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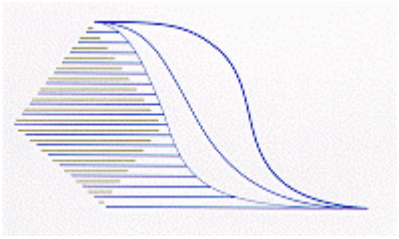

Price and Productivity Measurement in a Pharmaceutical Sector Sub-Market: The Real Cost of Treating Hypertension

S. Morgan

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S. Morgan

Health Policy Research Unit
Centre for Health Services & Policy Research
429 – 2194 Health Sciences Mall
University of British Columbia
Vancouver, B.C.
V6T 1Z3

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Price and Productivity Measurement in a Pharmaceutical Sector Sub-Market: The Real Cost of Treating Hypertension*

Steve Morgan
Centre for Health Services and Policy Research, UBC

Economists routinely make assumptions about what consumers know and how that knowledge relates to what we describe as "rational" choice. Our information-related assumptions are generally optimistic. We usually assume that consumers make judgements about products based on accurate information regarding relevant characteristics. Where this is not so, we often assume that they chose to make decisions based on incomplete or imperfect information because of the cost of obtaining and verifying the accuracy of additional information. In the pharmaceutical sector, it has long been acknowledged by governments that patients generally do not and cannot know the truth regarding the appropriate use of medicines. The information that is required to make rational choices about drugs is simply beyond the comprehension of those without adequate medical and pharmacological training. In response to this, drug selection has been delegated to medical authorities. Accordingly, drug-related information gathering is one of the primary services that prescribing physicians are expected to provide.

In practice, the prescription decision-making process may be based on a sub-optimal information for a number of reasons. Doctors, the principal decision-makers in this sector, do not pay for drugs they prescribe on behalf of their patients. Moreover, when paid on a fee-for-service basis, doctors have incentive to see as many patients in as short a period as possible—subject, among other things, to the constraint of possible malpractice liability. The incentive to treat patients quickly and the lack of incentive to consider costs run counter to the incentive for physicians to engage in costly information gathering. Furthermore, physicians, like other people, have personal preferences—likes and dislikes over goods and risks. Their preferences can be influenced by interactions with manufacturers of products as well as professional (peer) pressure to remain on the "forefront" of medicine.

Doctors' personal preferences and their entrepreneurial incentives may cause them to chose drugs in a manner that is inconsistent with socially efficient choice. Socially efficiency occurs when drugs may be judged to be cost-effective as prescribed to patients based on scientific information available to prescribers at reasonable cost. If decision-making consistently fails to meet this standard, traditional economic price and quantity indexes will give biased measures of sector productivity. The direction of this bias will depend on the circumstances of the market in question.

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* The empirical analysis contained in this working paper is being updated with new data that permit greater detail in the analysis. Please do not cite results without permission of the author. Comments or suggestions would be gratefully received. morgan@chspr.ubc.ca

This study investigates potential information problems in pharmaceutical price and productivity measurement in the sub-market pertaining to drugs used in the treatment of hypertension. Pharmacological treatment of hypertension offers a particularly clear illustration of the distinction between scientific information, which might be considered measurable and socially valuable, and the unmeasurable influences (or "information") affecting doctors preferences for certain drugs. This treatment category is relatively old and well studied. It is also of enormous importance given the incidence of hypertension and the steadily growing expenditures on drugs to treat it.

The recommendations of national organizations of professionals interested in improving hypertension treatment are used here as a marker of scientific information that is readily available to prescribing physicians. These guidelines serve as a marker of "social preferences" for drug treatments, upon which "real-productivity" price and quantity indexes are based. Traditional economic indexes are compared with the real-productivity indexes to gauge the measurement bias that results from decision-making that is inconsistent with socially efficient choices based on the best available scientific evidence. Tests of drug tolerability are applied to see if patients who are prescribed hypertension drugs "reveal" preferences that are consistent with those "revealed" by their prescribing doctors.

Information and Medical Practice Guidelines

With the accumulation of evidence that variations in medical practice can seldom be explained by clinically relevant factors, medical practice guidelines have become commonplace (Grilli and Lomas 1994). Professional associations, government bodies and public health organizations have published guidelines or consensus recommendations for the treatment of countless conditions. In a majority of cases, the aim is to improve the quality of care provided by medical practitioners. In some cases, it has been to improve the cost-effectiveness of care delivered. The notable exception has been the development of industry-sponsored consensus conferences, which are ultimately held for promotional purposes (Sheldon and Smith 1993).

Guidelines published by recognized professional bodies are typically developed by means of consensus among recognized experts using the best available scientific information about the relative advantages and disadvantages of treatment alternatives. Guidelines usually deal with specific treatments or conditions. They are disseminated to the target audiences by various means, including direct mailing, journal publications, conferences, continuing medical education seminars and face to face communications. Most are available to physicians at what might be considered reasonable cost—in terms of time and effort (they are invariably distributed free of charge).

Do Practice Guidelines Guide Practice?

Given the prevalence and purpose of guidelines, a parallel stream of research has evolved for the purposes of evaluating their impact on doctors' behaviour. These researchers ask the question, as Lomas et al (1989) put it, "Do Practice Guidelines Guide Practice?"

Such studies have been conducted to evaluate practice patterns before and after the dissemination of guidelines, as well as physicians' awareness of and agreement with them. Evidence regarding the efficacy of guidelines is discouraging. Average compliance rates with guidelines are in the order of 50 percent (Grilli and Lomas 1994), but differ depending on the subject of the guidelines. Guidelines are least likely to be adhered to for complex tasks that have few immediate results and cannot easily be implemented on a trial basis (Grilli and Lomas 1994). Even when physicians report knowledge of and agreement with guidelines, actual knowledge of and compliance with guidelines appears poor (Lomas et al 1989). These results indicate that doctors believe that it is socially desirable to comply with guidelines even when they are not doing so themselves. This is further evidenced by the fact that, averaged across 10 studies, self-reported measures of compliance overestimate actual adherence[1] by approximately 27 percent (Adams at al 1999). Discouragingly, the average self-reporting bias appears greater than the average increase in compliance attributed to the dissemination of guidelines (Adams at al 1999). Guidelines appear to affect what doctors believe should be done more than what they actually do.

The purpose of the present study is not to evaluate hypertension treatment guidelines or their dissemination processes as tools to alter medical practice. Recognized national guidelines in Canada and the US are used here to determine what might be considered "socially desirable" practice patterns over the period of study—1986 to 1996. If actual practice patterns are inconsistent with recognized guidelines—whether driven by physicians' personal incentives, interests or otherwise—sector productivity measurement with traditional economic indexes of price and quantity will be biased.

Hypertension[2]

Hypertension is the condition wherein a patient's resting blood pressure is above normal levels for a sustained period. Measured in terms of millimeters of mercury (mm Hg) using a mercury manometer, a patient's blood pressure is recorded in two statistics corresponding to the two phases in contractions of the heart: systolic pressure and diastolic pressure. Systolic pressure is the pressure exerted when blood in the chambers of the heart is forced outward. Diastolic pressure is the pressure exerted when the chambers of the heart are being filled. Systolic blood pressure is typically reported first. "Normal" blood pressure is approximately 120 over 80mm Hg. Diastolic hypertension is marked by diastolic pressures above 90 to 100mm Hg. Isolated systolic hypertension occurs when diastolic blood pressure is approximately normal but systolic pressures are high—above 150 to 160mm Hg.

Elevated blood pressure may be caused by the presence of another illness. If an identifiable illness is the cause, then a patient's hypertension is classified as secondary hypertension because the elevated blood pressure is "secondary" to the (generally more serious) primary illness, such as renal failure. For most hypertensive patients, no attending illness causes the elevated blood pressures. These cases are known as essential hypertension.

[1] Based on objective measures such as audits of medical charts and prescribing records.

[2] This section is based on several references. ICES (1998) is the most closely related concise summary of hypertension.

Essential hypertension is far more common than secondary hypertension. Essential hypertension was the number one diagnosis for visits to doctors in the US and Canada during 1998. Essential hypertension was the primary diagnosis in approximately 5 percent (13.8 million) of all office visits in Canada. It accounts for about twice the number of visits for the second ranking diagnosis, diabetes.[3] According to IMS Health, in 1998, over 80 percent of visits to Canadian doctors ended with a prescription when essential hypertension was the primary diagnosis—compared to 59 percent of all patient visits. Because hypertension is a chronic illness, about 90 percent of doctor visits for essential hypertension are repeat visits by patients already diagnosed with the condition.

The Heart and Stroke Foundation of Canada estimates that approximately 22 percent of Canadian adults—26 percent of men and 18 percent of women—have hypertension (HSF 1999, p.30). Yet, it is estimated that approximately 50 percent of Canadians with hypertension are unaware that they have it (HSF 1999, Feldman et al 1999). Those going undetected are more likely to be younger to middle-aged hypertensives, since routine checks for high blood pressure increase with age, along with the prevalence of hypertension. About 90 percent of seniors reported having had their blood pressure taken by a doctor within the year preceding a 1996/97 survey conducted for Health Canada and the Heart and Stroke Foundation of Canada (HSF 1999 p. 30). One third of seniors reported that they had had high blood pressure diagnosed by a physician (HSF 1999 p. 30).

Treatment

Hypertension is a concern due to its correlation with the onset of adverse cardiovascular events such as coronary artery disease, congestive heart failure and stroke. The primary goal of hypertension treatment is to reduce morbidity and mortality associated with elevated blood pressures. To do so, treatments aim to reduce blood pressure and, by inference, reduce the risk of cardiovascular events.

Drug treatment typically requires that a patient take an antihypertensive drug at least once a day for an indefinite period. Due to the inconvenience and cost of daily drug maintenance, as well as the side effects and risks inherently associated with any drug therapy, non-drug therapies are a preferred first-step for patients with mild to moderate hypertension (JNC, various years; Reeves at al 1993; ICES 1998; Anonymous 1999). It is estimated that 50 to 70 percent of patients with mild hypertension can be successfully treated with diet and lifestyle modifications alone (ICES 1998). Reducing salt, fat and alcohol consumption, losing weight, quitting smoking, exercising and controlling stress are associated with significant reductions in blood pressure levels (JNC, various years; ICES 1998, Anonymous 1999).

When lifestyle changes alone are insufficient for bringing a patient's blood pressure down to acceptable levels, drugs may be used. The four most frequently used classes of hypertension treatment are diuretics, beta-blockers, ACE-inhibitors and calcium-channel blockers. Certain other drugs may also be used in the treatment of hypertension; these include alpha 1 blockers, central peripheral sympatholytics and direct

[3] Figures from IMS HEALTH Canadian Pharmaceutical Industry Review and the National Disease and Therapeutic Index. http://us.imshealth.com/ (accessed on Tuesday 21 December, 1999.)

vasodilators (TI 1995b). Diuretics are the oldest group of anti-hypertensives, most of which have been off patent for decades and are widely available in low-cost generic form. ACE-inhibitors and calcium-channel blockers, which are the most commonly used hypertension drugs today, began entering the market in the 1970s and 1980s. Newer, patented versions of ACE-inhibitors and calcium-channel blockers (as well as entirely new classes of hypertension drugs) continue to come onto the market today.

Difficulties with Antihypertensive Drug Choice

There are two clinical aspects of the pharmacological treatment of hypertension that cloud the "information" available during drug-related decision-making.[4] First, the treatment of hypertension involves a substantial placebo effect that makes it difficult for a physician to evaluate real productivity on a trial and error basis. In virtually all properly conducted clinical trials, average blood pressure has been shown to fall consistently with placebo treatment (TI 1995b, Wright et al 1999). Thus, no matter what a doctor prescribes for a patient with high blood pressure, it is likely to appear effective at reducing blood pressure (TI 1995b). Moreover, individual doctors will be unable to accumulate enough information to determine a statistically significant difference among drugs to treat hypertension.

The second informational problem with individual assessments of hypertension treatments is that efficacy in reducing blood pressure, in and of itself, is necessary but not sufficient for real productivity. The evaluation of hypertension treatment is frequently based on the assumption that all mechanisms to lower blood pressure will have the same pressure-related benefits to health, irrespective of the mechanisms themselves (Wright et al 1999). Reliance on surrogate health outcomes to measure efficacy may be a major informational problem in the evaluation of the real cost of treating hypertension. Hypertension treatments that offer no long-term health benefits may be approved for sale because clinical trials needed for regulatory purposes are short-run trials. If a product is reasonably safe and effective at reducing blood pressures in these short-run studies, it can be sold as a hypertension treatment. Much longer trials are needed to determine whether a drug is effective in reducing long-term morbidity and mortality associated with hypertension. In fact, the best selling anti-hypertensive drugs in the 1980s were later shown to *increase* long-term risks of death (more below).

