril group: IV nitrates 13,652 (47%), any nitrate 15,878 (55%), anti-platelets 26,905 (93%), fibrinolytic 19,917 (67%), IV
BB 2,578 (9%)
Placebo captopril group: IV nitrates 13,662 (47%), any nitrate 15,880 (55%), anti-platelets 26,941 (93%), fibrinolytic 19,783 (68%), IV BB 2,541 (9%)
Isosorbide group: IV nitrates 13,652 (47%), any nitrate 15,878 (55%), anti-platelets 26,921 (93%), fibrinolytic 19751 (68%), IV BB 2,541 (9%)
Placebo isosorbide group: IV nitrates 13,662 (47%), any nitrate 15,880 (55%), anti-platelets 26,925 (93%), fibrinolytic 19,949 (68%), IV BB 2,578 (9%)

Outcomes

Mortality: (day 2* was obtained from text 672-673, day 10: from page 672 figure 1 by blowing-up graph and calculate cumulative mortality at day 10; day 35: obtained from text on page 672-673)
* The authors of this trial reported mortality as "0-1 day mortality". Day 0= patients dead the same day they entered the trial and day 1= deaths on the day after randomization.
Captopril: N=29,028
2d: 549 (1.89%); 10d: 1536 (5.29%); end of treatment (35d-N/A): 2088 (7.19%)
Placebo Captopril: N=29,022,
2d: 593 (2.04%); 10d: 1644 (5.66%); end of treatment (35d-N/A): 2231 (7.69%)
Isosorbide: N=29,018
2d: 514 (1.77%); 10d: 1548 (5.33) graph; end of treatment (35d-N/A): 2129 (7.34%)
Placebo Isosorbide: N=29,032,
2d: 628 (2.16%); 10d: 1667 (5.74) graph; end of treatment (35d-N/A): 2190 (7.54%)
Total Non-fatal SAE: NR
Blood Pressure change during first 24 h: NR
Heart rate change during first 24 h: NR

Notes

Funding: The study was funded by Bristol-Myers Squibb and by Astra-Hassle.
Dates of conducting the trial: July 1991-August 1993

Jaffe 1983
**Methods**

Single-site study (US)
Open-label
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 24 hours
Follow-up: until hospital discharge

**Participants**

114 patients with myocardial ischemia or infarction within 12 hours of randomization and SBP of 100 mm Hg or greater and HR less 120 bpm

Attrition data:
Total randomized patients:
Nitroglycerin (N): n=57
Placebo (P): n=57
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost of follow-up: 0

Baseline characteristics:
Values expressed as mean ± SD for continuous data
Age (years):
N: 61±2
P: 60±2
Mean SBP:
N: 130±39
C: 134.8±33.7
Mean DBP:
N: 82.4±19.44
P: 89±28

Male/female:
N: 28/15
P: 30/12
Time to randomization (hours):
N: 6±0.4
P: 6.4±0.5
Previous AMI: (%)
N: 19
P: 21

**Interventions**

Nitroglycerin (N): n=57
Placebo (P): n=57
Drug regimens:
N: Intravenous infusion of nitroglycerin at initial dose of 10 mcg/min (adjusted to achieve targets*).
P: placebo (5% dextrose and water) no further details
*Target: either 10% reduction in SBP or achieve less than 95 mmHg at maximum dose of 200 mcg/min.
80% of patients achieved the target and it was achieved at mean of 1.74 ± 0.6 hours after starting the infusion.
The mean dose of nitroglycerin to obtain target was 57±21 mcg/min.
Mean dose administrated: NR
Co-interventions: Other than study treatment both groups were treated identically.

Outcomes
The results of this trial were reported in two papers (Jaffe 1983 and Roberts 1983). Mortality is not reported in either publication. However, in a review by Yusuf 1988 it is reported (based on a personal communication between Yusuf and Jaffe) that the mortality rate was Nitroglycerin =4/57, and Placebo=2/57. We could not confirm this information.
Non-fatal SAE: NR
Individual SAE: NR
Blood Pressure:
Data was obtained from graphs in fig 1, page 455.
The calculated weighted mean BP change during first 24 hours was:
Nitroglycerine (n=43): SBP-9.63±NR; DBP-8.67±NR
Placebo (n=42): SBP-8.9±NR; DBP-8.7±NR
Standard deviation of change was not reported
Heart rate: NR

Notes
Funding: National Institutes of Health

Johannessen 1987

Methods
Single-site study (Norway)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 10 days
Follow-up: 10 days
Participants

40 patients within 6 hours after onset of symptoms of AMI
Inclusion criteria: Any age if admitted to the hospital within 6 hours after onset of symptoms of a suspected first myocardial infarction* and with an ECG indicating anterior location.
*Diagnosis of AMI was based on a standard 12 lead ECG with new ST segment elevation > 1 mm in lead I and aVL or more than 2 mm in precordial leads.

Exclusion criteria: Heart rate below 50 bpm, SBP < 100 mm Hg, clinical signs of left ventricular failure, bronchial obstruction or any degree of heart block; patients on digitalis B-blockers, calcium antagonists or other cardioactive drugs

Attrition data: Screened: NR, Total randomized patients: 40, Timolol: n= 20, Placebo : n=20
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: NR

Baseline characteristics:
Except for heart rate and other specialized cardiac indexes, the baseline characteristics were not reported
Heart rate: Timolol: 77 ± 15, Placebo: 82 ± 14

Interventions

Timolol vs. Placebo

Drug regimen:
Timolol: 1 mg IV bolus, repeated after 10 minutes. Then, an infusion of 0.6 mg / hour for 24 hours; followed by oral timolol 10 mg bid for 10 days
Placebo: Isotonic saline as placebo and placebo tablets. No further details

Other interventions:
Concomitant treatment which was thought to influence contractility was avoided. Furosemide, oxygen, morphine, and propoxyphene were allowed. All patients ventricular thrombus were treated with oral warfarin.
Mean dose of furosemide during the first 4 days (mg/day):
Timolol group: 58±30
Placebo group: 50.5±60
Outcomes
Mortality: obtained from text, page 153
Timolol: 2day:1/20 ; 10day:2/20
Placebo: 2day:0/20 ; 10day:0/20
Total non-fatal SAE: NR
Blood Pressure change within first 24 hours: NR
Heart rate change within first 24 hours: NR

Notes
Funding: NR
Dates of conducting the trial : NR

Jugdutt 1983

Methods
Single-site study (Canada)
Open-label
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 24
Follow-up: 12 days

Participants
22 patients with first anterior, transmural AMI within 6 hr of onset
Inclusion criteria:
Patients needed to have adequate 2D-echo examination.
Exclusion criteria:
Patients with heart block or cardiogenic shock or history of past infarction or heart failure.
Baseline characteristics for the two randomized groups:
Nitroglycerin (N): n=11
Control (C): n=11
Continuous values are expressed as mean ± SE
Age(years)
N: 59±3
C:54±4
Onset of pain to admission ( hours)
N: 3±0.3
C: 2.7±0.7
Onset of pain to infusion ( hours)
N: 5.9±0.4
C: 5.4±0.3
History of hypertension (n)
N: 2
C: 1
SBP(mmHg)
N: 130±6
C: 129±6
DBP(mmHg)
N: 82±3
C: 83±4

Interventions
Nitroglycerin vs. Control
Drug regimen:
N: nitroglycerin IV infusion at initial rate of 5 mcg /min and increased by 5 to 20 mcg/min every 5 min in the first 30 min until MAP was reduced by 10 % ot its control value but not less than 80 mm Hg. The infusion was maintained for at least 24 hours.
C: control patients receive 5% dextrose at constant rate of 1 ml/min for 24 hours.
The average dose to lower MAP by 10 % was 29± 6 mcg/min and was achieve within 30 min.
The average duration of infusion was 38.8 ± 4 hours
Other interventions:
All patients received nasal oxygen and intravenous morphine and were continued on lidocaine infusion ( 1 mg/min) throughout the study treatment.
N: 2 patients received furosemide and digoxin
C: 7 patients received furosemide and 2 digoxin.

Outcomes
Mortality: obtained from table 1, page 1267
Nitroglycerin, n= 11: 2day: 0; 10day: 1; eof( ): N/A
Control, n=11: 2day: 0; 10day: 2; eof( ): N/A
Non-fatal SAE: obtained from page 1269
Nitroglycerin, n= 11: 0
Control, n=11: 2 (1 acute ventricular septal defect, 1 left ventricular failure)

Blood Pressure;
Data was reported as MAP over time. It was not possible to extract SBP or DBP data

Heart rate:
Data was obtained from graph in fig 2 page 1268.
The calculated weighted mean HR change was:
Nitroglycerin (n=11): 1±13
Placebo (n=11): 3±24
Standard deviation of change was not reported but imputed from end point

Notes
Funding: Canadian Heart Foundation and Special Services of the
University of Alberta Hospital

**Jugdutt 1988**

**Methods**
- Single-site study (Canada)
- Single-blind
- Method of randomization: NR
- Concealment of allocation: NR
- Duration of treatment: 48 hours
- Follow-up: 43 months

**Participants**
- 310 patients with acute myocardial infarction within 12 hours of onset.
- **IC:** Patients with AMI (ECG 0.2 mV in two adjacent precordial leads, enzymes, clinical pain), SBP >100 mm Hg, HR < 120 bpm and within 12 hours of onset.
- **EC:** >75 years, HR < 55, bpm, killip 4, >200/120, right ventricular infarction syndrome.
- Baseline characteristics for the two randomized groups:
  - Nitroglycerin (N): n= 154
  - Placebo (P): n= 156
- Continuous values are expressed as mean ± SD
  - Age:(years)
    - N:59±14
    - P:62±13
  - Male/female
    - N:120/34
    - P:115/41
  - SBP:(mmHg)
    - N:135±22
    - P:130±22
  - DBP:(mmHg)
    - N:88±18
    - P:84±18
  - MAP:(mmHg)
    - N:104±18
    - P:100±18

**Interventions**
- Nitroglycerin vs Placebo
- **Drug regimen:**
  - **N:** Intravenous infusion of nitroglycerin at initial dose of 5 mcg/min (upward titration up to reach target*)
  - **P:** Placebo (IV 5% dextrose) no further details
*The Targets were to reduce either:
10-30% LVFP reduction (but not more than 10% in MBP reduction)
10% SBP reduction (but not below 90 mmHg or 50 bpm HR increase)
10% MBP reduction (but SBP not below 90 mmHg)
10% MBP reduction (but MBP not below 80 mmHg)
Treatment started within 4 hours in 22% of patients, 6 hour (43%),
10 hours (73%).
Treatment lasted 48 hours (mean 39 hours) after randomization.
Mean dose administrated: NR
The mean dose of nitroglycerin to achieve target was 45 mcg/min
(range 4-192 mcg/min)
Co-interventions: during the first 48 hours all patients received
nasal oxygen, iv morphine, continuous lidocaine (1mg/min).
Thrombolysis was not mentioned.
Acute in-hospital phase:
Nitroglycerin group: anti-arrhythmics 82, digoxin 38, furosemide
53, ibuprophen 21, beta-blockers 24, calcium channel blockers 11,
anticoagulants 13, anti-platelets 4.
Placebo group: anti-arrhythmics 76, digoxin 35, furosemide 54,
ibuprophen 23, beta-blockers 42*, calcium channel blockers 26*,
anticoagulants 9, anti-platelets 3.
* p< 0.005 significance of difference comparing placebo vs.
nitroglycerin groups.

**Outcomes**

Mortality: (reported on text, page 915)
Nitroglycerin, n=154: 2d:NR ; 10d:7 ; eof(43 m):36
Placebo n=156: 2d:NR ; 10d:29 ; eof(43 m):50
Note: There is a discrepancy, in terms of number of deaths and
number of patients randomized, between different publications of
this trial. For example, in-hospital deaths for nitroglycerin and
placebo were reported as 14/154 (9%) and 29/124 (23%)
respectively, in the abstract; but 22/154 (14%) and 41/156 (26 %),
respectively, in the full-paper publication.
Non-fatal SAE: NR
Blood Pressure;
Blood pressure data was reported as MAP (fig 1, page 910). There
is no extractable data for SBP or DBP. The calculated weighted
mean MAP change was:
Nitroglycerin (n=154): -15.09±12.87
Placebo (n=156): -8.89±12.87
Standard deviation of change was not reported but imputed from end point
Heart rate
Data was obtained from graphs fig 1 page 910.
The calculated weighted mean HR change was:
Nitroglycerin (n=154):1.05±14.31
Placebo (n=156): -1.3±15
Standard deviation of change was not reported but imputed from end point

Notes
Funding: Canadian Heart Foundation, Ottawa, Ontario, Canada;
By Alberta Heritage Foundation for Medical Research, Edmonton;
and by Special Services of the University of Alberta Hospital.