Since drugs to treat chronic "risk-factors" are intended to reduce unwanted events in the long-run, the true value of such medicines may not be known ex-ante. Evaluating the long-term effects of drugs requires massive, properly designed and conducted randomized clinical trials. A number of these gold-standard trials have been conducted on hypertension treatments, the majority of which have focussed on the older products (Wright et al 1999). If a drug proves to offer no benefits or, worse, harms patients, its consumption may be considered wasteful—certainly when judged from the informational position of the ex-post. Even ex-ante, the use of newer, unproven medicines may be considered costly in terms of risk—perhaps unnecessarily so—if products exist for which

[4] There are also a few troubling issues concerning the diagnosis of hypertension and decisions of when to treat. Among these is white-coat hypertension—wherein patients' blood pressure is higher in physicians' offices than at home (MacDonald et al 1999). These issues are beyond the scope of this paper, which addresses drug choice once treatment is indicated.

there is an established body of evidence regarding safety and efficacy. Thus, the "stock" of true information available about a medicine ought to be considered when evaluating the rationality of medical decision-making. As discussed below, for over 20 years, guidelines for the treatment for hypertension appear to have incorporated this form of risk-aversion in their recommendations.

Combined, the existence of strong placebo effects and the need for scientific collection of evidence regarding long-term efficacy make hypertension treatment an ideal candidate for medical practice based on scientific guidelines. It should not be surprising, then, that consensus statements and guidelines for the treatment of hypertension have been generated and disseminated by professional associations for more than twenty years.

Guidelines for the Treatment of Hypertension

A study by the Veterans Administration published in 1970 offered the first clinically substantiated evidence about whether antihypertensive drugs reduced morbidity and mortality among hypertensive patients. Using scientific information made available from such studies, Canadian and American committees representing interested professional organizations began to publish guidelines for the treatment of hypertension in the late 1970s. The body that publishes the most widely recognized guidelines is the US Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC). Canadian guidelines are published by the Canadian Hypertension Society (CHS).

In addition to various direct dissemination efforts, summary reports of the JNC and CHS guidelines are published in major medical journals—the Archives of Internal Medicine and Canadian Medical Association Journal, respectively—every two to four years. With each publication, these guidelines spawn numerous additional summaries and commentaries in medical, nursing and pharmacy journals.

In 1977, JNC published its first report of the consensus-based recommendations of professional organizations interested in the treatment of hypertension (JNC 1977). Members of the 1977 JNC were the American Academy of Family Physicians, American College of Cardiology, American College of Physicians, American Heart Association, Veterans Administration, American Medical Association, National Kidney Foundation, National Medical Association and the United States Public Health Service (JNC 1977). The first Canadian guidelines published by a recognized national organization were also published in 1977. Those guidelines were published by the Canadian Cardiovascular Society, the Canadian Heart Foundation and the Ontario Council of Health—collectively, the predecessors to the CHS.

The Canadian and American guidelines of 1977 recommended treatment for "virtually all" patients with diastolic pressures consistently above 105mm Hg, with the aim to reduce diastolic blood pressure to 90mm Hg. Both outlined a "Step Care" approach to drug treatment (JNC 1977, p.259-61).

Step care is relatively simple. It begins treatment with a "first-line" drug alone. If blood pressures are not controlled by the initial drug, step care recommends the *addition* of drugs from other drug classes to the patient's first-line drug regiment. The initial drug would be discontinued only if it proved to be intolerable to the patient.

In 1977, thiazide diuretics were recommended as the first line of drug therapy by both the JNC and CHS because it was thiazides that had been proven to reduce morbidity and mortality in the Veterans Administration study. Doctors were encouraged to prescribe thiazides in low-doses for newly treated patients. The recommended dosage range for hydrochlorothiazide was 50-100mg per day—high by today's standards. The step care protocol then called for an increase in dose, as necessary, or the addition of a second and, possibly, a third drug until blood pressure levels were reasonably controlled. Most non-diuretic antihypertensive drugs that were commonly used in the 1970s are classified in this paper as "other" drugs—that is, they were not beta-blockers, ACE-inhibitors or calcium-channel blockers.

In 1980, the JNC task force published a second set of consensus recommendations—JNC II—based on new evidence from clinical trials. The JNC II continued to endorse the "step care" approach beginning with diuretics (JNC 1980, p.1282). Beta-blockers and selected other drugs were recommended as first-line drugs if diuretics were contraindicated and if specific co-morbidities were present. After initial therapy, the choice of second and third line drugs was more eclectic and could include beta-blockers or several "other" drugs, such as vasodilators. The recommended drug treatment for elderly patients was oral thiazide diuretics in "*smaller than usual doses,*" which the JNC II noted "…are frequently effective as the sole agent in controlling hypertension in [the elderly]" (JNC 1980, p.1284). The JNC II recommended that greater caution be used when choosing to add second step drugs for the elderly.

In 1984, separate guidelines for hypertension treatment were published by the CHS and the JNC. The 1984 CHS report was the first official publication of the CHS task force on the management of hypertension. Funded by the Medical Research Council, National Health Research and Development Program, and the Ontario government, thirty-one biomedical scientists met at the Canadian Hypertension Society's Consensus Conference on the Management of Hypertension, Toronto, in November of 1983. They published what was hoped to be the first of an annual series of conference recommendations in 1984 (Logan 1984).

The CHS and JNC III reports of 1984 were in near consensus regarding the treatment of hypertension. One of the only substantive differences was that the JNC took a more aggressive stance regarding when to treat hypertension (JNC 1984). Treatment protocols for non-elderly patients retained the step care format, with thiazide diuretics or beta-blockers recommended by both guidelines as the first-line drugs of choice (JNC 1984, Logan 1984). However, to reduce the side effects of diuretic use, the dosages of diuretics recommended in the Canadian and American guidelines were about half that recommended in early publications—e.g., 25 to 50mg of hydrochlorothiazide per day. For seniors, the JNC III recommended thiazides alone as first-line treatment or in combination with beta-blockers in "smaller than usual" doses (JNC 1984). The CHS did not address treatment of the elderly in 1984.

The CHS published consensus guidelines for the treatment of hypertension in the elderly in 1986 (Larochelle et al 1986). The recommended protocol for treating elderly hypertensives involved step care with thiazide diuretics as the preferred first-line drug. If thiazides were contraindicated, beta-blockers were recommended as alternate therapy (Larochelle et al 1986). The CHS specifically addressed the use of the newer

antihypertensive drugs in the treatment of the elderly by noting that ACE-inhibitors and calcium-channel blockers may be useful, "...but further study is required before they can be recommended for the elderly" (Larochelle et al 1986, p.745).

The JNC published its fourth round of guidelines, JNC IV, in 1988. These were significant because they marked a deviation from the step care model and would be inconsistent with the Canadian guidelines for the first time. The JNC IV was also the first publication of the JNC that involved the American Pharmaceutical Association—a drug manufacturers trade association—as a member organization on the National High Blood Pressure Education Program Coordination Committee. This committee had to endorse the final report of the JNC before it was published (JNC 1988, endnote p. 1037).

Pharmacologic treatment protocols in the JNC IV significantly deviated from earlier models. The JNC IV no longer recommended a clear step care model because second and third "steps" in the JNC IV suggested the *addition* or the *substitution* of drugs from other classes rather than strictly adding them to the existing drug regiment (JNV 1988, p. 1027-1028). Perhaps most importantly, choices at each "step" became more eclectic than ever before. The initial therapy recommended in the JNC IV was no longer limited to diuretics and beta-blockers; ACE-inhibitors and calcium-channel blockers were also listed as possible first-line therapies.

The choice of drug was to be tailored to the "special considerations" of the patient (JNC 1988, p.1028). Among the special considerations were lifestyles, physiologic and biochemical measurements, and economic considerations, making it clear that the JNC IV endorsed trial-and-error prescribing by individual physicians. The discretionary approach to drug choice was applied to the JNC IV protocol for treating the elderly (JNC 1988, p.1034), but under "special considerations" it is noted that elderly respond better to diuretics or calcium antagonists than beta-blockers or ACE-inhibitors (JNC 1988, p.1029). In order to minimize the side-effects of diuretic treatments the recommended dosage levels for diuretics fell, once again, to half the previous recommendations: e.g., 12.5 to 50mg of hydrochlorothiazide per day.

In 1989, the CHS published the report of its consensus conference on the pharmacologic treatment of hypertension (Myers et al 1989). In large part, the purpose of this conference was to evaluate evidence about the use of ACE-inhibitors and calcium-channel blockers. Like the JNC IV, the CHS report of 1989 moved away from the step care approach because it advocated the substitution of mono-therapies as second and third-line treatments based on the idea that treatment regiments should be simple. It also endorsed a more discretionary drug choice protocol—or lack thereof (see Spence 1989). However, the 1989 CHS report seems clearer in its endorsement of low-dose thiazide diuretics or beta-blockers as initial therapy for non-elderly patients without coexisting medical conditions (Myers et al 1989, pp.1143-1144). Moreover, the 1989 CHS protocol for elderly patients continued to endorse the use of thiazide diuretics in small doses, with reference to the recommendations published in 1986 (Myers et al 1989, p.1144). The 1989 CHS report also made specific recommendations about certain classes of drugs. Notably, it stated that "Calcium antagonists are generally recommended as second-line therapy," and that "Nifedipine [a calcium antagonist] should be considered as a second or third-line drug…" (p.1145). At the time, Nifedipine was one of the most heavily

promoted and widely prescribed drugs in Canada and the US—it was also the drug at the center of the calcium-channel blocker controversy in the 1990s (more below).

In 1993, the JNC produced another somewhat unexpected report—the JNC V. The JNC V was then described as "steps forward and steps backward" (Weber and Laragh 1993). The steps forward were that the JNC took a broader approach to classifying hypertensive patients, it emphasized the need to treat patients with isolated systolic hypertension, and it increased the emphasis on the non-drug treatment of hypertension (JNC 1993). The step "backward" was the reversal of the JNC IV recommendations to add ACE-inhibitors and calcium-channel blockers to the list of potential first-line treatments for uncomplicated hypertension. The JNC V protocol reverted to thiazide diuretics or beta-blockers as the preferred first line treatments, followed by their substitution or combination. ACE-inhibitors, calcium-channel blocker or other drugs appear as third-line drugs (JNC 1993, p.170-171). For the elderly, it is noted in the JNC IV that "All classes of antihypertensive drugs have been shown to be effective in lowering blood pressure in older patients. However, only diuretics and beta-blockers have been used in controlled trials that have shown a reduction in cardiovascular morbidity and mortality" (JNC 1993, p. 178). On that basis, diuretics and beta-blockers are endorsed as preferred first-line treatments unless contraindicated.

The CHS also published a new set of guidelines in 1993, and was happy to report consensus with the recently published JNC V (Carruthers et al 1993, Ogilvie et al 1993, Reeves et al 1993). Unlike previous JNC consensus conferences, the basis of the 1993 CHS report was meetings of several special committees that would each publish a report on specific aspects of hypertension diagnosis and treatment. The new format for CHS conferences also involved new funding sources. In addition to funds from the Medical Research Council and Health Canada, numerous drug companies funded the 1992 CHS consensus conferences.[5] In return for this, representatives of these companies participated in the two-day discussions but did not have a vote on the final recommendations. However, companies did review the final drafts of recommendations from the Diagnosis and Pharmacotherapy working group and from the Elderly and Diabetes group. Perhaps in response to the obvious conflicting interests in the new process, the CHS evolved a system of grading its recommendations. Recommendations in the 1993 reports were graded (from A to D) according to the quality of scientific evidence that they were based upon (Carruthers et al 1993).

The CHS would continue to take a more conservative "when to treat" approach than the JNC. Recommended first-line drugs for uncomplicated essential hypertension were diuretics or beta-blockers (grade A). This was followed by substituting the untried first-line drug (grade A), then by the combined use of diuretics and beta-blockers (grade A). As with the JNC V, ACE-inhibitors, calcium-channel blockers and other drugs became third-line choices (grade B) (Ogilvie et al 1993). With these recommendations, the authors of the CHS report of pharmacologic treatment note that…

[5] The companies were Merck Frosst Canada, Rhone Poulec Rorer, Knoll Pharmaceuticals Canada, Servier Canada, Abbot Laboratories, Shering Canada, Searl and Co. of Canada, Sandoz Canada, Nordic Merrell Dow, Bristol Myers Squib, Pfizer Canada, ICI Pharma, Wyeth Ltd., Hoffmann-La Roche, Miles Canada, Astra Pharma and Parke-Davis.

> …the role of diuretics and beta-blockers in initial therapy for mild or uncomplicated hypertension is well supported. The actions of ACE-inhibitors and calcium entry blockers appear to be comparable, and some practitioners argue for the addition of these other drug groups to diuretics and beta-blockers for initial monotherapy, with the *expectation* of improved outcome for cardiovascular disease. Unfortunately, not enough long-term clinical trials have been done with the main endpoints of illness or survival rates to conclude that these drugs may be recommended along with diuretic or beta-blocker therapy … Other purported attributes of the newer compounds, such as favourable effects on the quality of life and neutral effects on serum lipid levels, have not as yet been related to improvements in long-term rates of illness or death. Consequently, decisions to favour one treatment over another remain speculative. (Ogilvie et al 1993, p. 577, emphasis added)

The 1993 CHS recommendation for first-line drug treatment for elderly with uncomplicated hypertension was low-dose thiazide diuretics (grade A). When thiazides are contraindicated or not preferred, the beta-blockers were recommended as second line drugs (grade B) (Reeves et al 1993).

Table 1 summarizes the drug-treatment recommendations of the Canadian and American guidelines from 1977 to 1993. Guidelines were published again in 1997 (JNC VI) and 1999 (CHS). These guidelines, which did not change treatment protocols dramatically, are described in appendix A since they do not relate to the period of study below.

It is worth stressing that the recommendations from the national guidelines are based on consensus processes that focussed on the clinical risks and benefits of the drugs in question. They were not designed based on cost-effectiveness or cost-minimization criteria. Recent findings from scientific reviews of the evidence concerning the relative efficacy of hypertension drugs have also recommended diuretics as the drugs of choice based solely on the criteria of safety and efficacy:

> Low-dose thiazide [diuretic] therapy can be prescribed as the first-line treatment of hypertension with confidence that the risk of death, coronary artery disease and stroke will be reduced. The same cannot be said for high-dose thiazide therapy, beta-blockers, calcium-channel blockers or ACE inhibitors. (Wright et al. 1999, p.25)

It has also been noted that, due to the low cost of diuretics, diuretics are definitely the preferred first-line treatment based on the criteria of cost-effectiveness:

> Based on the evidence available at this time and using the criteria of effectiveness and cost, thiazides [diuretics] are clearly the drug of first choice. Based on the criteria of efficacy, tolerability and

Table 1: Major Canadian and American Guidelines for Hypertension Treatment 1977 to 1999

Study, Date	Step Care	First-line for Non-Elderly	First-line for Elderly	HCTZ Dose / Day
JNC I, 1977	Yes	Diuretic*		50 - 100mg
CJR, 1997	Yes	Diuretic*		
JNC II, 1980	Yes	Diuretic* or Beta-Blocker	Diuretic*	
CHS, 1984	Yes	Diuretic* or Beta-Blocker		25 - 50mg
JNC III, 1984	Yes	Diuretic* or Beta-Blocker	Diuretic* or Beta-Blocker	25 - 50mg
CHS, 1986	Yes		Diuretic*	25 - 50mg
JNC IV, 1988	Partial	Diur.*, Beta-B., ACEI or CCB	Diur.*, Beta-B., ACEI or CCB	12.5-25mg
CHS, 1989	Partial	Beta-Blocker or Diuretic*	Diuretic*	25 - 50mg
JNC V, 1993	Partial	Diuretic* or Beta-Blocker	Diuretic* or Beta-Blocker	12.5-50mg
CHS, 1993	Partial	Diuretic* or Beta-Blocker	Diuretic*	12.5-25mg

ACEI = ACE-inhibitor
CCB = calcium-channel blockers.
CHS = Canadian Hypertension Society.
CJR = Canadian Joint Recommendations (by the Canadian Cardiovascular Society, the Canadian Heart Foundation and the Ontario Council of Health).
JNC = Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure.
* Refers to thiazide or thiazide-like diuretics. Loop diuretics and potassium sparing diuretics to be used only when specially indicated.

> convenience, thiazides [diuretics] are equivalent to or better than all other drugs. (BC Therapeutics Initiative Newsletter 1995)

Adverse News about Calcium-channel Blockers

In the mid 1990s, three scientific studies indicated that patients on a short-acting calcium-channel blocker had a significant increase in risk of death compared to those on other antihypertensive drugs or placebos (see Maclure et al 1998 and Stelfox et al 1998). The particular drug tested was the most popular selling hypertension drug in North America during the 1980s and its long-acting version had become the most popular drug of the early 1990s. Due to the widespread use of the group of drugs implicated by the studies, news about the negative findings circulated well before the studies were published in 1995. Manufacturers of calcium-channel blockers immediately launched a campaign to intimidate and discredit the authors of the critical articles—threatening lawsuits, attempting to block publication and paying for widespread dissemination of "dear doctor" letters that questioned the authors' credibility (Deyo et al 1998). Amidst the controversy, a special edition of the Canadian television show "the Fifth Estate" aired, criticizing the government for downplaying the risks of calcium-channel blockers. Later, Stelfox et al (1998) surveyed authors who had published letters or articles concerning calcium-channel blockers during the debate. They found that 96 percent of the authors who supported the continued use of calcium-channel blockers had financial ties to manufacturers of calcium-channel blockers. In contrast, 37 percent of authors who raised or echoed concerns about the potential risks posed by calcium-channel blockers

had such financial ties. Stelfox et al (1998) did not record the magnitude of these financial ties.

Debate concerning the safety of calcium-channel blockers continues today. Manufacturers claim that the long-acting versions of these drugs are safe and effective, though conclusive evidence regarding their long-term impact on health status has yet to become available. Perhaps in an attempt to overshadow the controversy, long-acting calcium-channel blockers are among the most heavily promoted hypertension drugs on the market.

The Impact of Hypertension Guidelines and Adverse News

There have been three studies that attempt to evaluate directly the impact of JNC and CHS guidelines on physicians' prescribing habits (Siegel and Lopez 1997, McAlister et al 1997, Hill et al 1988). A priori, one might predict a relatively acceptable rate of compliance with hypertension treatment guidelines because the task involved is not complex (compared to many other procedures), its surrogate measure of efficacy is quickly observed and recommendations could easily be implemented on a trial basis. Despite these favourable conditions, none of the JNC and CHS guideline studies found a positive impact on the prescribing habits of physicians attributable to the publishing of the guidelines.

Maryland-based doctors reported prescribing behaviours that were not different following the JNC III report in 1984 than before, despite reasonable awareness of and access to the guidelines (Hill et all 1988). Siegel and Lopez (1997) found that, contrary to the recommendations of the 1992 JNC V, prescriptions for calcium-channel blockers increased from 33 to 38 percent of all hypertension prescriptions in the US between 1992 and 1995. This occurred during the period in which adverse news about calcium-channel blockers was widespread in the media. Siegel and Lopez (1997) also found that ACE-inhibitors increased—from 25 to 33 percent of all hypertension prescriptions over the same period—contrary to recommendations of the JNC.

Findings in Canada were similar. McAlister et al (1997) found that in 1995, doctors in Edmonton-based primary care offices and medical referral clinics prescribed diuretics or beta-blockers to only 23 percent of newly diagnosed hypertensive patients. Moreover, they found that only 43 percent of patients who were prescribed drugs other than diuretics or beta-blockers had documented contraindications to either first-line drug class (McAlister et al 1997). By inference, then, the percentage of patients for whom guidelines indicated diuretics or beta-blockers could have been 67 percent or more rather than the 23 percent who received them.

Another Canadian study addressed the impact of the adverse news about calcium-channel blockers (Maclure et al 1998). They found that first-line prescribing of calcium-channel blockers for elderly patients in British Columbia fell gradually from 22 percent in 1994 to 15 percent in 1996. Maclure et al (1998) also documented a decreased use of diuretics or beta-blockers as first line treatments, contrary to published guidelines. This documentation is significant because it was based on an audit of diagnostic codes found on medical billings pertaining to this patient population—the same population looked at in the present study.

Table 2: First-Line Prescribing in 1996 for Elderly People in British Columbia in Relation to Relative Contraindications*

Coexisting Illness	n	%	RC for Thiazides?	% Prescribed Thiazides	RC for Beta-Blockers?	% Prescribed Beta-Blockers	% Prescribed ACEI, CCB or "Others"
None	15189	41%	No	41%	No	11%	48%
Depression	3993	11%	No	42%	Yes	15%	43%
Asthma	2255	6%	No	43%	Yes	6%	51%
PVD	365	1%	No	38%	Yes	7%	55%
HL	1964	5%	Yes	36%	Yes	14%	50%
Diabetes	1925	5%	Yes	26%	Yes	7%	67%
Arrhythmia	949	3%	Yes	33%	No	19%	48%
Gout	749	2%	Yes	29%	No	13%	58%
Two or more	9863	26%	?	33%	?	11%	56%
Total	37252			38%		11%	51%

Source: Maclure et al (1998) table 3.
* Maclure and colleagues regard relative contraindications as "…disorders that many physicians regard as reasons to avoid diuretics or beta-blockers, although evidence supporting some of these reasons may be weak" (Maclure et al 1998, p.352).
ACEI = ACE-inhibitors.
CCB = calcium-channel blockers.
HL = hyperlipidaemia.
PVD = peripheral vascular disease.
RC = Relative Contraindication

Table 2 summarizes data in Maclure et al (1998) regarding first-line prescribing in 1996 for elderly British Columbians in relation to relative contraindications. They regard relative contraindications as "…disorders that many physicians regard as reasons to avoid diuretics or beta-blockers, although evidence supporting some of these reasons may be weak" (Maclure et al 1998, p.352). Consistent with the findings of McAlister et al (1997), Maclure et al (1998) found that "…in 1996 physicians continued to prescribe CCBs or ACE inhibitors as first-line therapy to 42% of newly treated patients, contrary to guidelines" (p.952). Patients who did not have documented relative contraindications to diuretics received them only 40 percent of the time. Surprisingly, those who did have documented relative contraindications received diuretics approximately 30 percent of the time (Maclure et al 1998, p.352). From the profile of coexisting illnesses documented in Table 2, it appears that diuretics or beta-blockers could have been rationally prescribed as first-line therapy, in accordance to guidelines and popular (but sometimes unsubstantiated) beliefs about relative contraindications, to approximately 65 percent of patients.

It would appear from these findings that, in Canada and the US, doctors are not prescribing diuretics and beta-blockers in accordance to guidelines. Moreover, the findings of Maclure et al (1998) indicate that variations in what is prescribed to patients bear only a weak relationship to documented coexisting illnesses. In most studies, increased marketing of the newer drugs or physicians' desire to be perceived as being on

the forefront of medicine are offered as potential explanations for the failure of practice to resemble guidelines.

Analysis of Hypertension Treatment for BC Seniors: 1986 to 1996

Description of Data

This analysis is based on a unique database extracted at the Centre for Health Services and Policy Research, UBC with permission form the British Columbia Ministry of Health and Ministry Responsible for Seniors. The database contains an observation for every antihypertensive prescription dispensed to beneficiaries of the BC Pharmacare Plan A in the period of January 1986 to December 1997. Pharmacare Plan A covers all community-dwelling BC residents who are 65 and over. All beneficiaries of Pharmacare Plan A are insured for the ingredient costs of prescription medicines, net of dispensing fees. The data used here contain ingredient costs only.

Observations in the database consist of the following fields of information: (1) a case study identification number for each patient, (2) the patient's year of birth, (3) the date the prescription was filled, (4) the drug identification number (DIN) corresponding to the drug dispensed, (5) the quantity of the drug dispensed and (6) the ingredient cost of the prescription. The database consisted of 9.89 million observations representing antihypertensive prescriptions filled by over 390,000 patients. For the period of 1986 to 1996, the cost data reflect the transaction cost of the drugs dispensed. Pharmacare has recently implemented a new system of classifying drug costs that makes the data for 1997 unreliable. In 1997, the Pharmacare plan introduced a modified reimbursement scheme for the Plan A—the reference pricing program—the out-of-pocket costs of which appear to be missing from the Pharmacare database used here. Unfortunately, price information—including all price indexes—is therefore only reported for the period 1986 to 1996. The quantity information for all eleven years is accurate and used in the analysis of prescribing patterns.

Observations were grouped into five broad categories, corresponding to the class of hypertension treatment the prescription pertained to. These categories were diuretics, beta-blockers, ACE-inhibitors, calcium-channel blockers and "other" drugs used in the treatment of hypertension. Appendix B lists the members of each drug class.

Elementary Price and Quantity Indexes

The first step in the manipulation of the database involved aggregating data into elementary indexes that would be used in the construction of the aggregate economic indexes of price and quantity. Elementary indexes of price and quantity were constructed from this database by calculating the unit value and total quantity of drugs dispensed per quarter. Quarterly observations were chosen because they provide sufficient detail regarding price movements and facilitated the task of counting patients actively receiving hypertension treatment at any point in time (described below).

Rather than aggregate to the DIN level, this analysis uses a unit value approach to aggregating across brand-name and generic versions of chemically identical products.