Limburg 1990

Methods
Single-site study (Netherlands)
Double-blind
Method of randomization: randomization tables by manufacturer
Concealment of allocation: NR
Duration of treatment: 14
Follow-up: 6 months

Participants
26 patients within 24 hours after onset of symptoms of acute stroke
Inclusion criteria: Supratentorial ischemic stroke with hemiparesis
Exclusion criteria: Lacunar syndromes, serious underlying diseases, previous disabling strokes, using CCB, not being able to start within 24 hours
Attrition data: screened/excluded at: NR
Total randomized patients: Flunarizine : n= 12, Placebo : n= 14
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: NR
Baseline characteristics:
Median Age, years (range): Flunarizine (F): 66 (56-84), Placebo (P): 67.5 (22-89)
Sex m/f : F: 3/9, P: 6/8
SBP/DBP (mm Hg) : NR

Interventions
Flunarizine vs. Placebo
Drug regimen:
Flunarizine: as an IV bolus of 0.1mg/kg in 5% glucose solution,
followed after 3 h by a continuous infusion of 0.3 mg/kg/24 h during 72 hours. Subsequently the drug was administered orally during 11 days as 10 mg/ day
Placebo: inert vehicle administered similarly
Other interventions: NR

Outcomes
Mortality: obtained from text, page 121, and table 2, page 122: total =8
Flunarizine: 2day: NR; 10day (7d):2/12; eof (6 m-N/A): 3/12
Placebo: 2day: NR; 10day (7d):4/14; eof (6 m-N/A): 5/14
Total non-fatal SAE: NR
Individual SAE: NR
Blood Pressure data: NR
Heart rate data: NR

Notes
Funding: Janssen Pharmaceutica, Tilburg, The Netherlands

Lis 1984
Methods
Multi-centre (2 in Uk).
Double blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 48 hours
Follow-up: 4 months

Participants
140 patients with clinical and electrocardiographic evidence of myocardial infarction occurring within 24 hours of admission.
Exclusion Criteria
Isolated peripheral hypoperfusion, outside 30-75 years range, SBP?95 mm Hg, HR< 50 or >130 bpm, heart disease other than CAD, already receiving vasodilators, and symptoms > 12 hour prior to admission.
Total withdrawals: (discontinuation of drug)
Nitroglycerin (n=64): 17 - 12 due to hypotension, 1 ventricular fibrillation, 1 due to SVT, 3 phlebitis.
Placebo (n=76): 8 - 4 due to hypotension, 1 cardiac arrest, 1 heart block, 2 phlebitis.
Total lost of follow-up: attendance at the 4-month follow-up was 77%.
Baseline characteristics for the two randomized groups:
Nitroglycerin (N): n= 64
Placebo (P): n= 76
Age (years): NR
Mean SBP (mmHg):
N: 129
P: 136
Mean DBP (mmHg):
N: 83.8
P: 85.5

**Interventions**

Nitroglycerin (N): n= 64
Placebo (P): n= 76
Drug regimen:
N: Intravenous nitroglycerin infusion of 10 mcg/min (adjusted according to hemodynamic target*).
P: placebo (10% ethanol solution), no further details
* bp target:
  - If initial SBP was > 135 = the aim was reduction of 30 mm Hg
  - If initial SBP was 124-134 = the aim was reduction of 15 mm Hg
  - If initial SBP was 95-119 = the aim was reduction of 5 mm Hg
Mean nitroglycerin dose administrated during the first 24 h was 70 mcg/min

**Outcomes**

Mortality: (reported on text, and table 1, page 181)
Nitroglycerin, n= 64: 2day: NR; 10day: 3; eof(4m): 5
Placebo, n= 76: 2day: NR; 10day: 6; eof(4m): 10

Note: The total deaths at day 10 reported in the original publication by Lis 1984 was 9. But, the distribution of these 9 deaths according to the allocation group was not reported.

However, in Yusuf 1988 meta-analysis the distribution at day 10 was reported as 3 for nitroglycerin and 6 for placebo. Giving the benefit of doubt we decided to keep those numbers as reported in Yusuf 1988. We also decided to keep that distribution since it was proportional to that reported in the original publication for the end of follow-up. Thus, it should not affect the overall effect size

Non-fatal SAE: NR
Individual SAE: NR (page )
Ventricular fibrillation:
Nitroglycerin, n= 64: 1
Placebo, n= 76: 0

Blood Pressure;
Data was obtained from graphs in figure 1 page 181.
The calculated weighted mean BP change was:
Nitroglycerin (n= 64): SBP-17.64±13.2; DBP-9.68 ±9.99
Placebo (n=76): SBP-11.53±17.76; DBP-6.51 ±12.21
Standard deviation of change was not reported but imputed from end point
Heart rate
Data was obtained from graphs in figure 1 page 181.
The calculated weighted mean HR change was:
Nitroglycerin (n= 64): 6.30±13.3
Placebo (n=76): 1.3 ±16
Standard deviation of change was not reported but imputed from end point

Notes
Funding: Not Reported

Marangelli 2000
Methods
Multi-centre (10 in Italy)
Double-blind
Method of randomization: computer software
Concealment of allocation: central coordinating center
Duration of treatment: 24 hours
Follow-up: 90 days

Participants
90 patients within 4 hours after onset of symptoms of their first acute anterior myocardial infarction who already had given a thrombolytic treatment.
Inclusion criteria: AMI defined as typical chest pain lasting > 30 min unresponsive to sublingual trinitroglycerin, with electrocardiographic signs of ongoing myocardial infarction (ST segment elevation > 0.1 mV in leads D1 and aVL and or > 0.2 mV in two or more precordial leads from Vi-V6). Killip class I, with technically excellent two-dimensional digital echocardiograms (defined as a stop-frame identifying > 85% of the endocardial border).
Exclusion criteria: Age > 75 years, pre-existing heart failure, previous MI, coronary surgery or angioplasty in the 6 months preceding the infarction, significant valvular disease, cardiomyopathy, congenital heart disease, contraindications to thrombolytics or heparin, killip class > 1 signs of hypoperfusion; heart rate < 60 b/min, SBP < 100 mm Hg, arrhythmias, refuse to give consent, chronic obstructive pulmonary disease, obesity, pacemaker.
Attrition data: Total randomized patients: 90, Verapamil (V): n=44, Placebo (P): n=44
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost of follow-up: 2 (not available for analysis, no further details)

Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Age (years) V: 55.8 ±9.7, P: 57.8±10.6
SBP (mm Hg): NR
Time to treatment (min): V:169 ±65, P: 141±83
Time to thrombolysis (min): V:178±68, P: 153±80

Medical history:
Verapamil: hypertension 15, diabetes 12, smoke 24, hypercholesterolemia 8, angina 26
Placebo: hypertension 16, diabetes 8, smoke 22, hypercholesterolemia 12, angina 28

Interventions
Verapamil vs. Placebo
Drug regimen:
Verapamil: 5 mg iv bolus follow by an infusion of 2 mcg/kg/min over 24 hours. This treatment was started before beginning thrombolytic therapy
Placebo: identical (in appearance) to verapamil formulation

Other interventions:
All patients received thrombolysis: tissue-type plasminogen activator-rt-PA (15 mg IV bolus followed by an infusion of 0.75 mg/kg up to a maximum of 50 mg over 30 min, and a further infusion of 0.50 mg/kg up to a maximum of 35 mg over 60 min); Heparin 500 IU IV bolus, followed by an infusion of 1000 IU/hour (1200 IU/hour in >80 kg patients); and aspirin 160 -325 mg / day.
Verapamil group: ACEi 26, beta-blockers 9, CCB 3, nitrates 20, diuretics 13, cortisone 1.
Placebo group: ACEi 27, beta-blockers 15, CCB 7, nitrates 26, diuretics 19, cortisone 0

Outcomes
Mortality: obtained it from text, page 340
Verapamil: 2day:NR; 10day (Hospital):1/44; eof (90 days):NR
Placebo: 2day:NR; 10day (Hospital):0/44; eof (90 days):NR
Total non-fatal SAE: NR
Blood Pressure change during first 24 hours: NR
Heart rate change during first 24 hours: NR

Notes
Funding: NR
Dates of conducting the trial: March 1995-May 1995

MIAMI 1985

Methods
Multi-centre (104-International )
Double-blind
Method of randomization: computer generated number
Concealment of allocation: number coded sealed envelopes
Duration of treatment: 15
Follow-up: 15

Participants
5778 patients within 24 hours after onset of symptoms of suspected AMI

Inclusion criteria: Men and women 75 years old or less with chest pain of acute onset and suspicion of acute myocardial infarction of at least 15 min of duration, ECG signs and symptoms indicating AMI* within the last 24 hours.

* AMI was diagnosed if 2/3 criteria fulfilled: 1) chest pain with a duration of at least 15 minues; 2) two values above the normal range for enzymes and; 3) appearance of new Q waves or loss of R waves or ST-segment elevation followed by T-wave inversion in at least 2 electrodes in a 12-lead standard ECG.

Exclusion criteria: current treatment with beta blockers or CCB within 48 hours , HR less than 65 bpm, SBP less than 105 mm Hg, left ventricular heart failure, signs of poor peripheral circulation, 2 or 3 degree AV block, other serious diseases influencing short-term prognosis.

Attrition data: Screened: NR, total randomized patients: 5778,
Metoprolol : n= 2877, Placebo : n= 2901
Total withdrawals (discontinuation of drug): Metoprolol: 441 (15.3%), Placebo : 401 (13.8%)
Withdrawals due to adverse events: Metoprolol: 373 (13 %), Placebo : 214 (7.4%)
Total lost to follow-up: 2, Metoprolol : 0, Placebo : 2
Baseline characteristics:
Note: continuous variables are expressed as median
Age (years): Metoprolol (M): 60, Placebo (P): 60
Gender male/female (%): Metoprolol (M): 78/22, Placebo (P): 77.2/22.8
Time to treatment: (hours): M: 6.8, P: 6.5
Heart rate: M: 80, P: 80
SBP (mm Hg): M: 140, P: 140
No. of patients with AMI; other diagnosis (%)
Metoprolol (M): 2041 (71%); 836 (29%)
Placebo (P): 2017 (69.5%); 883 (30.5%)
Patients with AMI: anterior; inferior; other (%)
Metoprolol (M): 974 (48%); 786 (38%); 281 (14%)
Placebo (P): 958 (47%); 800 (40%); 259 (13%)
Medical history (%)
Metoprolol group: previous infarction 459 (16.0), angina pectoris (27.7), congestive heart failure (3.9), hypertension (13.6), diabetes (6.7), smokers (50.6)
Placebo group: previous infarction 467 (16.1), angina pectoris (29.5), congestive heart failure (3.6), hypertension (14.1), diabetes (7.6), smokers (52.1)

**Interventions**

Metoprolol vs. Placebo

Drug regimen:
Metoprolol: 5 mg x 3 IV bolus with a 2-minute intervals (HR should be > 49 bpm, and SBP > 99 mm Hg and dyspnea or cold sweating not worsening); then 100 mg orally every 6 hours for 2 days, and then 200 mg every 12 hours for 13 or 14 additional days.
Placebo: no further details

Other interventions:
The general management of patients was according to local practice. Other B-blockers were not allowed. Thrombolysis was not reported

Metoprolol group: antiarrhythmic 552 (19.2%), cardiac glycosides 391 (13.6%)*, diuretics 1233 (42.9%), narcotic analgesics 1269 (44.1%)*, nitrates 1527 (53.1%), CCB 252 (8.8%)*, atropine 205 (7.1%)*, sympathomimetics 163 (5.7%)
Placebo group: antiarrhythmic 624 (21.5%), cardiac glycosides 482 (16.6%)*, diuretics 1206 (41.6%), narcotic analgesics 1431 (49.4%)*, nitrates 55.3 (1602%), CCB 343 (11.8%)*, atropine 135 (4.7%)*, sympathomimetics 121 (4.2%)
* p<0.001
**Outcomes**

Mortality: obtained from figure 1, page 204

Metoprolol (n=2877): 2day:29 (0.01) ; 10day:100 (0.035) ; eof(15 days): 123 (0.043)

Placebo (n=2901): 2day:41 (0.014) ; 10day:110 (0.038) ; eof(15 days): 142 (0.049)

Total non-fatal SAE: NR

Blood Pressure change during first 24 hours: NR

Heart rate change during first 24 hours: NR

**Notes**

Funding: the funding source is not reported but trial medication was supplied by Astra Co,

Dates of conducting the trial: November 1982 - March 1984

**MILIS 1984**

**Methods**

Multi-centre (5-USA)

Single-blind

Method of randomization: NR

Concealment of allocation: NR

Duration of treatment: 10 days

Follow-up: 36 months

**Participants**

269 patients within 18 hours after onset of symptoms of AMI

Inclusion criteria: Less than 76 years, typical chest pain for more than 30 min, ECG new Q waves, >0.1 mv ST elevation, or depression or both, or LBBB, OR idioventricular rhythm.