This aggregation is based on a 9-digit American Hospital Formulary Service (AHFS) number assigned to each product. AHFS numbers are unique to a specific drug by strength and dosage form, but not by manufacturer or brand-name. The unit value approach to products with the same AHFS number treats them as identical goods by summing their total sales and dividing this by their total quantity to arrive at a common unit value (Diewert 1995). This "a-pill-is-a-pill" methodology imposes the assumption that brand-name and generic versions of a drug represent equal amounts of productivity.

Elementary Indexes of Real Productivity

National guidelines for the treatment of hypertension are used here as the basis of the health-outcomes based real productivity measures. Notwithstanding the increased involvement of pharmaceutical manufacturers in both the Canadian and American consensus processes, the CHS and JNC guidelines have been generated by recognized national bodies interested in promoting best medical care. Their recommendations were based on the best available scientific evidence regarding proven reduction in morbidity and mortality associated with high blood pressure. These recommendations are widely recognized and easily accessed by prescribers. They are taken here as indication of the most socially desirable treatment protocol. Clearly, the perspective that the treatment guidelines represent involves a certain degree of risk aversion or preference for the use of medicines with proven track-records of safety and efficacy. This was indicated by cautions regarding the use of newer medicines found in the guidelines (quoted at length above). This form of preference does not detract from the notion that these guidelines represent "real" objectives in the sense that it is, indeed, desired that medical practice conform reasonably with recommended treatments. This caution and conservatism is justified, as shown by the case of short-acting calcium-channel blockers.

Since 1977, the CHS and JNC national guidelines have consistently listed diuretics among (often alone as) the preferred first-line drugs to treat uncomplicated hypertension—especially for elderly, who respond best to thiazide diuretics. It therefore seems reasonable to assume that, unless contraindicated, diuretics are as "productive" or better, from a societal perspective, than any other antihypertensive drugs. This assumption is in stark contrast with the implicit productivity weight that traditional economic indexes must put on diuretic drugs. The average calcium-channel blocker is 150 times more expensive per day of treatment than Hydrochlorothiazide, which is one of the oldest diuretics and the drug most frequently recommended by hypertension guidelines. Because of its low cost, Hydrochlorothiazide would receive 0.0067 times the weight placed on the average calcium-channel blocker in traditional Laspeyres or Paasche indexes of price and quantity.

The health-outcomes based productivity measures used here are built on an assumption best described as "a-treatment-is-a-treatment." Real productivity will be defined according to the number of prescribed "patient-days" of therapy and by the number of "discrete patients" treated for hypertension, regardless of the class of hypertensives being used. This is analogous to the "a-pill-is-a-pill" approach to comparing equivalent brand-name and generic drugs. Whereas that approach assigned equal productivity values to chemically equivalent products, the a-treatment-is-a-

treatment approach assigns equal values to days of treatment (or patients treated) with chemically different drugs that treat the same condition.

The assumption that all treatment regiments are of equal "value" may appear troubling due to the fact that specific drugs may be contraindicated for patients with certain coexisting illnesses. Thus, to those patients, the contraindicated drugs are of no value—or of negative value! Diversity in medical "needs" makes it difficult to assign average values to any medical procedure or drug, making health-related productivity measurement difficult. Fortunately, perhaps, guidelines for hypertension can be interpreted as a fixed coefficient production function. In this light, the optimal relative demands for inputs from different drug classes are determined by the prevalence of relative risk factors in the treated population. Observable patient characteristics indicate when treatments are or are not appropriate first-line therapies. It is therefore possible to gauge the optimal vector of first-line inputs into the hypertension-related social welfare "production function" based on reasonably objective measures.

The findings of McAlister et al (1997) and Maclure et al (1998) indicate that diuretics or beta-blockers would be appropriate first-line treatments for approximately two thirds of patients. Movement towards a treatment profile where diuretics or beta-blockers are prescribed for approximately two thirds of newly treated hypertension patients would accordingly indicate an improvement in sector productivity, from the societal perspective. Movements in the opposite direction could be judged as deviations away from the socially preferred mix of treatment inputs and, therefore, a decline in sector productivity. More could be had for less, so to speak, if the treatment protocol move in the direction of those recommended.

It should be noted that assuming that all drugs used over the course of study are as effective as diuretics might be considered *generous* in light of virtually all clinical evidence available during the period under study. Specifically, the a-treatment-is-a-treatment assumption does not discount purchases for the uncertainty associated with taking medicines that did not have a body of scientific evidence to substantiate claims about safety and long-term efficacy. Such gambles appear to have resulted in exposing patients to increased risks of death in the case of short-acting calcium-channel blockers.

The simplified assumptions implicit in the methodology used here are necessary because the available database does not include information regarding comorbidities. Despite their rather gross nature, these assumptions are probably accurate within reason—especially given that the variations in antihypertensive prescribing for elderly patients in British Columbia reported by Maclure et al (1998) bore only a weak relationship to documented coexisting illnesses. Changes in the profile of first-line prescribing and continuing drug use will be evaluated to determine whether prescribing moved toward or away from the recommended drugs.

Calculating Drug Treatment Exposure: Patient-Days

Two measures of drug exposure and, thus, elementary indexes of real health production were calculated from the observed market transactions in the database. The first was based on the number of days of maintenance therapy represented by the quantity of physical pills and tablets purchased in each quarter. The most common method of determining drug utilization levels by populations is to use dose standardization methods

to calculate exposure by standardized patient-days (Merlo et al 1996). Simply, this involves the division of the units of drugs purchased by a standardized dose. Among the possible candidates for standard dosages are the minimum marked dose, the defined daily dose and the prescribed daily dose.

The minimum marked dose is the minimum amount of a drug that will give the desired therapeutic effect. It is determined a priori and typically equals the smallest dose of the drug marketed by a manufacturer (Merlo et al 1996). This measure suffers several disadvantages, including the fact that it ignores drug dose titration that occurs in hypertension care, rendering it inappropriate for this study.

The defined daily dose is an international standard developed by the World Health Organization for comparing drug utilization across countries and regions. A defined daily dose is determined a priori as the assumed average daily dose of a drug for use in its main indication by adults (Merlo et al 1996). Despite international appeal, the greatest weakness of defined daily doses is that they are updated only periodically to account for changes in average doses used for the main indication of a drug. In the case of certain hypertensives, diuretics in particular, the recommended daily dose has fallen dramatically over the past ten years. An additional weakness of defined daily doses is that they are not necessarily "defined" for all products available in the Canadian marketplace, leaving estimation to the analyst.

The third candidate for dose standards is the prescribed daily dose. This is the average daily dose of a drug prescribed to a given population. Prescribed daily doses are not assigned a priori; rather, they must be calculated for each study. The advantage of the prescribed daily dose is that it reflects actual prescribing habits, thereby accounting for changes in dosage strengths, whether recommended or not. Its primary disadvantage is that it must be estimated from available data. Despite difficulties posed by estimation, this analysis uses prescribed daily doses because these measures will capture the potential cost-reducing effects of prescribing lower dosages of antihypertensive drugs over the period of analysis.

Prescribed daily doses were calculated by tracking patients who had repeat prescriptions for antihypertensive medications from the same broadly defined therapeutic class. More than 90 percent of prescriptions in each category were repeat prescriptions—about 80 percent of these were for patients who refilled their prescriptions at least every 90 days. The estimated prescribed daily dose was the average number of pills per day between repeat prescriptions, calculated for each drug type on a quarterly basis. A certain amount of "noise" could be expected in this methodology—due, for example, to intermittent hospitalization of patients. Such noise will make the calculated prescribed daily doses imperfect representations of the true therapeutic dosages used by the recipient population or intended by the prescribing physicians. Nevertheless, there are no reasons to suspect that such noise would change systematically across treatment types or over time. Thus, there should be no expected aggregate measurement biases using this averaging technique.

Calculating Drug Treatment Exposure: Discrete Patients

The second measure of drug exposure used in this study is based on the number of discrete patients receiving hypertension therapy during a given quarter. Indexes using

measures of cost per patient treated were calculated because there is a potential for patient-day exposure measures to bias the price and productivity indexes over the period of study. This stems from the fact that recommended treatment protocols changed from step care models, wherein patients would be prescribed additional drugs if therapies were only partially effective, to eclectic choice models where substitution from mono-therapy to mono-therapies was endorsed. Because a single discrete patient can consume more than one patient-day of drugs per day, the patient-day quantity and price indexes may be biased. This bias will depend on changes in the prevalence and cost of multiple drug therapy use. If fewer patients were prescribed multiple-therapies, patient-day price indexes will overstate costs because more discrete patients could be treated with a given number of patient-days.

To construct the indexes of discrete patients, every patient in the database was assigned to one of eight categories for every quarter of the study period. The categories corresponded to the type of antihypertensive drug received by the patients during the given quarter. The categories were (1) no antihypertensive drugs, (2) diuretics only, (3) diuretics plus any other drug, (4) beta-blockers only, (5) ACE-inhibitors only, (6) calcium-channel blockers only, (7) other antihypertensive drugs only, and (8) combinations of any two or more non-diuretic drugs. Diuretics in combination with other drugs were isolated because the use of diuretics received the majority of recommendations as first-line treatment in hypertension guidelines. Isolating diuretics has no impact on the aggregate indexes themselves, but facilitates evaluation of prescribing habits. Quarterly indexes of the total number of patients and the average cost per patient in each of these categories were constructed.

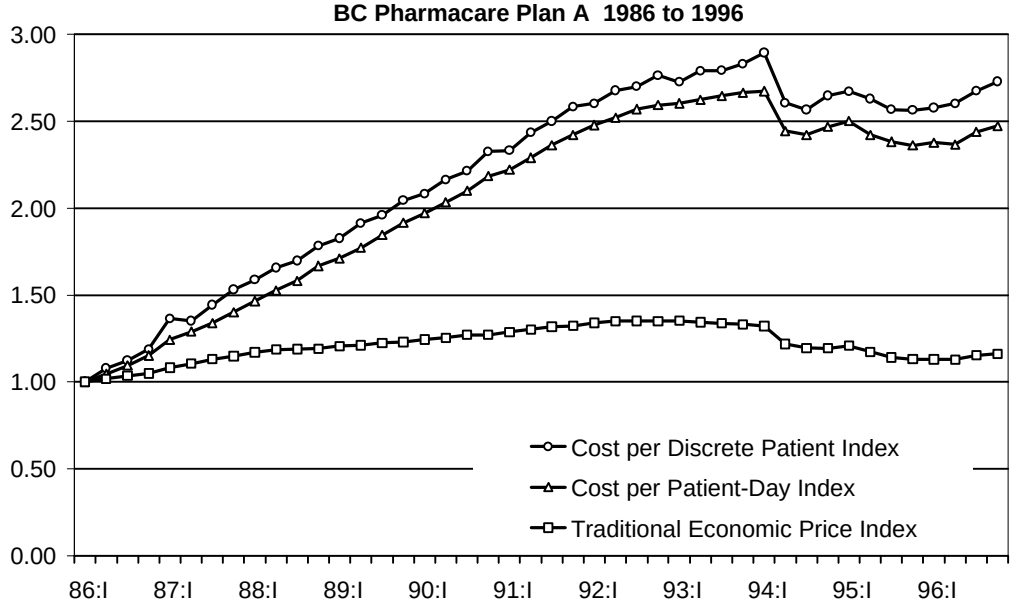
Findings

Price Indexes

Indexes for all classes of drugs combined are illustrated in Figure 1. The economic index is a chained Laspeyres index, with quantity weights updated each period. It represents an estimate of the true sector-specific cost-of-living index within the traditional economic approach to measurement. Under the assumptions of that approach measurement, the Laspeyres index is an upper bound on the "exact" sector-specific cost-of-living index for two reasons. First, Laspeyres indexes theoretically bound exact cost-of-living indexes from above. Second, new goods are "linked" into the Laspeyres index used here during their second period of availability without adjustment. Thus, only changes in their price levels are captured by the index. That is, the index ignores the "new-goods" effect of entrants. Since numerous ACE-inhibitors and calcium-channel blockers entered the market over the course of study (see Appendix C), this will result in an index that *overstates* price changes provided the assumptions of the traditional economic approach to measurement are satisfied.[6] From 1986 to 1996, the average growth rate of the economic index was 1.5 percent per annum.

[6] Under the assumptions of the traditional economic approach to measurement, the reservation price technique for capturing the "new goods" effect of an entrant always captures a decline in real prices. Otherwise, the new good would not be purchased when it was introduced.

Figure 1
Alternative Indexes of the Price of Hypertension Treatments
BC Pharmacare Plan A 1986 to 1996



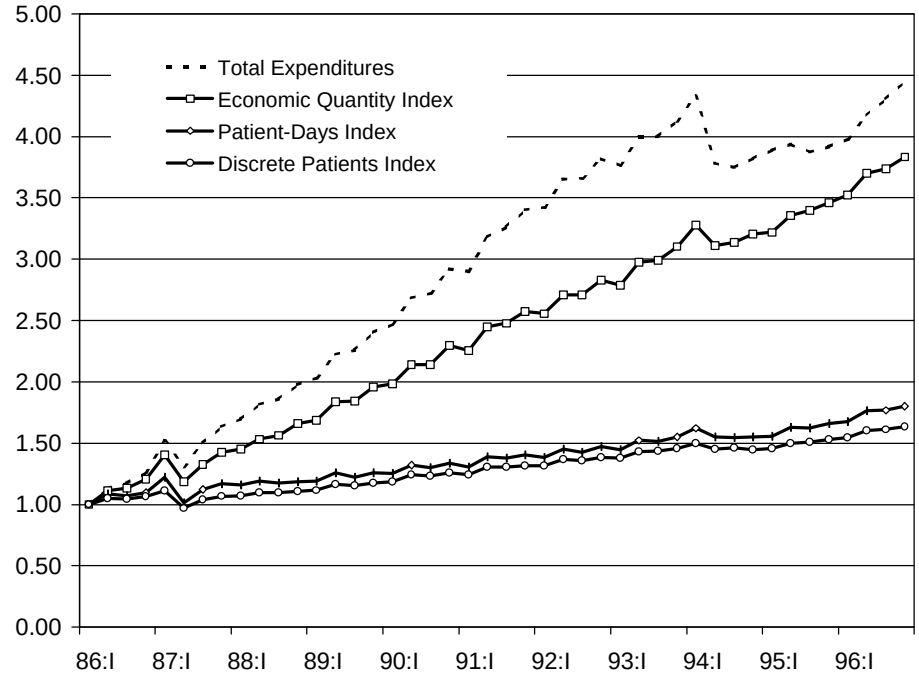
The cost per patient-day index illustrated in Figure 1 uses the estimated number of patient-days of maintenance therapy (described above) as the basis for productivity measurement. Similarly, the cost per discrete patient index uses the number of discrete patients receiving hypertension treatment as the basis for productivity measurement. This measure accounts for changes in the use of multiple-therapy over time. Growth rates for the cost per patient-day and cost per discrete patient indexes were 9.5 and 10.5 percent per annum, respectively, from 1986 to 1996. The fact that costs per patient increased faster than the cost per patient-day indicates an increase in the use of multiple drugs per patient over the period of study. This is an unanticipated change because the national prescribing guidelines gradually encouraged more mono-therapy, not multiple-therapy, over the period.

There was a statistically significant (at p=0.01) change in the trend of all indexes beginning at 1994.[7] The 1994 date marks the beginning of the Low Cost Alternative plan (which increased the incentive for pharmacists' to dispense generic drugs) and the time when major media events covered the calcium-channel blocker controversy. All indexes grew at a faster rate before 1994 than after. The rate of change in the health outcomes indexes was not significantly different from zero after 1994, while the economic index fell at a rate that was slow but significant (at p=0.05).

As is clear from Figure 1, the traditional economic index is far lower than the health outcomes based indexes. The difference between health outcomes based price indexes and the traditional economic index increased rapidly from 1986 to 1994, then

[7] Regression analyses of these trends are listed in appendix D.

Figure 2
Alternative Indexes of Quantity of Hypertension Treatments
BC Pharmacare Plan A 1986 - 1996



stabled off. Increases in the health-outcomes based indexes relative to the economic index is indicative of changes in consumption patterns from drugs that were low-cost to drugs that were high-cost on a per-treatment basis. Such changes would not be captured by the economic index because, when the assumptions of the traditional economic model are met, increased use of high-cost products would only occur if their relative price reflected their relative productivity. Thus, switching to high-cost therapies instead of low cost therapies is captured by the economic index as an increase in the quantity of output purchased. This is revealed in Figure 2, which illustrates the quantity indexes that are dual to the price indexes listed in Figure 1.

The quantity indexes illustrated in Figure 2 are obtained by deflating expenditure growth by the respective price indexes. It is noteworthy that Pharmacare's annual spending on hypertension drugs nearly quadrupled from $15.8 million in 1986 to $58.7 million in 1996.

The traditional economic index of aggregate quantities attributes most of the observed change in expenditures on hypertension drugs to changes in the quantity of output generated through the market transactions described by the underlying data. The reason for this is that the tradition economic approach weighs changes in the use of drugs by the share of expenditures on them. Thus, increased use of high-cost hypertension drugs is said to generate more output than increased use of low-cost drugs. Recall,

however, that the metric of sector-specific output for the traditional economic indexes is a utility-theoretic concept of social welfare that is "revealed" by consumption patterns.

The health outcomes based indexes, on the other hand, do not assign units of productivity based on "preferences" revealed by the level expenditures on particular drugs. Rather, the productivity metrics of patient-days of treatment and discrete patients treated are based on the actual number of patients receiving hypertension drugs and the actual number of days that they receive them. The indexes based on these measures of real output grew by 63 and 80 percent, respectively, over the period of study. These changes are modest by comparison to the 280 percent increase (a near quadrupling) in the traditional economic index of quantity. As with the aggregate price indexes, the difference between the health outcomes based quantity indexes and the traditional economic quantity index reflects an underlying increase in the use of higher priced therapies rather than lower priced ones, as well as the use of more therapies per patient treated.

To determine whether the substitution of high cost-treatments for low-cost treatments should be considered an improvement in real productivity, it is necessary to look at how prescribing patterns evolved over the period of analysis. If the movements towards higher cost medicines were coincident with movements toward treatment protocols recommended in national guidelines, then there may be grounds to favour the traditional economic measures of price and quantity in this sector. If otherwise, the health outcomes based indexes should be considered closer to the true social costs and real outcomes generated by transactions in this market segment.

Aggregate Drug Exposure Profiles

Table 3 shows the annual average number of discrete patients receiving drugs to treat hypertension during each quarter, along with the distribution of these patients across different treatment regiments. The table also indicates what percentage of the drug recipients were persistent in their treatment for two years following their first prescription during the period of study. Persistence was defined as those who filled a prescription for any kind of hypertension drug every quarter for at least eight consecutive quarters, or those did so during at least two quarters of each of two consecutive years.

Table 3 :Treatment Classification for All Seniors Receiving Antihypertensive Drugs.

	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
N*	91986	92663	96648	101832	108673	114424	119838	126157	129472	132459	141384
% Persistent+	86%	93%	93%	92%	91%	91%	90%	90%	89%	89%	88%
Diuretics	35%	33%	30%	26%	23%	20%	18%	16%	15%	14%	14%
Diuretics Plus	22%	21%	20%	18%	17%	16%	15%	15%	15%	15%	16%
Beta-Blockers	20%	19%	19%	18%	17%	16%	15%	14%	13%	13%	13%
ACE-Inhibitors	2%	3%	6%	9%	12%	14%	17%	18%	19%	20%	21%
CCB	8%	10%	13%	16%	18%	20%	21%	22%	23%	22%	20%
Other	7%	6%	5%	4%	4%	3%	3%	2%	2%	2%	3%
ND Combo	6%	7%	8%	9%	10%	11%	12%	12%	13%	13%	14%

*Annual average number of patients per quarter receiving drugs to treat hypertension.
+Seniors who filled prescriptions every quarter or intermittently for two consecutive years or more.
CCB = calcium-channel blockers.
ND = Combination of non-diuretic drugs.

In interpreting this table, and all subsequent tables, attention must be paid to the difference between the measures for 1986 and 1996 as compared to the years in-between. The data used here track the purchase of medicines by many people who used hypertension treatments before 1986 and many who used them after 1996. This will make it difficult to determine precisely the nature of patients "persistence" at the tails of the observation period—though transaction records for 1997 facilitate this for the 1996 observations. In addition, since data for prescriptions filled in 1986 account for many patients who would had long been using hypertensives, there is no way of determining which of them recently "started" hypertension treatment using the available database—treatment "starts" are, however, estimated for all other years (more below).

Since diuretics were the most common hypertensive treatment used in the 1970s and early 1980s, it is not surprising that a large percentage of patients receive diuretics in 1986. Once tritrated on a therapy, patients typically remain on that therapy (a proposition examined below). The exposure to diuretics among the treated population of elderly hypertensives in BC fell dramatically over the course of this study. Approximately 57 percent of those receiving hypertension drugs in 1986 received diuretics. By 1996, this figure fell to approximately 30 percent. Exposure to treatment with beta-blockers also fell over this period, from 20 percent to 13 percent. The declining exposure to these drugs was mirrored by increased exposure to ACE-inhibitors and calcium-channel blockers, which rose from 2 and 8 percent to 21 and 20 percent, respectively. Also notable was the increased exposure to multiple-therapies that did not include diuretics—from 6 percent to 14 percent. Of these multiple non-diuretic therapies, the percentage involving beta-blockers fell from approximately 75 percent in 1986 to 50 percent in 1996 (data not shown). Combined, and including combination drug use, the use of diuretics and/or beta-blockers fell from 80 percent in 1986 to 50 percent in 1995.

Appendix E contains regression results for the treatment classifications of patients. There were statistically significant (at p=0.01) changes in the trend of drug use

Table 4: The Average Cost Per Patient Treated, Grouped by Drug Class

	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
Diuretics	$34	$37	$39	$50	$42	$45	$47	$46	$40	$34	$30
Diuretics Plus	$267	$332	$375	$511	$453	$496	$529	$543	$514	$494	$502
Beta-Blockers	$125	$152	$168	$221	$188	$197	$204	$202	$181	$161	$152
ACE-Inhibitors	$367	$376	$372	$464	$386	$401	$416	$414	$371	$373	$391
CCB	$399	$467	$492	$635	$529	$554	$572	$568	$554	$536	$543
Other	$105	$121	$130	$171	$153	$164	$181	$196	$187	$207	$249
ND Combo	$519	$633	$698	$935	$817	$873	$915	$923	$872	$838	$847

CCB = calcium-channel blockers.
ND = Combination of non-diuretic drugs.

following 1994. Exposure to calcium-channel blockers fell over this period, whereas it had increased before 1994. The use of diuretics and beta-blockers increased, whereas they had decreased before 1994. And, the use of ACE-inhibitors grew at a faster rate after 1994 than before. Exposure to combination therapies increased over the period of study, which explains the difference between the indexes based on discrete patients and patient days.

Table 4 lists the average cost of treatment in the various categories as used by the patients listed in Table 3. As shown, the cost of treating patients for a year varied dramatically across categories and over time. The cost of treating patients with diuretics alone was only a fraction of the cost of treating patients on any other drug or combination. Calcium-channel blockers, followed by ACE-inhibitors, were the most expensive forms of mono-therapy prescribed to this patient population. By far the most expensive courses of therapy overall involved combinations of non-diuretic drugs. The cost of treatment in this category also rose dramatically with the increased use of ACE-inhibitors in combination with calcium-channel blockers (with or without additional agents)—from about 1 percent to 30 percent of combination therapies (data not shown).

Given the changes in treatment profiles listed in Table 3 and the difference in the cost of these treatments listed in Table 4, it is not surprising that the price indexes measured in terms of patient-days and patients treated rose dramatically over time. The question remains whether these changes reflect improvements in therapy or not.

First-Line Treatments

The source of the decline in diuretic and beta-blocker exposure among all seniors receiving hypertension drugs was a dramatic change in the profile of first-line drug treatments. Table 5 lists the distribution of "first-line" hypertension treatments for patients aged 66 and older who received drugs to treat hypertension *for the first time* during each quarter. Only patients over 66 years of age were selected to be sure that, for at least one year before the first recorded prescription, these patients had not received hypertension drugs in BC. (Thus, first-line treatment profiles could not be constructed for 1986.) Furthermore, only patients who continuously or intermittently filled

Table 5: Classification of First-Line Treatments for Persistent* Patients Aged 66 and Older

	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996+
N	8,405	7,423	8,156	9,143	7,389	7,372	7,762	8,153	8,491	10,214
Diuretics	36%	31%	25%	24%	19%	18%	18%	17%	20%	23%
Diuretics Plus	11%	9%	9%	8%	6%	6%	7%	6%	7%	7%
Beta-Blockers	19%	16%	16%	15%	14%	13%	13%	13%	14%	16%
ACE-Inhibitors	6%	13%	17%	19%	26%	27%	27%	29%	28%	26%
CCB	19%	23%	24%	24%	27%	26%	24%	24%	18%	13%
Other	5%	3%	3%	3%	2%	2%	2%	3%	5%	8%
ND Combo	5%	5%	6%	7%	6%	7%	7%	8%	8%	7%

*Those who filled prescriptions every quarter or intermittently for two consecutive years or more.
+Includes patients only persistent for one year.
CCB = calcium-channel blockers.
ND = Combination of non-diuretic drugs.

hypertension prescriptions over at least a two-year period are listed in Table 5. This is because approximately 25 percent of all patients who receive their first hypertension treatments do not obtain another again for at least two years (the chosen length of time for following up on patients in this study).