Exclusion criteria: Less than 18 years, pregnant, cardiogenic shock, serious illness, pacemaker, AMI within 2 weeks, receiving nitrates or BB that could not be discontinued for more than 72 hours. Contraindications to BB

Attrition data: Screened: 7597, Not eligible for this trial 6,718, Of those eligible (n=879, group A), 178 were excluded for physician refusal, 140 for patient refusal and 161 other reasons. (total excluded=479)

Total randomized patients: 400

Propranolol: n= 134

Placebo : n= 135

Hyaluronidase: n=131*

* this group will not be considered any further
Baseline characteristics:
Mean Age (years): Propranolol (P): 54.9, Placebo (Pbo): 54.6
Male (%): P: 72.4, Pbo: 74.1
Location of ischemia/infarction: anterior, inferior, other
Propranolol (P): 54.5%, 40.9%, 4.6%
Placebo (Pbo): 61.7%, 35.3%, 3%
ECG findings
P: LBBB 0.8%, ST elevation 82.6%, ST depression 13.6%
Pbo: LBBB 1.5%, ST elevation 84.2%, ST depression 12.8%

Mean time between onset and treatment (hr) P: 8.5, Pbo: 9.3
Mean HR (bpm): P: 79.6, Pbo: 81.3
BP : NR

Medical hx
Propranolol group:
Smokers (47%), higher education (62%), Regular drinkers (18.1%) HTN (50.8%), PREVIOUS AMI (14.9%), angina(42.5%), CHF (3%), diabetes (20.2%), previous cardiac arrest (1.5%), previous cardiac surgery (3.7%), arrhythmias (7.5%),
Placebo :
Smokers (53%), higher education (60.6%), Regular drinkers (24.2%) HTN (37%), PREVIOUS AMI (14.1%), angina(35.6%), CHF (6.7%), diabetes (18.5%), previous cardiac arrest (0.0%), previous cardiac surgery (5.9%), arrhythmias (7.4%)

Interventions
Propranolol vs. Placebo
Drug regimen:
Propranolol: 0.1 mg/kg over 6 minutes, after 3 hours a second bolus of 0.025 mg/kg. Then, after 3 more hours oral propranolol was given at a dose of 20 mg to up to 600 mg/per day (to keep HR between 45 and 60 bpm and SBP > 90 mm Hg). Treatment continued for 7 days, and then tapered to one half during the 8th and 9th days and discontinued on the 10th day
Placebo: No further details

Other interventions:
Medication within 3 weeks
Propranolol group:
Beta-blockers (24.6%), nitrates(17.9%), sl. nitroglycerin (23.1%), anti-arrhythmics (3%), anticoagulants (0%), digoxin (9.7%), diuretics (29.9%), oral hypoglycemics (4.5%)
Placebo group:
Beta-blockers (17.8%), nitrates(17%), sl. nitroglycerin (20%), anti-arrythmics (1.5%), anticoagulants (3%), digoxin (7.4%), diuretics (18.5%), oral hypoglycemics (2.2%)

Outcomes
Mortality:
Propranolol group:
2day: NR
10day: 4/134 (obtained from table 1, page 40F (Am J Cardio; 57)
eof( at 36 months): 24/134 (obtained from text, (NEJM 1984; 311: p.221)

Placebo group:
2day: NR
10day: 8*/135 ( *The total, in-hospital or 1-month, deaths for both groups was 12 [NEJM 1984; 311: p.223]. If 4 deaths occurred in the propranolol group (Am J Cardio 1986; 57:38F-42F) It is assumed that the remaining 8 deaths occurred in the placebo group)
eof( at 36 months): 20/135 (obtained from text, (NEJM 1984; 311: p.221)

Total non-fatal SAE: NR
Blood Pressure: NR during first 24 hours
Heart rate: NR during first 24 hours

Notes
Funding: Ayerst Laboratories
Dates of conducting the trial : August 1 1978- February 1, 1983

Mitchell 2002
Methods
Multi-centre (21-USA)
Open-label
Method of randomization: computer-driven response system and generation list. Randomization was stratified by type of ischemic syndrome.
Concealment of allocation: telephone system ensured proper sequence allocation, providing security against potential randomization bias.
Duration of treatment: up to 36 hours
Follow-up: 6 weeks

Participants
108 patients within 12 hours after onset of symptoms of AMI
Inclusion criteria: Acute transmural myocardial infarction, TMMI, (ie, ST elevation) or unstable angina/non-Q-wave myocardial infarction (UA/NQW). Having at least one B-blockade relative contraindication such as left ventricular dysfunction, mild congestive heart failure, history of bronchospastic airway disease (without bronchospasm), prolonged ECG-PR interval, controlled diabetes mellitus, hypotension (SBP >100 mm Hg) bradycardia (>55 bpm), concomitant AV node-blocking CCB- diltiazem verapamil).

^TMMI was defined as angina type chest pain of > 20 minutes duration, unresponsive to sublingual nitroglycerin and ST elevation of > 10 mm in at least 2 of the 3 inferior leads (II, III, avF) or in at least 2 contiguous precordial leads (V1-V6) or in leads I, aVL. UA/NQW was defined as chest pain at least 5 minutes, unrelieved by sl nitroglycerin and either positive CK-MB or concomitant ST-depression (>0.5 mm). T-wave inversion of ? 1 mm or transient (< 20 minutes) ST segment elevation.

Exclusion criteria: Bradycardia (<55 bpm), hypotension (SBP < 100 mm Hg) , prolonged PR (>0.30 seconds), 2-3 degree AV block, severe congestive heart failure, acute bronchospastic episode, pregnancy; atrial fibrillation, wolff-parkinson-white syndrome, permanente ventricular pace makers, planned surgical revascularization, drug or alcohol abuse, serious advanced illness; receiving B-blockers within 24 hours, CCB within 48 hours.

Attrition data: Screened: NR, total randomized patients: 108, Esmolol: n= 55, No esmolol or Control group: n= 53 Total withdrawals (discontinuation of drug): 12 (all in esmolol group) Withdrawals due to adverse events: 12 (all in esmolol group- hypotension bronchospasm, AV block, bradycardia) Total lost to follow-up: NR Baseline characteristics: Mean age in years (range): Esmolol (E): 58.1 (31.7-88.3), No esmolol or Control group (X): 60.4 (35-84.4). Male: E: 26%, X: 40% Race: white, black, other (%): E: 35, 18, 2 ; X: 35,11,7 Heart rate, bpm, (range) E: 81.0 (58-125), X :78.7 (56-109)
SBP (mm Hg): E: 128.1 (95-200), X: 130.7 (97-197)
ECG criteria: ST elevation, non-ST elevation (%): E: 23, 32; X: 21, 32

**Interventions**

Esmolol vs. Control group (no esmolol group)

Drug regimen:
- Esmolol: 500 mcg/kg IV over 1 minute. Followed by infusion of 50 mcg/kg/min (titration in increments of 50 mcg/kg/min every 5 to 15 minutes) 10 mcg/min* for 16 to 30 hours^; 30 minutes before discontinuation oral metoprolol was started (12.5 to 100 mg for 6 weeks
- No esmolol or Control group: received the standard medical therapy but no IV beta-blocker or Oral beta-blockers during the first 24 hours. Then, oral metoprolol (12.5 to 100 mg) was started and continued for minimum of 6 weeks.
  - ^ until a peak dose of 300 mcg/kg/min or end safety point (developing of new rales, pulmonary edema, 2-3 degree AV block, shock, bronchospastic episode.

Other interventions:
- All patients received standard medical therapy (including thrombolytic therapy, intravenous heparin, aspirin, nitrates, narcotics), Oral verapamil or diltiazem were allowed only to the control group but other CCB were used in esmolol group (12 pts) and in the Control group (9 pts)

**Outcomes**

Mortality: obtained from table II, page 110
- Esmolol group (E)
  - At 2day: NR; 10day (in hospital): 2/55; eof(6 weeks): 2/55
- No esmolol or Control group (X)
  - At: 2day: ; 10day (in hospital): 1/53; eof(6 weeks): 1/53
- Total non-fatal SAE: NR
- Blood Pressure change in first 24: NR
- Heart rate change in first 24: NR

**Notes**

Funding: Not stated, but Baxter Pharmaceutical Products Inc, New Providence, NJ, provided the study medication

Dates of conducting the trial: 1975

**Muller 1984**

**Methods**

Multi-centre (6-US)
- Double-blind
- Method of randomization: NR
- Concealment of allocation: NR
Duration of treatment: 14
Follow-up: 6 months

Participants
181 patients within 6 hours after onset of a threatened AMI
Inclusion criteria: Diagnosis was based on chest pain for more
than 45 minutes and new or presumably new ST segment elevation
or depression of at least 0.1 mV or new Q waves of at least 30
msec width and 0.2 mV depth in at least two of three
diaphragmatic leads (II,III, aVF) or at least two of six precordial
leads, or in I and aVL.
Exclusion criteria: Left bundle branch block, younger than 21 or
older than 80 years, SBP < 110 mmHg, previous major illnesses,
CABG or AMI (within 21 days), childbearing potential, inability
to cooperate, previous participation in trial.
Attrition data: Total screened: 3143, total randomized patients:
181, Nifedipine (N): n=93, Placebo (P): n= 88
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: Nifedipine: 15/93, Placebo : 13/88
Total lost of follow-up: NR
Baseline characteristics:
Except for mortality, baseline and all results are given as per
protocol, not as per ITT.
According to per protocol there was Not significant difference
between the two groups in any variable. For example,
History of previous MI:
Nifedipine: 16/89 (18%)
Placebo: 14/82 (17%)

Interventions
Nifedipine vs. Placebo
Drug regimen:
Nifedipine: 2 capsules of 10mg (total 20 mg) every 4 hours for 14
days.
Placebo: two identical-appearing placebo capsules, no further
details.
Therapy was reduced to 10 mg or eliminated if severe adverse
effects. For example, SBP < 85; or 30 mm Hg of more from
baseline.
Other interventions:
In general nitrates and b-blocking drugs would be avoided. For
patients with threatened MI could receive them 24 or more hours
after the qualifying episode of angina.

**Outcomes**

Mortality: obtained it from table 4, page 744
Nifedipine: 2day: NR ; 10day (14 day):7/93 ; eof: not aplicable
Placebo: 2day: NR ; 10day (14 day):2/88 ; eof: not aplicable
Total non-fatal SAE: NR
Blood Pressure data on first 24 hours: NR
Heart rate data on first 24 hours: NR

**Notes**

Funding: Pfizer Pharmaceuticals Inc., New York. NY.
Dates of conducting the trial: initiated in 1979

**Nabel 1991**

**Methods**

Single-site study (US)
Double-blind
Method of randomization: performed by the manufacturer by a four block-size randomization code
Concealment of allocation: All participants (patients, physicians nurses and pharmacist) had no information on the study medication. Code was broken after all data were collected
Duration of treatment: 3 months
Follow-up: 3 months

**Participants**

38 patients within 6 hours after onset of symptoms of AMI

Exclusion criteria:
Chest pain relieved by nitroglycerin, less than 20 min, age >75, contraindication to thrombolytic or captopril, SBP / DBP > 180 / 110 mm Hg, current therapy with cytotoxic drugs or serious advance illness, pregnancy , prior Q wave infarction.

Attrition data: Screened: NR, Total randomized patients: 38,
Captopril: n= 20, Placebo : n= 18
Total withdrawals (discontinuation of drug): 1 captopril
Withdrawals due to adverse events: 1 from captopril group ( due to hypotension SBP < 85 mm Hg)
Total lost to follow-up: NR
Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Age (years) : Captopril (C): 52.9 ± 13, Placebo (P): 56.4± 10
Gender M/ F: C:19/1, P:12/6,
Time to rt-PA (hours): C: 3 ± 1.8, P: 3 ± 1.3
SBP/ DBP (mm Hg) NR
Interventions

Captopril vs. Placebo

Drug regimen: initially, intravenous captopril, 2 mg, over 1 min. Then, additional 8 mg (if SBP > 85 mm Hg, after 2 minutes). Then, 3 to 4 hours after, oral treatment 12.5 mg twice and titrated up to 25 and 50 mg bid. If tolerated. Continuing medication for 3 months.

Placebo: No further details

Other interventions: given according to group (%):

Captopril group: beta-blockers 5 (25), CCB 6 (30), diuretics 3 (15), anti-arrhythmic 1 (5), nitrates 9 (45),

Placebo group: beta-blockers 8 (44), CCB 5 (28), diuretics 1(6), anti-arrhythmic 0(0), nitrates 9 (50).

Outcomes

Mortality: obtained from text, page 470

Captopril: 2day: NR; 10day: 0/20; eof(3 months): N/A

Placebo: 2day: NR; 10day: 1/18; eof(3 months): N/A

Total non-fatal SAE: NR

Blood Pressure change during first 24 hours: NR

Heart rate change during first 24 hours: NR

Notes

Funding: Bristol-Myers Squibb
Dates of conducting the trial: March 1988 and May 1989

Natale 1999

Methods

Single-site study (Italy)
Double-blind

Method of randomization: a list by sets of 10 (5 for verapamil and 5 for placebo), no further details

Concealment of allocation: NR

Duration of treatment: 6 months

Follow-up: 6 months

Participants

70 patients within 12 hours after onset of symptoms of the first anterior acute MI who did received IV thrombolytic treatment within 6 h of onset.

Inclusion criteria: Aged 18-75 years, good echocardiographic window. diagnosis of AMI was based on typical pain lasting ? 30 minutes and ST-segment elevation ? 1 mm in at least two contiguous precordial leads and or in DI and aVL.

Exclusion criteria: Overt heart failure, ejection fraction < 45%,
SBP < 90 mm Hg, second or third-degree AV block or SA block, left ventricular hypertrophy, congenital or valvular heart disease, liver or kidney failure, treatment with BB or CCB on admission, inability to take part in the study

Attrition data: Total randomized patients: 70, Verapamil: n= 35, Placebo: n=35
Total withdrawals (discontinuation of drug): 24, Verapamil: 14, Placebo: 10
Withdrawals due to adverse events: 11 (not reported according to randomization group)
Total lost of follow-up: 0

Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Age (years): Verapamil (V): 60 ± 10.6, (26-74, range); Placebo (P): 56±9.1, (39-73, range)
Males/females: V: 30/5, P: 30/5
Pre-thrombolysis time (hours): V: 2.8 ±1.5, P: 2.5 ±1.1
SBP (mm Hg): V: 136±19, P: 137±24
DBP (mm Hg): V: 80±13, P: 83±14
HR (bpm): V: 77±13, P: 76±13

Medical history:
Verapamil: Smokers 15, diabetes 4, hyperlipidaemia 9, hypertension 14, ischemic heart disease 9, angina 9, PTCA 1.
Placebo: Smokers 25*, diabetes 3, hyperlipidaemia 6, hypertension 10, ischemic heart disease 14, angina 8, PTCA 0

Interventions
Verapamil vs. Placebo
Drug regimen:
Verapamil: 5 mg / hour IV infusion for 24 hours, followed by oral administration of verapamil retard 120 mg t.i.d. for 6 months
Placebo: placebo, no further details
Other interventions:
All patients received IV accelerated recombinant tissue-type plasminogen activator (100 mg). BB or other CCB was not permitted.

Outcomes
Mortality: obtained from text, page 318
Verapamil: 2day: NR ; 10day: 2 (before discharged) ; eof: not applicable
Placebo: 2day:NR ; 10day: 0 (before discharged) ; eof: not applicable
Total non-fatal SAE: NR

Blood Pressure;
Data was obtained from graphs in Fig 1, page 320.
The mean BP change during first 24 hours (up to hour 24) was:
Verapamil (n=35): SBP= -15.40 ±14; DBP= -9.53 ± 9.35
Placebo (n=35): SBP= -12.59 ± 17.14; DBP= -9.05±12.47
Heart rate: not reported during up to the first 24 hours.

Notes
Funding: Not reported

Norris 1978
Methods
Single-site study (New Zealand)
Open-label
Method of randomization: NR
Concealment of allocation: by the envelope method
Duration of treatment: 27 hours
Follow-up: hospital stay

Participants
43 patients within 4 hours after onset of symptoms of AMI
Inclusion criteria: Men and women aged up to 65 admitted within
4 hours of the onset of AMI ( patients were subdivided into two
subcategories: Group 1-patients with ST-segment depression 1-3
mm in any lead or T-wave inversion without ST abnormalities.
Group 2- patients with normal ECG )
Exclusion criteria: Unstable angina (repeated attacks of pain over
the last days or weeks); patients with contraindications to
propranolol (history of cardiac failure, bronchial asthma, heart rate
< 60 bpm), taking b-blockers within 72 hours, CK elevation
caused by electrical defibrillation or muscular injections; patients
with ST-segment elevation > 2 mm in precordial leads and AVF;
pathological Q waves not due to a known previous infarct.

Attrition data: Screened: NR, total randomized patients: 43,
Propranolol: n= 20, No propranolol (control) group : n= 23
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: NR
Baseline characteristics:
Mean age, in years (range): Propranolol (P) :54 (45-65), No
propranolol (control) group (X) : 51(32-65)
Interventions

Propranolol vs. No propranolol (control) group

Drug regimen:
Propranolol: 0.1 mg/kg over 10 min followed by a total of 320 mg orally over the next 27 hours
Other interventions:
Oral furosemide or IV lignocaine were allowed.

Outcomes

Mortality: obtained from text, page 908
Propranolol: 2day: 0/20; 10day (hospital): 0/20
No propranolol (control) group 2day: 0/23; 10day (hospital): 0/23
Total non-fatal SAE: NR

Blood Pressure:
Data was obtained from figure 1, page 908.
The mean BP at end point (24 h) was:
Propranolol (n=20): SBP -21.95 ±17.88 ; DBP-11.69 ±14.22
Control (n=23): SBP -16.02 ±15.25 ; DBP -4.33 ± 15

Heart rate:
Data was obtained from figure 1, page 908.
The mean HR at end point (24 h) was:
Propranolol (n=20 ): -9.22 ±10.16
Control (n=23 ): 2.21 ±12

Notes

Funding: Medical Research Council, National Heart Foundation of New Zealand

Norris 1980

Methods

Two-site study (New Zealand)
Open-label
Method of randomization: NR
Concealment of allocation: by the envelope method
Duration of treatment: 27 hours
Follow-up: hospital stay

Participants

62 patients within 4 hours after onset of symptoms of AMI

Inclusion criteria: Men and women aged up to 65 admitted within 4 hours of the onset of AMI. No history of bronchial asthma, SBP > 100 mmHg, heart rate greater than 60 /min and without
breathlessness of basal rales.

Uncomplicated transmural infarction as evidence by a) typical history of prolonged chest pain with onset less than four hours previously and b) ST segment elevation in ECG greater than 2 mm in anterior chest leads, > 1 mm in II, III aVF or pathological Q waves.

Exclusion criteria: Patients who had had DC cardioversion (cardiac arrest), evidence of overt cardiac failure, hypotension, interstitial or pulmonary oedema
Attrition data: Screened: NR, total randomized patients: 62, Propranolol: n= 33, control (No propranolol) group : n= 29
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: NR
Baseline characteristics:
Mean age, in years (range): Propranolol (P) :51 (31-64), No propranolol (control) group (X) : 51(37-65)
Sex: M/ F: P: 31/ 2, X: 27/ 2
Position of the infarct : anterior, inferior, antero-inferior, subendocardial: P: 17, 13,0,3; X: 14,14,1,0,
History of previous infarction: NR
SBP/DBP (mm Hg): NR

**Interventions**
Propranolol vs. Control (No propranolol) group
Drug regimen:
Propranolol: 0.1 mg /kg over 10 min followed by a total of 320 mg orally over the next 27 hours (40 mg at one,3, 7 11, 15,19,23, 27 hours after entry to the trial ( before each oral dose, SBP should be > 100 mm Hg and HR > 50 bpm)
Other interventions:Oral furosemide or IV lignocaine were allowed.

**Outcomes**
Mortality: obtained from table 2, page 619
Propranolol: 2day: NR; 10day (in hospital): 1/33 ; eof: NR
No propranolol (control) group : 2day: NR; 10day (in hospital): 0/29 ; eof: NR
Total non-fatal SAE: NR
Blood Pressure change in first 24: NR
Heart rate change in first 24: NR
Notes
Funding: Medical Research Council, National Heart Foundation of New Zealand
Trial conducted between March 1977 and March 1979

Norris 1984

Methods
Multi-centre study (4, New Zealand)
Open-label
Method of randomization: NR
Concealment of allocation: by the envelope method
Duration of treatment: 27 hours
Follow-up: hospital stay

Participants
735 patients within 4 hours after onset of symptoms of AMI

Inclusion criteria: Patients under 70 years old within 4 hours of the onset of AMI (complaining of chest pain for more than 30 min), provided no contraindications to beta-blockers (bronchitis requiring bronchodilators, current treatment for cardiac failure, dyspnea or widespread chest rales, systolic blood pressure below 110 mm Hg or HR below 60 bpm.
Exclusion criteria: Delayed (more than 4 hours) and contraindications
Attrition data: Screened: NR, Total randomized patients: 735, Propranolol: n= 364, No propranolol (control) group: n= 371
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: NR
Baseline characteristics: (±SD)
Mean age, in years: Propranolol (P): 55 ± 9, No propranolol (control) group (X): 54 ± 10
Sex (M/ F): P: 299 / 65, X: 289 / 82
History of previous infarction P: 94 / 364 (25.8 %), X: 95 / 371 (25.6 %)
ECG findings on entry: pathological Q waves, ST-segment elevation, ST depression, T wave changes only, normal ECG
P: 69,165.32,47,106 (29%), X: 77,147,47,56,115 (31%)
SBP/DBP (mm Hg): Propranolol (P): 144 ± 24 / 91 ± 14, No propranolol (control) group (X): 145 ± 25 / 91 ± 15

Interventions
Propranolol vs. No propranolol (control) group
Drug regimen: Propranolol: 5-8 mg over 5 min followed by a total
of 320 mg orally over the next 27 hours (40 mg at one, 3, 7, 11, 15, 19, 23, 27 hours after entry to the trial (before each oral dose, SBP should be > 100 mm Hg and HR > 50 bpm). Note: mean dose given was 6.5 mg (IV), and 236 mg (oral).

Control group: If oral beta-blockers being taken at the time of entry to the trial they were usually continued during the acute phase of infarction.

Other interventions according to study groups:
Note: Oral furosemide or IV lignocaine were allowed.

Propranolol: Long-term beta blocker continued 0, morphine or other analgesic 193, diuretic 61, pressor agent 10, digoxin 16, lignocaine 66, atropine 25, pacemaker 6.

No propranolol (control) group: Long-term b-blocker continued 83, morphine or other analgesic 206, diuretic 50, pressor agent 8, digoxin 14, lignocaine 68, atropine 15, pacemaker 4

Outcomes
Mortality: obtained from text, page 885
Propranolol: 2day: NR; 10day (in hospital): 15/364; eof: NR
No propranolol (control) group: 2day: NR; 10day (in hospital): 14/371; eof: NR
Total non-fatal SAE: NR
Blood Pressure change during first 24 hours: NR
Heart rate change during first 24 hours: NR

Notes
Funding: Medical Research Council, National Heart Foundation of New Zealand
Trial conducted during May 1981 - March 1984

Owensby 1985
Methods
Single-site study (New Zealand)
Open-label
Method of randomization: Stratified according to timing of entrance (< 4 and > 4 hours), no further details.
Concealment of allocation: by sealed envelope method
Duration of treatment: 2 days
Follow-up: During hospital

Participants
100 patients within 12 hours after onset of symptoms of suspected AMI

Inclusion criteria:
Under 72 years, previously healthy and active, suspected of AMI*,
* typical symptoms, ECG S-T elevation > 1 mm at least one lead or evolving pathological Q waves.

Exclusion criteria:
Already receiving beta-blockers or contraindications (history of asthma, bracycardia < 60 bpm, AV block, clinical or radiographic evidence of cardiac failure.

Attrition data:
Screened: NR
Total randomized patients: 100
Pindolol: n= 50
No pindolol (control) : n= 50

Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: NR

Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Mean age in years (range)
Pindolol (P): 55.4 (28-71)
No pindolol or control (X): 54.4 (35-71)
Males, females
P: 38, 12
X: 42,11
Site of infarction: inferior, anterior, other
P: 28, 12, 10
X: 21,17, 12
Medical History
Pindolol (P):
smoking 40, Hypertension 13, IHD 12, previous AMI 4
No pindolol or control (X):
smoking 42, Hypertension 13, IHD 16, previous AMI 9
SBP/DBP (mm Hg)
Pindolol (P): 143.86 /89.44 ; 75.88
No pindolol or control (X): 140.20 / 89.93 ; 76.10

**Interventions**
Pindolol vs. No pindolol (control)
Drug regimen:
Pindolol: 3 mg IV over 15 minutes every 8 hours x 3, followed by 5 mg orally every 8 hours for 6 doses
No pindolol group or control group was manage identically as pindolol group (except for pindolol) with oxygen, anticoagulation (15,000-30,000 U/day) for five days, narcotic analgesics, sedatives, nitrate preparation, diuretic and anti-arrythmic agents if necessary.