Combined, patients who do not persist with therapy account for a small but growing share of total costs. These non-persistent patients accounted for less than 1 percent of costs in 1986 and 3 percent of costs in 1996. While the treatment profiles of non-persistent patients includes all therapy types, the share of non-persistent patients that use diuretics was constantly greater than that of patients who were persistent with therapy (See appendix F). This should not, however, be interpreted as proof that diuretics do not work. Since these patients do not "switch" to other hypertension treatments, it appears that they are receiving these drugs for non-chronic conditions or that they are discontinuing therapy for clinical reasons other than drug tolerability (J. Wright, personal communication, Dec 1999).

First-line treatment was determined by the drugs used during a patient's first quarter of hypertension treatment. This will account for some early-treatment volatility. When newly treated patients are immediately switched from one treatment to another, they will show up in the combination categories.

The data in Table 5 clearly indicate why there has been gradual erosion in the share of hypertensive patients being treated with diuretics and beta-blockers over the period of study. Diuretics or beta-blockers—alone or in combination with other drugs—were used as first-line treatments for 68 percent of newly diagnosed elderly hypertensives in 1986. This figure is consistent with the estimated two thirds of seniors for whom these drugs would have been appropriate (see discussion above). Their use as first-line treatments fell to a low of 38 percent in 1994, and then rose to 48 percent by 1996.

Statistical analysis of the trend in first-line treatments (listed in appendix G) indicates that there was a significant decline in the number of patients being treated with

diuretics or beta-blockers prior to 1994. There was a significant rise in the number of patients treated with ACE-inhibitors and calcium-channel blockers over this period. The total number of patients being first treated for hypertension did not increase over the period of study (the 1996 figure in Table 5 is "large" because it is based on a looser definition of persistence). First-line treatment with calcium-channel blockers declined following 1994, while first-line use of all other drugs increased from 1994 to 1996. The rate of increase in the use of ACE-inhibitors as first-line treatments after 1994 was not significantly different from that before 1994.

The full effect of the changes in first-line prescribing is felt over the long-run. Because hypertension treatment requires continuous drug maintenance, today's flow of new patients will affect current and future stocks of patients on drug therapy. The high exposure to diuretics among the elderly population early in the period of study—depicted in Table 3—was a result of the "stock" of long-treated patients who likely had been on diuretics for many years before they "aged into" the database used here. The dramatic changes in first-line drug use over the period of study—depicted in Table 5—will influence the average cost of hypertension treatment in BC for many more years.

Therapeutic Trajectories

To investigate how patterns of drug use have changed for those taking drug therapy, "therapeutic trajectories" were constructed for all newly treated patients who received continuous treatment for their hypertension. This allows for tests of the proposition that once started on therapy, patients are likely to continue on it. It also offers an indirect test to see if increased use of newer drugs reflected increased productivity not captured by the cost per patient-day and cost per discrete patient indexes.

During the 1980s and 1990s, while guidelines consistently recommended diuretics and beta-blockers as first-line therapies, doctors may have prescribed the newer drugs because their patients had voiced dissatisfaction about the side-effects of older medicines. There was no evidence that newer hypertension drugs were more effective, and they were far more expensive than older drugs, so their selection could only be "rationalized" based on perceptions of superior tolerability. If better tolerability was to justify the higher expense of newer drugs, then the persistence on the newer therapies should have been significantly higher than that on the older drugs. After being prescribed older drugs, one might conjecture that hypertensives would voice concerns, thereby initiating a change in therapy, more often than patients who received newer drugs—if the older medicines were less tolerable than new ones.

Table 6: Transitions for 66+ Year Old Patients Who Refill Continuously For Two Years

1987-1989															
First Line		**Year One**							**Year Two**						
		D	**D+**	**B**	**A**	**C**	**O**	**ND**	**D**	**D+**	**B**	**A**	**C**	**O**	**ND**
Diuretics	**24%**	**74%**	11%	3%	5%	5%	1%	1%	**67%**	11%	4%	9%	7%	1%	2%
Diuretics Plus	**11%**	9%	**53%**	8%	10%	11%	3%	5%	11%	**43%**	9%	12%	14%	3%	8%
Beta-Blockers	**18%**	2%	9%	**70%**	5%	6%	1%	8%	3%	9%	**61%**	6%	10%	1%	10%
ACE-Inhibitors	**13%**	2%	8%	3%	**74%**	5%	1%	7%	3%	9%	2%	**69%**	7%	1%	8%
CCB	**24%**	1%	5%	2%	3%	**83%**	0%	6%	1%	6%	3%	4%	**78%**	0%	8%
Other	**3%**	3%	10%	3%	6%	7%	**62%**	9%	4%	11%	4%	11%	10%	**51%**	8%
ND Combo	**6%**	1%	8%	11%	11%	20%	2%	**46%**	2%	9%	10%	11%	25%	2%	**41%**
N	**13,280**	**20%**	**13%**	**16%**	**14%**	**26%**	**3%**	**8%**	**19%**	**13%**	**14%**	**15%**	**27%**	**3%**	**9%**

1990-1992															
First Line		**Year One**							**Year Two**						
		D	**D+**	**B**	**A**	**C**	**O**	**ND**	**D**	**D+**	**B**	**A**	**C**	**O**	**ND**
Diuretics	**15%**	**69%**	9%	2%	9%	7%	1%	2%	**62%**	11%	3%	12%	8%	1%	3%
Diuretics Plus	**8%**	8%	**51%**	5%	15%	11%	2%	8%	9%	**44%**	6%	16%	15%	2%	8%
Beta-Blockers	**14%**	1%	7%	**71%**	5%	7%	0%	10%	2%	8%	**62%**	6%	10%	1%	12%
ACE-Inhibitors	**25%**	2%	7%	2%	**74%**	8%	1%	7%	3%	9%	3%	**66%**	11%	1%	8%
CCB	**27%**	1%	4%	2%	5%	**82%**	0%	6%	1%	6%	2%	6%	**76%**	0%	9%
Other	**2%**	1%	5%	1%	7%	9%	**68%**	9%	4%	6%	3%	10%	11%	**56%**	10%
ND Combo	**8%**	0%	6%	10%	12%	20%	2%	**50%**	1%	7%	10%	13%	23%	1%	**45%**
N	**13,924**	**12%**	**10%**	**13%**	**24%**	**29%**	**2%**	**10%**	**12%**	**11%**	**12%**	**23%**	**29%**	**2%**	**11%**

1993-1995															
First Line		**Year One**							**Year Two**						
		D	**D+**	**B**	**A**	**C**	**O**	**ND**	**D**	**D+**	**B**	**A**	**C**	**O**	**ND**
Diuretics	**16%**	**67%**	12%	3%	11%	4%	0%	2%	**60%**	14%	3%	13%	6%	1%	3%
Diuretics Plus	**8%**	10%	**45%**	7%	17%	14%	1%	6%	11%	**41%**	7%	18%	14%	1%	8%
Beta-Blockers	**14%**	2%	6%	**72%**	5%	6%	1%	9%	2%	8%	**64%**	6%	8%	1%	11%
ACE-Inhibitors	**29%**	3%	7%	2%	**74%**	7%	1%	6%	4%	9%	2%	**67%**	9%	1%	8%
CCB	**23%**	2%	6%	3%	5%	**77%**	0%	8%	3%	7%	4%	7%	**69%**	0%	10%
Other	**3%**	2%	5%	1%	4%	3%	**80%**	5%	3%	4%	1%	6%	5%	**72%**	8%
ND Combo	**9%**	1%	5%	12%	14%	18%	1%	**49%**	3%	7%	12%	15%	19%	1%	**44%**
N	**14,361**	**13%**	**10%**	**13%**	**28%**	**24%**	**3%**	**10%**	**13%**	**11%**	**12%**	**27%**	**23%**	**3%**	**11%**

ND = Combination of non-diuretic drugs.

To investigate this possibility, transition matrices were constructed for newly treated hypertensives over the age of 66. They are listed in Table 6. For purposes of parsimony, patients were grouped into cohorts based on when they started treatment. Three matrices are listed here: corresponding to the cohorts that started treatment in the periods 1987-1989, 1990-1992 and 1993-1995. (Recall that the classification system used prevents first-line estimation in 1986 and persistence estimation for 1996.) The leftmost columns of each matrix list the proportion of patients that started in each treatment category along with the total number of patients who started treatment during the three-year period. This is followed by matrices identifying the proportion of patients from each first-line treatment group that went on to use other therapies after one year and

two years. The diagonal elements in bold print identify those patients that continued using drugs from the same treatment category after one or two years.

The diagonal figures in Table 6 help to substantiate the claim that once started on a therapy, patients are likely to continue using that therapy. This is true, at least, for patients who start on most mono-therapies. Between two-thirds and three-quarters of patients who are on a mono-therapy of diuretics, beta-blockers, ACE-inhibitors or calcium-channel blockers during the first quarter of their treatment remain on those therapies after one and two years of treatments, conditional on the fact that their hypertension is treated persistently. Patients who begin treatment on a multiple-therapy (with diuretics or otherwise), are far more likely to switch to another course of therapy after one or two years. Using multiple drugs within the first quarter is likely a sign of treatment intolerance or inadequacy, so it is not surprising that these patients switch to other courses of therapy. Another trend to note from the matrices in Table 6 is that treatment regiments appear to have become gradually more volatile over time. This is somewhat consistent with the increasingly eclectic nature of national hypertension guidelines.

At first glance, the diagonal figures in Table 6 might indicate that diuretics had persistence rates that were worse than other drugs during the 1990s. However, the data in this table indicate that a step-care approach to diuretic therapy is being used. Between 9 and 14 percent of those who begin treatment with diuretics are advanced to the "diuretic plus other drugs" combination category. This would appear to imply that the diuretic drugs were tolerable for these patients, but blood-pressures were not adequately controlled. Similar step-care movements can be inferred from the transition patters of patients on beta-blockers, ACE-inhibitors and calcium-channel blockers.

Conspicuous in its absence is a major difference between the treatment trajectories of patients starting on diuretics and beta-blockers and those of patients starting on ACE-inhibitors and calcium-channel blockers. After one or two years, patients switch to mono-therapy of the newer drugs more frequently than mono-therapies of the older drugs, but the net effects of switching are small, even after two years. High rates of treatment persistence, combined with evidence of step-care are not consistent with the hypothesis that diuretics and beta-blockers are substantially less tolerable than ACE-inhibitors and calcium-channel blockers. This should not be surprising in light of the fact that the best available clinical information suggests that low-dose diuretics are as tolerable as or better tolerated than any other group of antihypertensive drugs (Wright et al 1999).

Advertising and Noncompliance with Guidelines

The findings from the previous section suggest that prescribing patterns—driven in large part by trends in first-line prescribing—moved toward the use of newer drugs, contrary to prescribing guidelines. Causes for noncompliance with guidelines may include time constraints, financial incentives and possibly patient demand. As alluded to above, the most frequently cited possible cause of continued non-adherence to hypertension prescribing guidelines is advertising. It is certain that the differences in

product ages among the hypertension classes are important determinants of market dynamics and especially advertising levels.

The lifecycle of an average drug product can be roughly broken into two phases, corresponding to its patent status. In the initial phase, when a product is patented, it is heavily marketed because the resulting sales are captured exclusively by the patent holder. This characterizes many of ACE-inhibitors and calcium-channel blockers during the 1980s and 1990s. After the patent on a drug expires, generic competitors often enter the market. Generic entry results in lost market share—in units and dollar-volume—if consumers (or pharmacists acting on their behalf) choose lower-cost generics. Subject to this form of competition, brand-name companies' incentive to advertise falls. The total market—in units—for the pioneering product and its generic competitors will likely decline as advertising declines. This is particularly likely when competing substitutes are patented and therefore promoted. Advertising efforts by newer competitors can dramatically alter the prescribing habits of physicians.[8] This may explain the decline in the use of diuretics and beta-blockers.

Detailed marketing information was too costly to obtain for this study. However, it is known that ACE-inhibitors and calcium-channel blockers were the most heavily marketed hypertension drugs in the late 1980s and through the 1990s. Due to the high cost of market research data, Wang et al (1999) conducted their own page-audit of the New England Journal of Medicine (NEJM) to determine how heavily alternative hypertension drugs had been promoted between 1985 and 1996—the same period of analysis for this study. The NEJM was chosen as representative of reputable medical journals. They found that calcium-channel blockers had been the most heavily promoted drugs, and that advertising for these products increased steadily over the decade. In 1985, ads for calcium-channel blockers accounted for 4.6 percent of all drug ads in the NEJM; by 1996, they accounted for 26.9 percent of all drug ads in the journal. This made calcium-channel blockers the most heavily promoted of all classes of drugs advertised, including the entire category of antibiotics combined. Advertising for ACE-inhibitors increased and then declined again over this period. ACE-inhibitor ads accounted for approximately 4 percent of drug ads in the NEJM during 1985 and again in 1996. In contrast, advertisements for diuretics and beta-blockers declined steadily over the period analyzed. They accounted for 4.2 and 12.4 percent of drug ads in 1985 and 0.8 and 0 percent of drug ads in 1996, respectively (Wang et al 1999). In financial terms, makers of calcium-channel blockers spent $54 million (US) advertising their products in the US during 1997, while only $1.4 million was spent advertising beta-blockers and less on diuretics (IMS statistics cited in Anonymous 1999). In Canada, six brands of ACE-inhibitors (five of which were launched during the 1990s) and two brands of calcium-channel blockers were on IMS Health's list of top 50 products by promotional expenditures for 1998. No diuretics or beta-blockers made that list.