Other interventions:
Pindolol group: morphine 22, nitrates 44, diuretics 20, anti-arrythmics 26, DC cardioversion 2
Control group: morphine 34, nitrates 45, diuretics 20, anti-arrythmics 24, DC cardioversion 3

Outcomes
Mortality: obtained from table 3, page 708
Pindolol: 2day: NR ; 10day (hospital):1/50 ; eof : N/A
No pindolol or control (X): 2day:10day (hosp):1/50 ; eof : N/A
Blood Pressure:
Data was obtained from fig 1, page 707.
The mean BP change during first 24 hours (20 h) was:
Pindolol (n=50): SBP-22.13 ±20.28 ; DBP-9.92 ±12.06
Control (n=50): SBP-13.06 ±22.92 ; DBP-10.89 ±13.94
Standard deviation of the change was not reported but imputed from end point

Heart rate:
Data was obtained from fig 1, page 707.
The mean HR change during first 24 hours (20 h) was:
Pindolol (n=50):-3.33 ±13.38
Control (n=50):-0.14 ±21.39
Standard deviation was not reported but imputed from end point

Notes
Funding: Not Reported (NR)
Dates of conducting the trial : NR

Paci 1989
Methods
Single-site study (Italy)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 28 days
Follow-up: 28 days

**Participants**
41 patients within 12 hours after onset of symptoms of stroke
Inclusion criteria: Sudden and persistent neurological deterioration due to a focal event in the carotid arterial distribution diagnosed as completed stroke, admitted to the hospital within 12 h after the onset of symptoms.
Exclusion criteria: Transient ischemic attack, progressing stroke and cerebral hemorrhage were excluded. Patient unable to give informed consent or who have severe systemic disorders, recent myocardial infarction, congestive heart failure, abnormal hepatic pulmonary or renal functions or history of previous stroke.
Attrition data: Screened: 54 (13 did not meet inclusion criteria, 4 TIA, 1 brain-stem infarction, 1 progressing stroke, 5 as capsular hemorrhage). 1 was excluded ?glioma, 1-dissection of aorta.
Total randomized patients: 41, Nimodipine: n= 19, Placebo : n= 22
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: Total NR ( one patient withdrew due to skin rash- nimodipine group)
Total lost to follow-up: NR
Baseline characteristics:
Female: Nimodipine (N): 8, Placebo (P): 5
Age (years): N: 62 ±5, P: 63±6
Stroke localization (left hemisphere) N: 11, P: 13
SBP (mm Hg): N: 156.4 ±4.9, P: 149.3±5.5
DBP (mm Hg): N: 94.7 ±2.9, P: 85.9±2.4
Medical history (%)
Nimodipine: diabetes 5, smoking 6, high-fat 11, alcohol abuse 2, hyperlipidemia 5
Placebo: diabetes 3, smoking 10, high-fat 9, alcohol abuse 1, hyperlipidemia 5

**Interventions**
Nimodipine vs.placebo
Drug regimen:
Nimodipine: 40 mg t.i.d orally for 28 days
Placebo: identical aspect and duration No further details
Other interventions:
All patients received standard treatment : 20% mannitol-100 ml t.i.d for 7 days, nursing, physiotherapy, and ethically necessary
drugs (mostly anti-hypertensive agents and antibiotics). Steroids, antiplatelet drugs, hyperosmolar agents, other calcium entry blockers and cerebral vasodilator were not administered.

**Outcomes**
Mortality: obtained from text, page 285
Nimodipine: 2day: 0; 10day:0; eof(28d-N/A):0
Placebo: 2day: 0; 10day:0; eof(28d-N/A):0
Total non-fatal SAE: NR
Blood Pressure; Not reported during / up to the first 24 hours of treatment
Heart rate: Not reported during / up to the first 24 hours of treatment

**Notes**
Funding: NR
Dates of conducting the trial: NR

**Peter 1978**

**Methods**
Single-site study (New Zealand)
Open-label
Method of randomization: Not Reported
Concealment of allocation: envelope method
Duration of treatment: 27 hours
Follow-up: in Hospital

**Participants**
95 patients within 12 hours after onset of symptoms of AMI

Inclusion criteria:
Moderate severity of AMI, within 12 hours of the onset of prolonged chest pain, ECG evidence of either epicardial injury (> 2 mm ST elevation in anterior leads or > 1 mm in II, III, aVf, or pathological Q waves, and no contraindications.

Exclusion criteria:
More than 65 years old, chest x-rays or signs of pulmonary edema, less than 60 bpm, AV block > 1st degree, had received BB within 72 hours, DC shock for ventricular arrhythmias, history of asthma.

Attrition data:
Screened: NR
Total randomized patients: 95
Propranolol: n= 47
no treatment (control) : n= 48
Note: cases were subdivided into three subgroups according to whether the pain started at 1) less than 4 hours, 2) 4-8 hours, or 3) 8-12 hours

Propranolol: n= 18, 17, 12
no treatment (control): n= 19, 17, 12
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR

Total lost to follow-up: NR

Baseline characteristics:
Age in years (range)
Propranolol (P): 54 (37-64)
no treatment or control (X): 54 (37-64)

Position of infarct: anterior, inferior, superior
P: 17, 25, 5
X: 21,23,4

Interventions
Propranolol vs. open control
Drug regimen:
Propranolol: 0.1 mg/kg IV bolus over 10 minutes, followed by 320 mg orally over the next 27 hours* (40 mg at 1,3,7,11,15,19,23,27 hours)
Control: No specific treatment
* Treatment was stopped if cardiac failure or AV block developed or HR < 50 bpm
Other interventions: oral furosemide and lidocaine were allowed as necessary.

Outcomes
Mortality: obtained from table 2, page 1092
Propranolol: 2day:NR ; 10day (hospital):1/47 ; eof (>30 d): NR
no treatment (control) 2day:NR ; 10day (hospital):2/48 ; eof (>30 d): NR
Blood Pressure:
Data was obtained from figure 2, page 1093.
The mean BP change during first 24 hours (up 24) was:
Propranolol (n=47): SBP -22.50±15; DBP-13.64 ±14
Control (n=48): SBP-7.50 ±17; DBP-3.29 ± 14
Standard deviation of the change was not reported but imputed from end point

Heart rate:
Data was obtained from , page .
The mean HR change during first 24 hours (x) was:
Propranolol (n= 47): -10.61± 13.71
Control (n= 48):-0.47 ±13.86
Standard deviation of the change was not reported but imputed from end point

Notes
Funding: Medical Research Council and the National Heart Foundation of New Zealand

Pimenta 1985
Methods
Single-site study (Brazil)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 3 days
Follow-up: 22 months

Participants
20 patients within 6 hours after onset of symptoms of AMI
Inclusion criteria: Clinic and ECG compatible with transmural AMI, aged < 75 years, free of heart failure, arrhythmias, A-V block.
Exclusion criteria: Receiving treatment with BB or other that might interfere with results
Attrition data: Screened: NR,
Total randomized patients: 20, Nifedipine, n= 10, Placebo, n= 10
Total withdrawals (discontinuation of drug): 2, Nifedipine: 2/10, Placebo: 0/10
Withdrawals due to adverse events: 2, Nifedipine: 2/10, Placebo: 0/10
Total lost of follow-up: 0
Baseline characteristics:
Age (years): Nifedipine (N): 57.5 ± 5.3, (51-69, range), Placebo (P): 52.4±9.84, (39-73, range)
Males/females: N: 7/3, P: 7/3
Time to treatment (hours) : V: 3.90 ±1.44, P: 3.44 ±1.13
SBP/ DBP (mm Hg): NR
HR (bpm): NR
Type of AMI: N: inferior 2, anterior 8, P: inferior 6, anterior 4

**Interventions**
Nifedipine vs. Placebo
Drug regimen:
Nifedipine: 10 mg / 6 hours for 72 hours, followed by nifedipine 30 mg/ day
Placebo: for 72 hours (no further details), followed by nifedipine 30 mg/ day
Other interventions:
All patients received opiaceos, oxygen (3-5 l/min) benzodiazepine drugs

**Outcomes**
Mortality: obtained it from text, page 11
Nifedipine: 2day: NR; 10day: 1/10 (acute phase); eof: (N/A)
Placebo: 2day: NR; 10day: 0/10 (acute phase); eof: (N/A)
Total non-fatal SAE: NR
Blood Pressure data during first 24 hours: NR
Heart rate data during first 24 hours: NR

**Notes**
Funding: Not reported

**Pizzetti 2001**

**Methods**
Single-site study (Italy)
Open-label
Method of randomization: randomization block (no further details)
Concealment of allocation: patients were blindly assigned (no further details)
Duration of treatment: 3 days
Follow-up: 6 months

**Participants**
90 patients within 3 hours after onset of symptoms of first AMI
Inclusion criteria: Age < 70 years, diagnosis of AMI was based on ST segment elevation (> 2 mm in at least 2 leads, lasting > 30 min and not responsive to nitrates), dyskinesia on echocardiography and increased CK levels; no contraindication to thrombolytic therapy, admission within 3 hours of symptom onset.
Exclusion criteria: Previous myocardial infarction, CABG, heart failure or cardiogenic shock, bradycardia ( < 50 bpm) AV block, sick sinus syndrome, < 100 SBP, and other cardiovascular or sever hepatic or renal disorders.
Attrition data: Screened 281, 191 excluded,
Total randomized patients: 90, Diltiazem (D) : n=43, Placebo (P):
n=47
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost of follow-up: NR
Baseline characteristics:
Age (years): Diltiazem (D):56±11, Placebo (P): 55 ±11
Sex (M/F): D: 27/16, P:39/8
BP (mm Hg) : NR
Time to thrombolysis (min): D: 123 ±63; P: 144 ±56
Anterior infarction: D: (56 %), P: (51 %)
Medical history (%)
Diltiazem: hypertension 22(51) diabetes 14(38),
Hypercholesterolemia 18 (42), smoking 28 (65)
Placebo: hypertension 20 (43) diabetes 17(36),
hypercholesterolemia 21 (43), smoking 35 (74)

Interventions  
Diltiazem vs. Placebo
Drug regimen:
diltiazem: 0.15mg/kg bolus, followed by an infusion of 0.15 mg/kg/hour lasting 3 days. The maximum daily dose was 300 mg.
Placebo: no further details
Other interventions:
All patients received intravenous nitrates, titrated according to blood pressure, aspirin (300 mg followed by 100 mg/day), recombinant tissue-type plasminogen activator (100 mg; 15 mg bolus, 50 mg in 30 min, 35 mg in 60 min) heparin (5000 IU bolus, followed by infusion 1000IU/hour), propranolol (1 mg iv bolus every 15 min to max 5 mg, then, atenolol oral 25-100 mg/day according to target < 140/90.
Diltiazem group:
Beta-blockers 6 (14%), nitrates 40(93%), heparin 43(100 %), ACEI 10 (23%), amiodarone 1(2%)
Placebo group:
Beta-blockers 13(28%), nitrates 42 (89%), heparin 47(100%), ACEI 10(21%), amiodarone 2(4 %)

Outcomes  
Mortality: obtained it from text and table IV, page 761
Diltiazem: 2day:NR ; 10day: 1/43 (during admission); eof(6 months ): 3/43
Placebo: 2day:NR ; 10day: 1/47(during admission) ; eof(6 months): 2/47
Total non-fatal SAE: NR
Blood Pressure;
Data was obtained from fig 1, page 761.
The mean BP change during first 24 hours (up to hour 24) was:
Diltiazem (n=43): SBP -18.36 ± NR; DBP NR
Placebo (n=47): SBP -34.09 ± NR; DBP NR
Heart rate
Data was obtained from fig 1, page 761.
The mean HR change during first 24 hours (up to hour 24) was:
diltiazem (n=43): -8.19 ±NR
Placebo (n=47): -3.97 ±NR

Notes
Funding: Not stated, however it was acknowledged that Sanofi-Synthelabo, Milan Italy supplied drug
Dates of conducting the trial : March 1996-Dec 1998

PRACTICAL 1994
Methods
Single-site study (New Zealand)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 3 months
Follow-up: 12 months

Participants
225 patients within 24 hours after onset of symptoms of AMI
Inclusion criteria: Chest pain associated with either ST elevation in > 2 contiguous ECG leads, new pathologic Q waves or elevation on CK
Exclusion criteria: Persistent hypotension with systolic blood pressure < 90 mm Hg, a history of sensitivity to ACE inhibitors or the use of ACE inhibitors within 1 week of the AMI, valvular stenosis, severe renal or hepatic disorders, or a clear indication for treatment with an ACE inhibitor.
Attrition data: Screened: 523, Excluded: 298 (101-consent declined, 80-administrative, 46-taking ACEI, 41-after 24 hours, 27-hypotension, 2-malignancy, 1-known adverse effect to ACEi)
Total randomized patients: 225, Captopril: n=75, Enalapril: n=75, Placebo: n=75
Total withdrawals (discontinuation of drug): 42, Captopril :18, Enalapril: 12, Placebo: 12
Withdrawals due to adverse events: NR
Captopril: total NR, (5-hypotension, 3-rash)
Enalapril: total NR, (5-hypotension, 4-rash, )
Placebo: total NR, (2-hypotension, 1-rash)
Total lost to follow-up: NR
Baseline characteristics:
Age (years), Captopril (C):64, Enalapril (E): 63, Placebo (P): 64
Men / women: C: 48/16; E: 59/ 16; P: 58/ 7
Thrombolytic therapy (%): C:51 (68),E:56 (75), P:55(73)
Mean SBP (mm Hg): C: 133, E:139, P:129
Location and type
C: anterior 34(45), inferior 40(53),q wave 52(69),non-q wave 23(31)
E: anterior 37(49), inferior 33(44),q wave 52(69),non-q wave 22(29)
P: anterior 37(49), inferior 38(51),q wave 55(73),non-q wave 19(25),
Prior medical history (%)
Captopril: AMI 13(17),CHF 2(3),CABG 5(7),PTCA 2(3),
Enalapril: AMI 10(13),CHF 0(0),CABG 5(7),PTCA 1(1),
Placebo: AMI 8(11),CHF 4(5),CABG 0(0),PTCA 1(1),

Interventions
Captopril vs. enalapril vs. Placebo
Drug regimen:
Captopril: 6.25 every 2 hours x 3 doses, followed by 25 mg 3 tid x 12 months
Enalapril: 1.25 mg every 2 hours x 3 doses followed by 5 mg tid x 12 months
Placebo: same regimen, No further details
Other interventions:
All patients received thrombolitics, B-blockers. Open-label ACE might be given for a clear indication.

Outcomes
Mortality: obtained from fig 5, page 1185
enalapril: 2day:NR ; 10day:1/75; eof (12mo-N/A): 2 /75
captopril: 2day:NR ; 10day:6/75; eof (12mo-N/A): 10 /75
Placebo: 2day:NR ; 10day:5/75; eof (12mo-N/A): 12/75
Total non-fatal SAE: NR
Blood Pressure: Not reported for the first 24 hours
Heart rate: NR

Notes
Funding: Not stated but trialist acknowledged that Merck Sharp & Dohme (NZ) Ltd and Bristol-Myers Squibb Ltd for supplying
active drug and placebo
Dates of conducting the trial : NR

Salathia 1985

Methods
Single-site study (UK)
Double-blind
Method of randomization: in two separate blocks (mobile coronary and for other admissions)
Concealment of allocation: NR
Duration of treatment: 1 year
Follow-up: 1 year

Participants
800 patients within 6 hours after onset of symptoms of AMI

Inclusion criteria: Suspected AMI* within 6 hours of the onset.
* The diagnosis of AMI was based on enzymes aspartate aminotransferase, lactic dehydrogenase and total creatin phosphokinase more than double.

Exclusion criteria: Delay from onset of pain exceeded 6 h, ventricular fibrillation, agonal rhythm, SBP < 90, HR > 100 bpm, clinical pulmonary oedema or congestive heart failure, bradycardia < 60 bpm, had received beta-blockers within 48 hrs, AV block greater than 1 degree

Attrition data: Screened: 3350, Total randomized patients: 800, Metoprolol: =416, Placebo: n= 384
Total withdrawals (discontinuation of drug): NR
Total withdrawals due to adverse events: NR
Due to bronchospasm in hospital: Metoprolol: 3, Placebo: 1
Total lost to follow-up: (at 1 year-) Metoprolol: 3, Placebo : 1

Baseline characteristics:
Age n (%): < 65 years, > 65 years
Metoprolol: 287 (69%); 129 (31%)
Placebo: 261(68%), 123(32%)
Gender n (%), male, females
Metoprolol (M): 290 (69.7%);126 (30.3%)
Placebo (P): 282 (73.4%), 102 (26.6%)
BP (mm Hg): NR
Medical history n (%)
Metoprolol: previous MI 105 (25.2), hypertension 50(12),
smoking 194(46.6), angina 196(46.6), dyspnoea 117(28.1),
Placebo: previous MI 109(28.4), hypertension 42(10.9), smoking
182(47.4), angina 176 (45.8), dyspnoea 110 (28.6),

**Interventions**

Metoprolol vs. placebo

Drug regimen:
Metoprolol: initial 15 mg IV bolus over 5 min. Followed by oral
metoprolol* 50 mg every 6 hours for 48 hours, and then 100 mg
every 12 hours for one year
Placebo: injection and tablets with similar appearance. No further
details
*tablets were stopped if: patients declined to continue, diagnosis
was rejected, adverse reaction, interstitial or alveolar pulmonary
oedema, AV block > 1 degree, SBP <80 mm Hg for more than an
hour, persistent bronchospasm.

Other interventions:
Administration of other beta-blockers and verapamil was avoided,
no further details.

**Outcomes**

Mortality: obtained from text/figure 1, page 193
Metoprolol: 2day: NR; 10day (hospital): 25/416; eof(1 year): N/A
49/416
Placebo: 2day: NR; 10day (hospital): 20/384 ; eof(1 year): N/A
52/384
Total non-fatal SAE: NR
Blood Pressure change during first 24 hours: NR
Heart rate change during first 24 hours: NR

**Notes**

Funding: Not stated, but authors acknowledged that Astra
Pharmaceuticals supplied drug and placebo
Dates of conducting the trial: NR

**Schulman 1995**

**Methods**
Single-site study (US)
Double-blind
Method of randomization: with stratification according to infarct
location
Concealment of allocation: NR
Duration of treatment: 1 month
Follow-up: 1 month

**Participants**
43 patients within 24 hours after onset of symptoms of AMI

Inclusion criteria: BP ? 105/65. Diagnosis of AMI was based on
Evidence of ≥2 mV ST-segment elevation or new pathologic Q waves in ≥2 contiguous ECG leads.
Exclusion criteria: Renal (creatinine > 2.5 mg/dl), liver, neurologic or other life-threatening diseases and treatment with (within 1 week) or known contraindications to ACE inhibitors; prior AMI, aortic stenosis, or cardiomyopathies.

Attrition data:
Screened: NR, Total randomized patients: 43, Enalapril: n= 22, Placebo: n= 21
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: NR
Baseline characteristics:
Age (years): Enalapril (E): 58, Placebo (P): 63
Men/ women: E: 16/6, P: 11/10
Anterior myocardial infarction: E: 11, P: 12
SBP/DBP (mm Hg): E: 116/72, P: 125/71
Time to treatment: E: 19.8 ± 1.3, P: 17.1±1.3

Interventions
Drug regimen: (same as that of CONSENSUS II trial)
Enalaprilat: 1 mg IV over 2 to 3 hours*. Then, 6 hours after oral enalapril at dose of 2.5 mg bid titrated up to 20 mg/day at forth day and thereafter for 1 month.
Placebo: No further details
* The infusion was discontinued if systolic/diastolic blood pressure decrease to < 100/60 mm Hg.
Mean dose at hospital discharge was 12 ± 2 mg/day

Other interventions: according to study group:
Enalapril group: Thrombolytic therapy 19 (86%), IV nitroglycerin 19 (86%), IV beta adrenergic blockers 7(32%), CCB 3 (14%)
Placebo (P): Thrombolytic therapy 19 (90%), IV nitroglycerin 19 (90%), IV beta adrenergic blockers 4 (19%), CCB 3 (14%)

Outcomes
Mortality: obtained from text, page 766
Enalapril: 2day: NR; 10day: 2/22; eof (1 month): N/A
Placebo: 2day: NR; 10day: 1/21; eof (1 month): N/A

Total non-fatal SAE: NR
Blood Pressure:
Reported as mean BP (MAP) change from baseline to hour 6; as -5.8±2 in ACEI group, and -4.7 ± 2 mm Hg in placebo group. This data is not useful for the purpose of this review.

Notes
Funding: Merck Sharp & Dohme Research Laboratories
Dates of conducting the trial: NR

Sirnes 1984
Methods
Multi-centre (4, Norway)
Double-blind
Method of randomization: in blocks of 10
Concealment of allocation: given capsules from pre-numbered bottles, no further details
Duration of treatment: 6 weeks
Follow-up: 6 weeks

Participants
227 patients within 12 hours after onset of AMI
Inclusion criteria: Severe chest pain for at least 30 min, ECG suggestion AMI (not previously recognized ST elevation > 0.2 mV in precordial leads or > 0.1 mV in extremity leads or a Q wave > 0.04 sec). Patient was considered included after taken the first capsule sublingually.
Exclusion criteria: Age < 35, > 75 years, evaluation > 12 h after onset, use of CCB within last 48 h, other serious disease, death before inclusion, refuse to participate.
Attrition data:
Screened 885,
Total randomized patients: 227, Nifedipine : n= 112, Placebo : n= 115
Total withdrawals (discontinuation of drug): 5 protocol violation (2 nifedipine group, 3 placebo group)
Withdrawals due to adverse events: Nifedipine : 9/110, Placebo : 6/112
Total lost of follow-up: NR
Baseline characteristics:
Women (%): Nifedipine:23; Placebo: 29
Note: continuous variables are expressed as mean ± SD
Age (years): Nifedipine: 61±8, Placebo: 61±9
SBP (mm Hg): Nifedipine: 147±30, Placebo: 144±27
DBP (mm Hg): Nifedipine: 93±17, Placebo: 93±11
HR (bpm): Nifedipine: 75±18, Placebo: 77±22
Time to study entry (hours), Nifedipine: 5.4±3, Placebo: 4.9±2.9
Medical history (%)
Nifedipine: previous AMI 28, angina 60, long-term use of BB 18
Placebo: previous AMI 34, angina 53, long-term use of BB 24

Interventions
Nifedipine vs. Placebo
Drug regimen:
Nifedipine: 10 mg capsule sublingually, subsequently 10 mg orally five times per day for 2 days, and 10 mg four times a day for 6 weeks. Treatment was temporarily discontinued if severe reaction developed.
Placebo: no further details given.
Other interventions:
Other medical treatment was permitted according to local routine

Outcomes
Mortality: obtained it from figure 1, page 640
Nifedipine: 2day:NR ; 10day: 6/112 ; eof(6 weeks): not applicable
Placebo: 2day:NR ; 10day:4/115 ; eof(6 weeks): not applicable
Total non-fatal SAE: NR
Blood Pressure: (mm Hg)
Data was obtained from table 5, page 642
The mean BP change during first 24 hours (up to hour ~16) was:
Nifedipine (n=110): SBP -17.67±22 ; DBP -9.67 ±14
Placebo (n=112 ): SBP -5.67 ±23 ; DBP -2.33±13

Notes
Funding: Bayer A.G. Leverkusen, Federal-Republic of Germany
Dates of conducting the trial : NR

Theroux 1998
Methods
Single-site study (Canada)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 1 month
Follow-up: 1 month

Participants
60 patients within 6 hours after onset of AMI
Inclusion criteria: Chest pain within previous 6 hours with ST-elevation (1 mm ot motr in two or more adjacent leads), absence of a contraindication to thrombolysis or diltiazem and signed consent.
Exclusion criteria: Not stated
Attrition data: Screened: NR
Total randomized patients: Diltiazem: n= 30, Placebo: n=30
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events:
Diltiazem: 2/30  (hypotension or bradycardia or supraventricular block)
Placebo : 1/30 (developed shock before study drug was received)
Total lost of follow-up: NR
Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Age (years): Diltiazem (D):57±11, Placebo (P):60±9
Male: D: 25(83%), P:  24(83%)
BP (mm Hg); NR
Time of thrombolysis (minutes) : D: 175±64, P: 151±48
Site of AMI:
D: anterior 12 (40), inferior 18(60)
P: anterior 13 (45), inferior 16(55)
Medical history (%)
Diltiazem: smokers 16(52), diabetes 2(6), hypertension 6(19), coronary artery disease 10(33)
Placebo: smokers 13(45), diabetes 3(10), hypertension 6(21), coronary artery disease 10(34)

**Interventions**
Diltiazem vs. Placebo
Drug regimen:
Diltiazem: 10 mg iv bolus in 10 min followed by an infusion at a rate of 10 mg/h for 48 hours. Oral therapy with diltiazem 120 mg three times a day (360 mg /day) until 4 weeks of follow-up
Placebo: no further details
Other interventions:
All patients receive tissue-type plasminogen activator ( 7 mg iv bolus in 3 min followed by 53 mg in 57 min, 20 mg in 1 h and 10 mg/h for 2 h). Aspirin 325 mg orally at admission and daily thereafter. Heparin 1000 U/h with discontinuation after 72 hours.
Diltiazem group: Nitroglycerin  19, BB 12, ACEi 6
Placebo group: Nitroglycerin  23, BB 22, ACEi 12
Other CCB were prohibited.

**Outcomes**
Mortality: obtained from text, page 624
Diltiazem: 2day:0/30 ; 10day:0/30; eof(4 wks ): N/A
Placebo: 2day:1/30 ; 10day:2/30; eof(4 wks ): N/A
Total non-fatal SAE: NR
Blood Pressure;
Data was obtained from fig 2, page 624.
The mean BP change during first 24 hours (up to hour 24) was:
Diltiazem (n=30): SBP -16.26±16.21; DBP -8.02±11.64
Placebo (n=29): SBP -10.42±19.65; DBP -7.55±14.97

Heart rate
Data was obtained from fig 2, page 624.
The mean HR change during first 24 hours (up to hour 24) was:
Diltiazem (n=30):-3.73±11.61
Placebo (n=29): 1.50±14.65

Notes
Funding: Hoescht-Marion-Roussel

TIMI-IIB 1991

Methods
Multi-centre (24-US)
Open-label
Method of randomization: unclear
Concealment of allocation: NR
Duration of treatment: 6 days (comparison), then same active treatment in both study groups for 1 year
Follow-up: 1 year

Participants
1434 patients within 4 hours after onset of symptoms of AMI

Inclusion criteria: Within 4 hours of the onset of AMI*, < 75 years, no contraindications to beta-blockers.
* AMI was based on typical chest pain ? 30 min, ST elevation 0.1 mV in two contiguous leads.