[8] The ability to shift markets from one product type to another by advertising is so dramatic that brand-name firms will even cannibalize their own markets by launching newly patented modifications of their older products to continue the profitable life of the original innovation (Morgan 1998, Anderson 1997).

Drug Advertising in Economic Literature

The economics literature has traditionally focussed on narrowly defined measures of the potentially anti-competitive effects of drug advertising (Leffler 1981, Hurwitz and Caves 1988, Riso 1999, Rubin and Schrag 1999). Most frequently, economists focus on indicators of barriers to entry—particularly the frequency and impact of generic entry—and measures of reduced price competitiveness—such as decreased cross-price elasticity of demand. While some economists acknowledge the possibility that advertising can be misleading or even fraudulent, none has investigated how consumption patters may be affected by this. Leffler (1981), for example, defines "persuasion" as that which substitutes emotional decisions for rational, evaluative decisions, and argues that "...positive and normative analysis should therefor be prefaced by the particulars of the products advertised, the message delivered, and the buyers addressed" (Leffler 1981, p.46). Leffler (1981) then goes on to assume that advertising always relays truthful information in his empirical analysis of the impact of drug advertising. Several other authors—supporting both sides of the drug advertising and competitiveness debate—have made similarly optimistic assumptions about the "information" contained in advertising signals (Hurwitz and Caves 1988, Riso 1999, Rubin and Schrag 1999).

Advertising and Information

The health services literature regarding advertising is fare more extensive than the economic literature. It also clearly calls into question the accuracy and completeness of the informational content of drug advertising. In numerous studies, advertising has been shown to have a significant impact on prescribing patterns, often ranking as the most influential form of "information" (Hemminki 1975, Haayer 1982, Orlowski and Wateska 1992, Caudill et al 1996, Lexchin 1989 & 1993, Spingarn et al 1996, Wivell and O'Fallon 1992). Moreover, studies indicate that increased reliance on company-sponsored information is positively correlated with prescribing inappropriateness (see Lexchin 1997 and references therein). Noted physicians acknowledge that they are as susceptible as anyone to the "obvious and not so obvious" forms of persuasion used by drug companies (Squires, 1993, p.1391, Avorn 1996), which is sensible because were it not the case, drug companies would not spend more on advertising than they do on research and development—as they do now.

Most drug advertising serves the purpose of brand building and name-recall. This is clearly the purpose of reminder ads and gift giving. Drug marketing also takes forms that more closely resemble informational services. Among other such activities, drug companies sponsor continuing medical educational programs, consensus conferences and symposia. Drug company representatives (detailers) are also seen as an educational tool, one that accounts for an immense amount of marketing activity and a majority of promotional expenditures in the pharmaceutical industry.

According to IMS Health, Canadian drug companies detailed practicing physicians 3.2 million times in 1998—conservatively, about 50 details per practicing physician.[9] Canadian physicians rank interactions with drug representatives as either the first or the second most important source of prescribing information (Lexchin 1993).

[9] Based on the assumption that all 63,000 practicing physicians are detailers' targets.

Ostensibly, the claims made by drug representatives are regulated, but the personal nature of details makes effective regulation impracticable (Lexchin 1989). What is known about the "information" content of details suggests that profit motives outweigh the motive to educate because benefits of drugs are typically exaggerated and risks seldom mentioned (Lexchin 1989 & 1993, Hodges 1995).

The second most important channel of drug promotion is medical and professional journal advertising. IMS Health estimates that Canadian drug companies spent almost $69 million on journal advertisements in 1998, $14 million of which was for cardiovascular medicines. Journal advertisements are left to the auspices of self-regulation by the industry, resulting in the implicit endorsement of questionable marketing practices (Lexchin 1997). For example, journal advertising typically involves full-page glossy advertisements found at the beginning of the journal and amidst the articles. "Information" regarding the appropriate indications, doses, cautions, contraindications, side-effects and risks printed on separate pages, usually at the very back of the journal. This information is invariably printed in compressed fonts—often seven-point, which looks like this, but sometimes six-point, which looks like this. Because it is generally inconvenient to search for and then read the information that "accompanies" journal ads, the "informational content" is skipped by most readers (Lexchin 1994).

Given that advertising is intended to sell products and that the informational content of advertising is not always complete or accurate, it is not surprising that prescribing has increased for the most heavily promoted drugs in the hypertension market, contrary to the recommendations of national guidelines. In light of the available evidence, it is difficult to accept the standard economic assumption that changes in prescribing influenced by the "information" provided through drug marketing are necessarily optimal.

Conclusion

From 1986 to 1996, the cost of hypertension drugs used by recipients of Pharmacare Plan A increased from $15.8 million per year to $58.7 million. With expenditures rapidly reaching such high levels, it is useful to know whether British Columbians received more or less value for their money from expenditures on hypertension drugs over time. To conduct such an assessment, researchers typically decompose changes in aggregate expenditures into measures of aggregate price and quantity that allow one to gauge the real productivity represented by purchases in this market segment.

One way of performing such a decomposition is to construct indexes using the traditional economic approach to price and productivity measurement. For the hypertension treatments purchased under Pharmacare Plan A, a traditional price index grew a total of 15 percent from the first quarter of 1986 to the end of 1996. Considering that the Canadian consumer price index grew by 34 percent over this period, this transitional economic price index implies that real productivity actually increased in the hypertension sector. Deflating hypertension expenditures with the traditional economic price index yields a quantity index that grew 283 over the period. However, the notion of output that underlies the traditional economic price and quantity indexes does not

necessarily relate to the number of tablets and pills consumed, nor to the quantity or quality of hypertension treatment achieved in this sector. Traditional economic indexes relate to a utility-theoretic notion of social welfare generated by the purchases accounted for in the aggregate index. Provided the assumptions of the traditional economic model of consumer demand are met, the common economic indexes used would be reasonably good estimators of true social costs and welfare.

Among the assumptions that is clearly not met in this sector is the assumption that decision-making agents consider the full costs and benefits. Physicians, the principal decision-makers in this sector, certainly lack incentives to consider the financial costs of their prescribing. Furthermore, in part due to their financial incentives, physicians may base their decisions on information that is incomplete or inaccurate. Therefore, price and quantity indexes based on the traditional economic formulae will not necessarily relate to real social welfare or productivity in this sector. This is evident in the case of the indexes for hypertension drugs purchased under Pharmacare Plan A.

The economic indexes differed substantially from indexes based on measures of health outcomes. From 1986 to 1996, price indexes based on the cost per patient treated or per day of treatment purchased grew 172 and 147 percent respectively—ten times as much as the economic indexes. Over this period, the number of Pharmacare Plan A beneficiaries treated for hypertension and the number of days of therapy consumed by those patients (which form the basis for the health outcomes quantity indexes) grew 63 percent and 80 percent, respectively. These alternative indexes are rationalized by the scientific evidence and social preferences expressed in national guidelines for the treatment of hypertension.

The considerable difference between the health outcomes based indexes of price and quantity and the traditional economic indexes of price and quantity is due to increased use of high-cost medicines. The economic indexes account for this shift in treatment patterns as an increase in total output purchased, not a price change. This would be appropriate if purchases were always efficient with respect to maximizing social welfare at least cost. However, it is clear that this was not the case. The lowest cost drugs on the market were consistently judged by the national prescribing guidelines to be the first choice in hypertension care based on scientific evidence regarding their efficacy and tolerability. Despite the recommendations of national guidelines, a declining proportion of hypertensive patients were prescribed these drugs over the period of study. Since the observed changes in anti-hypertensive prescribing were inconsistent recommended care, the increased costs that resulted from the use of more expensive drugs could not have come with commensurate increases in social welfare. In fact, if the cost per patient treated for hypertension actually had grown according to the rate implied by the traditional economic price index, Pharmacare would have spent approximately $207 million less on hypertension drugs than they did from 1986 to 1996—$33 million less in 1996 alone!

The implied bias from using traditional economic indexes to measure productivity in this market segment is significant, not just for indexes related to this sub-market, but also for overall indexes of pharmaceutical sector price and quantity. Hypertension drugs accounted for approximately 30 percent of all drug expenditures for the elderly in British Columbia each year between 1986 and 1996. Therefore, the measurement bias from the

use of traditional economic indexes for hypertension drugs alone will have a powerful impact on the measure of overall price and productivity for purchases made under Pharmacare Plan A. Mismeasuring the real cost of hypertension treatment will bias (downward) price indexes for Pharmacare Plan A by about 3 percent per annum between 1986 and 1996. The average annual growth rate of a traditional price index for all Pharmacare Plan A purchases is approximately 1.3 percent over this period. Therefore, the measurement bias from the hypertension segment alone roughly triples the aggregate measure of the cost of care in this sector, making it approximately 4.3 percent per annum.

It is clear from the results of this study that more research needs to be conducted on alternative approaches to price and productivity measurement in the pharmaceutical sector. The potential hazard of not addressing the measurement bias from the use of traditional economic indexes is that policy may be guided by a perception that the sector is more "productive" (or efficient) than is actually the case. The traditional indexes reported here suggest that, if anything, utilization rates are the potentially problematic cause of expenditure inflation. Such a suggestion focuses policy attention on utilization-cubing measures that would possibly create further inefficiencies. It seems clear from the health services literature—and from the evidence presented above—that increased price per unit of care delivered stemming from inefficient drug selection is a major determinant of expenditure growth. This is not captured by conventional economic indexes because inefficiencies are simply not possible within the assumptions of the traditional economic model. Health-outcomes measures of pharmaceutical sector productivity, based whenever possible on recommended prescribing practices, will better indicate whether changes in the true quantity and/or quality of care delivered are consistent with changes in expenditures on drugs. Such indexes may focus the attention of researchers and policy makers on strategies to improve the social efficiency of the prescription decision-making process.

Appendix A: The 1997 and 1999 Guidelines

In 1997, the JNC published its sixth and most recent report—JNC VI (JNC 1997). Like the CHS, the JNC developed a classification system for the evidence upon which its recommendations were based. However, the system used by the JNC was not hierarchical in its "grading" structure. The JNC classification system merely classified evidence into categories such as meta-analysis, randomized clinical trial, opinion article, etc. As with the JNC V, JNC VI contained an increased emphasis on non-drug treatments and called for population-wide strategies for the prevention of hypertension. There were no changes in "when to treat," but the JNC VI lowered the target blood pressure for those receiving treatment to a diastolic pressure *below* 140mm Hg over 90mm Hg (JNC 1997, p. 2421 emphasis in original). Unless contraindicated, the JNC VI recommends thiazide diuretics or beta-blockers as preferred first-line drugs for non-elderly hypertensives. If a diuretic is not chosen as the first-step, it is "usually indicated" as the second-step in therapy (JNC 1997, p. 158). The JNC VI lists compelling indications for individualizing antihypertensive therapy beyond the simple diuretic or beta-blocker choice of uncomplicated hypertension. Unless contraindicated, the JNC VI recommends low-dose thiazide diuretics or low-dose beta-blockers in combination with thiazide diuretics for elderly patients, and diuretics for those with isolated systolic hypertension.

The most recent CHS guidelines were published in 1999 (Feldman et al 1999). As with the 1993 CHS report, the development of the 1999 guidelines was supported by pharmaceutical company partners[10] of the CHS (CHS 1999, p.S17). Again, recommendations were graded (from A to D) according to the quality of scientific evidence that they were based upon. The 1999 guidelines offer the same when to treat recommendations as those of 1993, with greater emphasis on non-pharmacologic treatment. Treatment protocols also resemble previous publications, with a few changes. The 1999 CHS drugs of choice for uncomplicated hypertensives under 60 are thiazide diuretics, beta-blockers or ACE-inhibitors (grade A). If these prove inadequate or intolerable, the guidelines recommend substitution among the first-line drugs or combinations with diuretics (grade A). In the 1999 CHS, the drugs of choice for uncomplicated hypertensives over 60 are low-dose thiazide diuretics (grade A) or long-acting dihypdropyridine calcium-channel blockers (grade A, based on evidence from a study published in 1997). An ACE-inhibitor may be considered if diuretic and calcium-channel blockers are ineffective, contraindicated or intolerable (grade B).