Exclusion criteria: Implanted pacemaker, resting ventricular rate < 55 bpm, SBP <100 mm Hg, moist rales or pulmonary edema + radiographic findings, advanced first-degree or more advance heart block; asthma, chronic obstructive lung disease, b-blocker, verapamil or diltiazem therapy on admission.
Attrition data: Screened: 2,948, Excluded before randomization (n=1514) due to B-blocker, verapamil or diltiazem therapy on admission (45.4%), resting ventricular rate < 55 bpm (27.1%), SBP <100 mm Hg (21.3%), moist rales or pulmonary edema + radiographic findings (16.4%), advanced first-degree or more advance heart block (12.4%); asthma, chronic obstructive lung disease (11%), implanted pacemaker (0.3%),
Total randomized patients: 1434, early metoprolol: n= 720 , No early metoprolol (deferred) group: n= 714
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: NR
Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Mean age (years):
Metoprolol (M): 54.8
No early metoprolol or deferred group (X): 55.2
Race: white n (%): M: 614 (85.3), X: 626 (87.7)
Sex: male n (%): M: 620 (86.1), X: 603 (84.4)
BP (mm Hg): NR
Medical History (%)
Metoprolol group:
Prior AMI 47(6.5), angina 313(43.5), CHF 6(0.8), hypertension 216(30), diabetes mellitus 77(10.7),
No early metoprolol group:
Prior AMI 63(8.8), angina 313(43.8), CHF 10(1.4), hypertension 219(30.7), diabetes mellitus 82(11.5)
Note: Prior myocardial infarction (overall): 7.7%

Interventions
Early Metoprolol vs. no early metoprolol (deferred for first 6 days)
Drug regimen:
Early Metoprolol:
Immediately after receiving rt-PA, patients received 3 IV bolus of 5 mg at 2-minute interval. Followed by, oral metoprolol at 25 mg every 12 hours for the first 24 hours and 100 mg every 12 hours thereafter*. 
No early metoprolol (deferred) group:
Metoprolol started on day 6; 50 mg twice daily for 1 day and then 100 mg twice daily thereafter

* Therapy was stopped if lengthening of PR interval beyond 0.26 sec, AV block 2 or 3 degree, wheezing or rales occurred. Therapy was temporary withheld if’ HR <45 bpm, SBP < 90 mm Hg.
Mean dose reported was not reported but percent of participants receiving B-blockers:
Early Metoprolol group:
IV B-blocker 651 (90 %), oral B-blocker during first day 563 (78%)
No early metoprolol (deferred) group:
IV B-blocker 33 (4.6%) oral B-blocker earlier than scheduled (day 6): 22.9%

Other interventions:
Most patients received rt-PA intravenously ? 4 hours after onset of symptoms (87.6% in the early metoprolol group vs. 86.4% in the no early metoprolol or deferred group). The total dose was 150 mg over 6 hours; however, because an unacceptable incidence of intracranial haemorrhage the dose was subsequently reduced to 100 mg in the remaining patients. Thus, initial 6 mg IV bolus followed by 54 mg in the first hour, 20 mg in the second hour and 5 mg in each of the next 4 hours.
Patients also received lidocaine of a bolus of 1-1.5 mg/kg followed by an infusion of 2-4 mg/min for 24 hours. Heparin 5,00 unit bolus followed by 1000 units/hr, dose adjusted to maintain an activated partial thromboplastin time of 1.5-2 times control values, then 10,000 IU SC twice daily until hospital discharge. Aspirin 80 mg/day started on day 1 in 93 of patients (6.5%) or day 2 (93.5%). This dose was increased to 325 mg/day on day 6.

**Outcomes**

Mortality: obtained from table 6, page 430

Early metoprolol group: (n=720)
At 6 days: 17; in hospital 22; at week 6: 26; at year 1: 34

No early metoprolol (deferred) group: (n=714)
At 6 days: 17; in hospital 25; at week 6: 25; at year 1: 35

Total non-fatal SAE: NR
Blood Pressure change during first 24 hours: NR
Heart rate change during first 24 hours: NR

**Notes**

Funding: National Heart, Lung and Blood Institute, National Institutes of Health

**Tonkin 1981**

**Methods**

Single-site study (1-Australia)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 7 days
Follow-up: hospital
<table>
<thead>
<tr>
<th><strong>Participants</strong></th>
<th>89 patients within 24 hours after onset of symptoms of first AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria:</strong></td>
<td>Suspected diagnosis of first AMI within 24 hours of onset</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong></td>
<td>Receiving Beta-blockers or having contraindications to these agents (sinus bradycardia, &lt;45 bpm, SBP &lt; 100 mm hg), P-R interval greater than 0.22 s, 2 or 3 degree AV block, moderate or severe heart failure, and obstructive airways disease.</td>
</tr>
<tr>
<td><strong>Attrition data:</strong></td>
<td>Screened: NR, Total randomized patients: 88, Timolol: n= 42, Placebo: n= 46</td>
</tr>
<tr>
<td><strong>Total withdrawals (discontinuation of drug):</strong></td>
<td>Timolol: 6 (due to diagnosis) +11 (due to contraindication) =17, Placebo: 8 (due to diagnosis) +11 (due to contraindication) =19</td>
</tr>
<tr>
<td><strong>Withdrawals due to adverse events:</strong></td>
<td>NR</td>
</tr>
<tr>
<td><strong>Total lost to follow-up:</strong></td>
<td>NR</td>
</tr>
<tr>
<td><strong>Baseline characteristics:</strong></td>
<td>72 of patients were male, Mean time delay to treatment (hours) Timolol: 11.94 ± 4.65, P: 10.09 ± 5.44</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>The rest of baseline characteristics are not reported</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Interventions</strong></th>
<th>Timolol vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug regimen:</strong></td>
<td>Timolol: 10 mg twice / day for 7 days, Placebo: No further details</td>
</tr>
<tr>
<td><strong>Other interventions:</strong></td>
<td>All patients were managed in a routine way, though IM injections were avoided. Anti-arrhythmic and anti-failure therapy were used as indicated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Outcomes</strong></th>
<th>Mortality: obtained from text, page 145</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timolol:</strong></td>
<td>2day: NR; 10day (in hospital): 1/42; eof (1 year): NR</td>
</tr>
<tr>
<td><strong>Placebo:</strong></td>
<td>2day: NR; 10day (in hospital): 1/46; eof (1 year): NR</td>
</tr>
<tr>
<td><strong>Total non-fatal SAE:</strong></td>
<td>NR</td>
</tr>
<tr>
<td><strong>Blood Pressure change during first 24 hours:</strong></td>
<td>NR</td>
</tr>
<tr>
<td><strong>Heart rate change during first 24 hours:</strong></td>
<td>NR</td>
</tr>
</tbody>
</table>

| **Notes** | Funding: Merck, Sharp and Dohme |

| **Van-de 1993** | Multi-centre (20-Netherlands) |
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 10-14 days
Follow-up: Hospital

Participants
201 patients within 5 hours after onset of symptoms of AMI

Inclusion criteria: Patients < 71 years of age, pain suggestive of acute MI*, onset of chest pain < 5 hours before initiation of therapy, no previous history of angioplasty or bypass surgery, no contraindications to thrombolytic therapy or to BB, no beta-blocker or CCB within 1 week.

*Diagnosis of AMI was based on pain lasting ≥ 30 min, ST elevation of 0.2 mV in two or more limbs leads, or leads V5-V6 or 0.3 mV in two or more precordial leads (V1 to V4) or ST elevation of 0.1 mV in two leads (II, III, AVF, or V5 and V6) associated with ST depression of 0.2 mV in two precordial leads.

Exclusion criteria: Contraindications: HR < 50 bpm, SBP < 90 mm Hg, CHF, shock, 2,3 AV block, bronchospasm, sick sinus syndrome

Attrition data: Screened: NR, Total randomized patients: 300, Atenolol: n= 103, Placebo: n=98
Note: another randomized group was alinidine, a derivative of clonidine, (n=99) which is not considered or discussed any further in this review
Total withdrawals (discontinuation of drug):8 , Atenolol: 3, Placebo 4, Alinidine 1
Withdrawals due to adverse events: NR
Total lost to follow-up: NR
Baseline characteristics:
Mean age, in years,(range) : Atenolol (A): 59 (39-70), Placebo (P): 57 (40-68)
Male: A: 80(80%), P: 80(85%)
Location of the infarction: anterior, inferior, Not reported
A: 33%, 66%,1%; P: 36%, 62%,2%
Time to treatment in minutes (range): A: 156 (85-300), P: 168(72-330)
HR ?bpm (range): A: 74 (55-111), P: 75(54-102)
SBP -mm Hg (range): A: 130 (100-170), P: 135 (100-170)

Medical history (%)
Atenolol: Previous MI 3(3), diabetes Mellitus 4(4), angina > 4 weeks 15(15),
Placebo: Previous MI 3(3), diabetes Mellitus 5(5), angina > 4 weeks 10(11),

**Interventions**

Atenolol vs. Placebo
Drug regimen:
Atenolol: 5 mg IV twice with a 10 min interval 10 mcg /min,
followed by oral treatment 25 to 50 mg of atenolol every 12 hours
for 10-14 days*
*Dose was adjusted according to hemodynamic; 70 received full intravenous dose
Placebo: two IV injections; no further details. It is not known if oral placebo was given.

Other interventions:
All patients received Alteplase 100 mg over 3 hours, and heparin 5000 IU bolus, followed by continuous infusion of 1,000 IU /h until angiography. Aspirin was not given

**Outcomes**

Mortality
Atenolol : 2day:NR ; 10day:1/103 ; eof (hospital ): 1
Placebo: 2day:NR ; 10day:2/98 ; eof(hospital): 4
Total non-fatal SAE: NR
Blood Pressure: not reported during the first 24 hours
Heart rate: not reported during the first 24 hours

**Notes**

Funding: Belgian National Fund for Scientific Research, ICI Pharma, Belgium and Boehringer Ingelheim, Belgium.
Dates of conducting the trial : June 1988- December 1990

**VENUS 2001**

**Methods**

Multi-centre (Netherlands)
Double-blind
Method of Randomization: Simple, equal blocks of 10 according to computer-generated lists.
Concealment of allocation: Numbered boxes contained one complete treatment or identical placebo course and were sequentially distributed among participants
Duration of treatment: 10 days
Follow-up: 3 months

**Participants**

454 patients within 6 hours after onset of symptoms of acute stroke

Inclusion criteria: Patients with acute stroke and hemiparesis

Exclusion criteria: Ability to raise arm or leg > 10 seconds against gravity, inability to start treatment within 6 hours, age <18 or > 85 years, previous participation in this trial, pregnancy, impaired consciousness (did not obey orders and did not open eyes on painful stimuli); other diseases likely to cause death within 1 year, previous stroke, resulting in serious handicap, dysphagia, excluding oral medication at trial onset; systolic blood pressure < 130 mm Hg, heart rate < 50 bpm; and 3 of the following 4 conditions: severe headache, vomiting, hypertension (SBP > 220 mmHg) and use of oral anticoagulants.

Attrition data: screened / excluded at screened: NR
Total randomized patients: 454, Nimodipine: n= 225, Placebo : n= 229
Total withdrawals (discontinuation of drug): 15, Nimodipine: 7/225, Placebo : 8/229
Withdrawals due to adverse events: NR
Total lost to follow-up: NR

Baseline characteristics:
Female: Nimodipine (N): 97(43%), Placebo (P): 85 (37%)
Age, median (range): N: 70.5 (24-91), P: 71.1 (31-93)

Medical history
Nimodipine (N): previous stroke 7(3%), cardiac disease 46(20%), other 105(47%)
Placebo (P): previous stroke 17(7%)*, cardiac disease 60(26%), other 108(47%)

Neurological examination
N: Hemiparesis 189(84%), impaired consciousness 1(0%), aphasia 66(29%)
P: Hemiparesis 187(82%), impaired consciousness 3(1%), aphasia 89(39%)*

Type of stroke
N: Ischemic 133(59), hemorrhagic 20 (9), no CT scan 9(32), no stroke 1(0),
P: Ischemic 128(56), hemorrhagic 15(7),no CT scan 79(34), no stroke 7(3)
**Interventions**
Nimodipine vs. Placebo

Drug regimen:
Nimodipine: 30 mg orally every 6 hours for 10 days
Placebo: No further details

**Outcomes**
Mortality: obtained text and table 2, page 463
Nimodipine: 2day: NR; 10day: 14/225(6%); eof (3 mo): NR*
Placebo: 2day: NR; 10day: 20/229(9%); eof (3mo): NR*

*Mortality alone was NR at 3 months but a composite of all-cause mortality or dependency in life (Modified ranking scale score > 3) as 32% vs. 27%, RR, 1.2; 95% CI 0.9-1.6, p value NS.

Total non-fatal SAE: NR
Blood Pressure on first 24 hours: NR
Heart rate on first 24 hours: NR

**Notes**
Funding: Dutch Prevention Fund (grant 28-2467). Trial medication was provided by Bayer AG, Germany
Dates of conducting the trial: ended on July 1998

**von Essen 1982**

**Methods**
Two-site study (41 in Germany; 15 in Switzerland)
Double-blind
Method of randomization: according to a randomization list, no further details
Concealment of allocation: NR
Duration of treatment: 14
Follow-up: 14

**Participants**
51 patients within 24 hours after onset of symptoms of AMI

Inclusion criteria: Acute chest pain typical of infarct, interval between acute symptoms and hospitalization < 24h, symptom of infarct with persistent pain, SBP > 110mm Hg, heart pulse = 60 bpm, CI 4.0 L/min/ m2

Attrition data: Screened: NR, total randomized patients: 51,
Metoprolol: n= 25, Placebo: n= 26
Total withdrawals (discontinuation of drug): NR
Metoprolol: 1 (due to bradycardia)
Withdrawals due to adverse events:
Metoprolol: 1 / 25
Placebo: NR
Total lost to follow-up: NR
Baseline characteristics:
Age (years): between 38-83 years old, overall mean 59, 45 men, 6 women
BP (mm Hg): NR
Time to treatment (hours: minutes) Metoprolol : 9:55± 5 Placebo : 12± 6
History of previous acute myocardial infarction; 5/51 (10%) Metoprolol : 1, Placebo : 4
History of diabetes 8/51(16%) , Metoprolol : 3, Placebo : 5
History of hypertension 18/51 (35%), Metoprolol : 8, Placebo : 10

Interventions
Metoprolol vs. placebo
Drug regimen:
Metoprolol: Initial 0.1 mg/kg body weight rapid IV infusion, 2 hours later 100 mg and then 100 mg every 12 hours
Placebo: No further details

Outcomes
Mortality: obtained from text, page 1267 & 1271
Metoprolol: at 2day:NR; 10day: 1* / 25; end of follow-up: (14d) 1/25
Placebo: at 2day:NR; 10day: 1* / 26 ; end of follow-up: (14d) 1/26
* It is assumed that these deaths occurred during the first 10 days, as it is stated that these deaths occurred right after the acute phase of 48 hours.
Total non-fatal SAE: NR
Blood pressure: NR
Heart rate: NR

Notes
Funding: Ciba-Geigy

Wagner 2002
Methods
Single-site study (Austria)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 1 day
Follow-up: 7 days

Participants
99 patients within 6 * hours after onset of symptoms of AMI with undergoing thrombolysis

* this is assumed value as in clinical practice ( in 2001) patients
are usually treated with thrombolysis within 6 hours. In addition, the mean time of chest pain was 2.1 hours.

Inclusion criteria: Diagnosis of AMI was based on chest pain lasting for more than 30 min, ST-elevation > 1 mm in one or more inferior leads or in at least two corresponding anterior leads and a typical rise and fall in Ck and CK-MB. Q-wave infarction was confirmed by serial electrocardiographic abnormalities, with development of Q-waves as well as typical rise and fall or CK-MB.

Exclusion criteria: Chest pain relieved by nitroglycerin or < 30 min in duration; 2) history of a myocardial infarction; contraindications to thrombolytic therapy or ramipril, serious advanced illness, hypotension SBP < 100 mm Hg, cardiogenic shock, use of ACE within 2 weeks, pregnancy, lactation, or inability to participate.

Attrition data: Screened: NR, total randomized patients: 99, ramipril : n= 51, placebo : n= 48
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: NR
Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Age (years): Ramipril (R): 55 ± 12, Placebo (P): 55±11
Male/female: R:79/21, P:69/31
Anterior / inferior MI: R : 25 /26, P : 22 / 26
Duration of chest pain (hours) : R: 2.1 ± 1.6, P: 2.1 ± 1.7
SBP/DBP (mm Hg): R: 139 ±19 / 77±13, P: 138 ±20 / 77±15
Heart rate: R: 80 ± 20, P: 79 ± 17
Medical history (%)
Ramipril: hypertension (43), diabetes (14), smoking (48), hyperlipidemia (34)
Placebo: hypertension (29), diabetes (16), smoking (52), hyperlipidemia (36)

Interventions
Ramipril vs. placebo
Drug regimen:
Ramipril: 2.5 mg orally prior to thrombolysis (rt-PA). Then, a second dose of 2.5 mg, 12 hours after.
Placebo: prior to thrombolysis and then a second dose 12 hours after, no further details. 24 hours the start of thrombolysis all
patients received ramipril with a starting dose of 2.5 mg

Other interventions:
All patients received 100 mg rt-PA according to the GUSTO-scheme 5000 IU heparin and 100 mg aspirin orally. Beta blockers were given as clinically appropriate.

Ramipril group: aspirin 10 (%), beta blockers 24 (%), CCB 1(%), diuretics 3 ( %), nitrates 1 (%)
Placebo group: aspirin 14(%), beta blockers 22(%), CCB 2(%),
diuretics 4( %), nitrates 1(%)

Outcomes
Mortality: obtained from text, page 183
Ramipril: 2day: NR ; 10 day (within 1 week) 1/51 : eof : N/A
Placebo: 2day: NR ; 10 day (within 1 week) 1/48 : eof : N/A

The causes of death were rupture of the anterior wall or the left ventricle in one patient and cardiogenic shock in the other one.

Total non-fatal SAE: NR
Blood Pressure;
Data was obtained from text in page 183.
Reported as mean BP at end point ( 24 h) :
Ramipril (n=51 ): SBP 108 ± 15 ; DBP 72 ± 12
Placebo (n= 48): SBP 112 ±14 ; DBP 73 ± 10

Heart rate
Data was obtained from text in page 183.
Reported as mean HR at end point ( 24 h) :
Ramipril (n= 51): 70 ± 12
Placebo (n= 48): 73 ± 11

Notes
Funding: Aventis Pharma (provided study medication)
Dates of conducting the trial : January 1999-February 2001

Yusuf 1983
Methods
Single-site study (UK)
Open-label
Method of randomization: NR
Concealment of allocation: using numbered, sealed envelopes.
Duration of treatment: 10 days
Follow-up: 1-4 years (Average 2)

Participants
477 patients within 12 hours after onset of symptoms of suspected AMI

Inclusion criteria: Suspected of AMI* within 12 hours of onset.

*According to ECG patients were subdivided into those with definite MI (i.e., ST-segment elevation of at least 1 mm limbs leads, or 2 mm in precordial leads (with or without Q waves), and those with threatened MI (all other who were again subdivided into those with suggestive T-wave inversion, ST depression or BBB- or those with no particular abnormality on ECG)

Exclusion criteria: HR <40 bpm, SBP < 90 mm Hg, 2nd degree AV block, heart failure requiring digoxin or furosemide 80 mg, or history of asthma, taking BB at entry, or thought requiring BB at admission, have contra-indication.

Attrition data: Screened: NR, Total randomized patients: 477, Atenolol: n= 244, No atenolol or control: n= 233
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost to follow-up: NR

Baseline characteristics:
Note: continuous variables are expressed as mean ± SD (if provided)
Mean age - in years: Atenolol (A): 56, No atenolol or control (X): 56
Female (%): A: 30 (12), X: 43 (18)
BP (mm Hg): A: 143 / 89, X: 145 / 91
HR (bpm): A: 77, X: 77
Time to randomization (hours): A: 5, X: 5
Heart failure at entry (%): A: 15 (6), X: 16 (7)
Site of myocardial infarction: anterior, inferior, both, indefinite (%)
A: 100(41), 86(35), 12(5), 46(19).
X: 91(39), 86(37), 5(2), 51(22).
Medical history (%)
Atenolol group:
Angina 25(10), hypertension 29 (12), myocardial infarction 44(18), diabetes 14(6)
Control group:
Angina 29(12), hypertension 28 (12), myocardial infarction 34(15), diabetes 9(4),

**Interventions**

Atenolol vs. no treatment (control)

Drug regimen:
Atenolol: 5 mg IV over 5 min, then 50 mg, orally, immediately after and 12 hours later. Then, 100 mg once daily for 10 days or until the patient develop contraindications died or was discharged.

Control: BB was not allowed unless clearly indication

Other interventions:
All patients received routine ancillary management
Atenolol group: n=244
atropine 23, inotropic 4, antiarrhythmic 58, other anti-hypertensive 14, CCB 9, oral anticoagulants 53,antiplatelets drugs 13, bronchodilator 3, intra-aortic balloon pump 0
No atenolol or control: n= 233
atropine 19, inotropic 6, antiarrhythmic 76*, other anti-hypertensive 41*, CCB 22*, oral anticoagulants 48,antiplatelets drugs 15, bronchodilator 4, intra-aortic balloon pump 2.

* statistically significantly different

**Outcomes**

Mortality: obtained from table 5 , page I-38
Atenolol: n= 244
2day: NR; 10day:7; eof (average 2 years ): 36
No atenolol or control: n= 233
2day: NR; 10day:16; eof (average 2 years ): 44
Total non-fatal SAE: NR

Blood Pressure: Not reported change during first 24 hours of all randomized patients
Heart rate: Not reported change during first 24 hours of all randomized patients

**Notes**

Funding: British Heart Foundation and ICI Pharmaceuticals
Dates of conducting the trial : August 1978- May 1981

**Zannad 1988**

**Methods**

Single-site study (France)
Double-blind
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 3 weeks
Follow-up: 3 weeks

Participants
34 patients with clinical, ECG and enzymatic evidence of AMI within 6 hours after onset of symptoms of AMI
Inclusion criteria: Chest pain, epicardial injury and pathological q waves, less than 6 hours since the onset of symptoms, no previous AMI, heart failure (KK II), or 3rd degree AV block, no ongoing use of amiodarone, BB or CCB, age < 75, ability to provide informed consent.
Exclusion criteria: Not stated
Attrition data: screened: NR
Total randomized patients: 34, Diltiazem: n= 17, Placebo: n= 17
Total withdrawals (discontinuation of drug): Diltiazem: 0/17, Placebo: 2/17
Withdrawals due to adverse events: NR
Total lost of follow-up: NR
Baseline characteristics:
Note: continuous variables are expressed as mean ± SD
Age- in years: Diltiazem (D):54 ±10, Placebo (P): 49 ±10
Male/female: D: 14/3, P: 14/3
Time of infarction (hours): Diltiazem (D):4.6 ±0.9, Placebo (P): 4.4 ±1.0
Inferior/ Anterior involvement : D: 11/6, P: 11/6

Interventions
Diltiazem vs. Placebo:
Drug regimen:
Diltiazem: 10 mg iv injection over 2 minutes, followed by a constant rate infusion of 15-20 mg / h over 72 hours. (adjusted if side effects). Oral treatment started 2 hours before infusion was discontinued ; as 60 mg every 6 hours for 3 weeks.
Placebo: No further details
mean dose reported was not reported
Other interventions:
Standard treatment: all patients received anticoagulant doses of heparin and a constant rate infusion of 800 to 800 mg/ 24 of lidocaine. The use of nitrates, betablocker, amiodarone or ccb was not permitted during study.

Outcomes
Mortality: obtained from text, page 1174
Diltiazem: 2day:1/17 ; 10day:1/17 ; eof(3 wks ):Not applicable
Placebo: 2day:0/17 ; 10day: 1/17 ; eof(3 wks ):Not applicable
Total non-fatal SAE: NR
Blood Pressure data: NR
Heart rate data: NR

Notes
Funding: Not Reported

Zharov 1991

Methods
Single-site study (Moscou USSR)
Open-label
Method of randomization: NR
Concealment of allocation: NR
Duration of treatment: 3 days
Follow-up: 25 days

Participants
115 patients with AMI within 12 h of onset
Inclusion criteria: NR
Exclusion criteria: NR
Attrition data for the three randomized groups:
Control (I): n=52
Isosorbide dinitrate (II): n=32
Nitroglycerin (III): n=31
Total withdrawals (discontinuation of drug): NR
Withdrawals due to adverse events: NR
Total lost of follow-up: NR
Baseline characteristics were not reported according to group:
There were 87 males, 28 females, mean age 61±0.9, primary AMI 70, repeated infarction 37 cases; 68 anterior, 23 anterolateral, 11 posterolateral, 13 posterior.

Interventions
Control (I): n=52
Isosorbide dinitrate (II): n=32
Nitroglycerin (III): n=31
Drug regimen:
I: receive only heparin (no further details).
II and III: the nitrate infusion were given at an initial rate of 25 mcg/ min and gradually titrated up until systolic blood pressure fell 12-25 % of initial value, but not below 90 mm Hg.
Other interventions: NR

Outcomes
Results based on following group population:
Control (I): n=52
Isosorbide dinitrate (II): n=32
Nitroglycerin (III): n=31
Mortality: obtained it from table 3, page 67
Control: 2day:2; 10day:NR; eof(25day): 16  
Isosorbide: 2day:NR; 10day:NR; eof(25day): 2  
Nitroglycerin: 2day:NR; 10day:NR; eof(25 day): 3  
Non-fatal SAE: NR  
Individual SAE:  
CHF: obtained it from table 3, page 67  
control:13/52 (25%)  
isosorbide: 5/32(16%)  
nitroglycerin: 4/31(13%)  
Aneurysm: obtained it from table 3, page 67  
control:11/52 (21%)  
isosorbide: 7/32(22%)  
nitroglycerin: 6/31(19%)  
Pulmonary edema: (data on this outcome was confusing as different numbers are given in table 1, 2 and 3).  
Blood Pressure; reported as change in BP (mm Hg) from baseline for the two nitrates groups as follow:  
Isosorbide (n=32): SBP: -14.7±3.8, DBP: 7.7±1.6 (text on page 65)  
Nitroglycerin (n=31): SBP: -15.2±4.9, DBP: -11.7±3.6 (text on page 67)  
BP data for the control group was not reported.  
Heart rate:  
reported as change in HR (bpm) from baseline for the one nitrate groups as follow:  
Nitroglycerin (n=31): -17.5±4.9 (text on page 67)  
BP data for the other two groups was not reported.  

Notes  
Funding: Not reported