[10] Company partners to the CHS include AstraZeneca Canada, Bayer Inc., Bristol-Myers Squibb Canada Inc., Hoescht Marion Roussel Canada Inc., Hoffman-LaRoche Limited, Merck Frosst Canada Inc., Novartis, Parke-Davis, Pfizer Canada Inc., Searle Canada, SmithKline Beecham Pharma and Wyeth-Ayerst Canada Inc.

Appendix B: Lists of Products

Table 7: Diuretics

AHFS	Generic Name
402800012	Bendroflumethiazide Tab 5Mg
402800014	Bendroflumethiazide Kcl 5/500Mg
402800031	Chlorothiazide Tab 250Mg
402800032	Chlorothiazide Tab 500Mg
402800041	Chlorthalidone Tab 50Mg
402800042	Chlorthalidone Tab 100Mg
402800044	Chlorthalidone Tab 50Mg/Plus
402800061	Hydrochlorothiazide Tab 25Mg
402800062	Hydrochlorothiazide Tab 50Mg
402800063	Hydrochlorothiazide Tab 100Mg
402800064	Hydrochlorothiazide Tab 25Mg/Plus
402800065	Hydrochlorothiazide Tab 50Mg/Plus
402800172	Indapamide Tab 2.5Mg
402800173	Indapamide Tab 1.25Mg
402810011	Amiloride Tab 5Mg
402810012	Amiloride/Hydrochlor Tab 5/50Mg
402810021	Spironolactone Tab 25Mg
402810022	Spironolactone Tab 100Mg
402810023	Spironolactone Tab 25Mg/Plus
402810024	Spironolactone Tab 50Mg/Plus
402810031	Triamterene Hcl Tab 50Mg
402810032	Triamterene Hcl Tab 100Mg
402810033	Triamterene Hcl Plus Tab 50/25Mg

Table 8: Beta Blockers

AHFS	Generic Name
240400012	Atenolol Tab 50Mg
240400014	Atenolol Tab 100Mg
240400101	Nadolol Tab 40Mg
240400102	Nadolol Tab 80Mg
240400103	Nadolol Tab 160Mg
240400105	Nadolol/Bendroflu. 40/5Mg
240400106	Nadolol/Bendroflu. 80/5Mg
240400131	Propanolol Tab 10Mg
240400132	Propanolol Tab 20Mg
240400133	Propanolol Tab 40Mg
240400134	Propanolol Tab 80Mg
240400135	Propanolol Tab 120Mg
240400136	Propanolol La Cap 160Mg
240400137	Propanolol Inj 1Mg
240400138	Propanolol La Cap 60Mg
240400139	Propanolol Tab Plus 40Mg
24040013A	Propanolol La Cap 80Mg
24040013B	Propanolol La Cap 120Mg
24040013C	Propanolol Tab Plus 80Mg
240400151	Timolol Tab 5Mg
240400152	Timolol Tab 10Mg
240400153	Timolol Tab 20Mg
240400154	Timolol Tab 10Mg/Plus
240800016	Atenolol/Plus Tab 50/25Mg
240800017	Atenolol/Plus Tab 100/25Mg
240800101	Metoprolol Tab 50Mg
240800102	Metoprolol Tab 100Mg
240800103	Metoprolol Sr Tab 200Mg
240800104	Metoprolol Tab 100Mg/Plus
240800106	Metoprolol Sr Tab 100Mg
240800107	Metoprolol Inj Iv 1Mg/Ml
240800131	Pindolol Tab 5Mg
240800132	Pindolol Tab 10Mg
240800133	Pindolol Tab 15Mg
240800134	Pindolol/Plus Tab 10/25Mg
240800135	Pindolol/Plus Tab 10/50Mg
240800201	Oxprenolol Tab 20Mg
240800202	Oxprenolol Tab 40Mg
240800203	Oxprenolol Tab 80Mg
240800204	Oxprenolol Slow Tab 80Mg
240800205	Oxprenolol Slow Tab 160Mg
240800211	Labetalol Tab 100Mg
240800212	Labetalol Tab 200Mg
240800213	Labetalol Inj 5Mg/Ml
240800251	Acebutolol Tab 100Mg
240800252	Acebutolol Tab 200Mg
240800253	Acebutolol Tab 400Mg

Table 9: ACE-Inhibitors

AHFS	Generic Name
240400021	Captopril Tab 25Mg
240400022	Captopril Tab 50Mg
240400023	Captopril Tab 100Mg
240400024	Captopril Tab 12.5Mg
240400025	Captopril Tab 6.25Mg
240800281	Enalapril Maleate Tab 2.5Mg
240800282	Enalapril Maleate Tab 5Mg
240800283	Enalapril Maleate Tab 10Mg
240800284	Enalapril Maleate Tab 20Mg
240800285	Enalapril Maleate Tab 40Mg
240800286	Enalapril Maleate Plus 10/25
240800291	Lisinopril Tab 5Mg
240800292	Lisinopril Tab 10Mg
240800293	Lisinopril Tab 20Mg
240800295	Lisinopril/Hydrochloro Tab 20/25
240800296	Lisinopril/Hydrochloro Tab 20/12.5
240800297	Lisinopril/Hydrochloro Tab 10/12.5
240800311	Quinapril Tab 10Mg
240800312	Quinapril Tab 5Mg
240800313	Quinapril Tab 20Mg
240800314	Quinapril Tab 40Mg
240800321	Fosinopril Tab 10Mg
240800322	Fosinopril Tab 20Mg
240800341	Cilazapril Tab 0.5Mg
240800342	Cilazapril Tab 1.0Mg
240800343	Cilazapril Tab 2.5Mg
240800344	Cilazapril Tab 5.0Mg
240800351	Benazepril Tab 5Mg
240800352	Benazepril Tab 10Mg
240800353	Benazepril Tab 20Mg
240800361	Ramipril Tab 1.25Mg
240800362	Ramipril Tab 2.5Mg
240800363	Ramipril Tab 5.0Mg
240800364	Ramipril Tab 10.0Mg

Table 10: Calcium-Channel Blockers

AHFS	Generic Name
240400071	Diltiazem Tab 30Mg
240400072	Diltiazem Tab 60Mg
240400073	Diltiazem Sr Cap 90Mg
240400074	Diltiazem Sr Cap 120Mg
240400075	Diltiazem Sr Cap 60Mg
240400076	Diltiazem Cr Cap 180Mg
240400077	Diltiazem Cr Cap 240Mg
240400078	Diltiazem Cr Cap 300Mg
240400079	Diltiazem Cr Cap 120Mg
240400111	Nifedipine Cap 5Mg
240400112	Nifedipine Cap 10Mg
240400113	Nifedipinepa Tab 20Mg
240400114	Nifedipine Tab 30Mg
240400115	Nifedipine Tab 60Mg
240400116	Nifedipine Ft Tab 10Mg
240400117	Nifedipine Pa Tab 10Mg
240400161	Verapamil Sr Cap 120Mg
240400162	Verapamil Inj 2.5Mg
240400163	Verapamil Sr Cap 180Mg
240400164	Verapamil Tab 80Mg
240400165	Verapamil Sr Cap 240Mg
240400166	Verapamil Tab 120Mg
240400167	Verapamil Sr Tab 120Mg
240400168	Verapamil Sr Tab 240Mg
240400169	Verapamil Sr Tab 180Mg
240400291	Nicardipine Cap 20Mg
240400292	Nicardipine Cap 30Mg
240400301	Felodipine Er Tab 5Mg
240400302	Felodipine Er Tab 10Mg
240400303	Felodipine Er Tab 2.5Mg
240400311	Amlodipine Tab 5Mg
240400312	Amlodipine Tab 10Mg

Table 11: Other Antihypertensive Drugs

AHFS	Generic Name
240800031	Clonidine Tab .025Mg
240800032	Clonidine Tab .1Mg
240800033	Clonidine Tab .2Mg
240800034	Clonidine Tab .1Mg/Plus
240800071	Hydralazine Tab 10Mg
240800072	Hydralazine Tab 25Mg
240800073	Hydralazine Tab 50Mg
240800074	Hydralazine Inj 20Mg
240800091	Methyldopa Tab 125Mg
240800092	Methyldopa Tab 250Mg
240800093	Methyldopa Tab 500Mg
240800094	Methyldopa/Plus Tab 250/15Mg
240800095	Methyldopa/Plus Tab 250/25Mg
240800096	Methyldopa/Plus Tab 250/150Mg
240800097	Methyldopate/Plus 250/250Mg
240800098	Methyldopate/Plus Inj 50Mg
240800111	Minoxidil Tab 2.5Mg
240800112	Minoxidil Tab 10Mg
240800141	Prazosin Cap .5Mg
240800142	Prazosin Tab 1Mg
240800143	Prazosin Tab 2Mg
240800144	Prazosin Tab 5Mg
240800145	Prazosin Cap 1Mg
240800146	Prazosin Cap 2Mg
240800271	Terazosin Hydrochloride Tab 1Mg
240800272	Terazosin Hydrochloride Tab 2Mg
240800273	Terazosin Hydrochloride Tab 5Mg
240800274	Terazosin Hydrochloride Tab 10Mg
240800301	Doxazosin Mesylate Tab 1 Mg
240800302	Doxazosin Mesylate Tab 2 Mg
240800303	Doxazosin Mesylate Tab 4 Mg

Appendix C: New Product Entrants

Table 12 :Canadian Launch Dates for Top Selling Antihypertensive Drugs

Chemical	Class	Brand	Date
Enalapril	ACE	Vasotec	Aug-87
Enalapril	ACE	Vaseretic	Oct-90
Diltiazem	CCB	Cardizem CD	Nov-92
Amlodipine	CCB	Norvasc	Sep-92
Nifedipine	CCB	Adalat XL	Apr-92
Nifedipine	CCB	Adalat Pa20	Apr-87
Lisinopril	ACE	Zestril	Nov-90
Lisinopril	ACE	Prinivil	Nov-90
Lisinopril	ACE	Zestoretic	Nov-92
Lisinopril	ACE	Prinizide	Dec-92

(Source: IMS Health 1999)

Appendix D: Regression Analysis for Price Indexes

Table 13: Regression Analysis for Trend in Price Indexes

	Economic Index	Day Based Index	Patient Based Index
Dependent Variable	ln(index)	ln(index)	ln(index)
R^2	0.901	0.965	0.957
Quarterly Growth Rate 86-93	0.009*	0.032*	0.032*
	(0.000)	(0.001)	(0.001)
Quarterly Growth Rate 94-96	-0.007$^+$	-0.001	0.002
	(0.003)	(0.005)	(0.006)
Constant	0.049*	0.080*	0.133*
	(0.010)	(0.020)	(0.023)
94-96 Dummy	0.359*	0.863*	0.743*
	(0.101)	(0.212)	(0.242)
Slope Change F(1,40)	35.271	36.227	22.452

*Significant at p=0.01

$^+$ Significant at p=0.05

Standard errors are in parentheses.

Appendix E: Regression Analysis of Patients Receiving Treatments by Classification

Table 14: Regression Analysis for Trends in Patients Receiving Treatments by Classification

	Total	DIR	DIR+	BET	ACE	CCB	OTH	NDC
R^2	0.98	0.97	0.67	0.70	1.00	1.00	0.98	0.99
Constant	84693*	32843*	19665*	18510*	-1779*	4998*	6576*	3880*
	(1252)	(407)	(398)	(153)	(271)	(195)	(85)	(194)
Q1 Dummy	-193	96	160	-279	81	-185	-102	36
	(1182)	(384)	(376)	(145)	(256)	(184)	(80)	(183)
Q2 Dummy	882	461	323	-115	322	-107	-94	92
	(1187)	(386)	(378)	(145)	(257)	(184)	(81)	(184)
Q3 Dummy	-139	435	-26	-142	14	-170	-38	-212
	(1178)	(383)	(375)	(144)	(255)	(183)	(80)	(183)
Quarterly Growth 86-93	1323*	-432*	-47*	-25*	799*	765*	-118*	381*
	(51)	(16)	(16)	(6)	(11)	(8)	(3)	(8)
Quarterly Growth 94-96	1784*	157	506*	247*	594*	-193*	100*	373*
	(265)	(86)	(84)	(32)	(57)	(41)	(18)	(41)
94-96 Dummy	-19821	-19882*	-18877*	-10376*	5774^{+}	31031*	-7129*	-361
	(10400)	(3383)	(3310)	(1273)	(2251)	(1616)	(708)	(1611)
Slope Change F(1,37)	2.9	45.3*	41.7*	67.9*	12.4*	523.9*	141.7*	0.0

*Significant at p=0.01

$^{+}$ Significant at p=0.05

Standard errors are in parentheses.

Appendix F: Classification of First-Line Treatment for Non-Persistent Patients Aged 66

Table 15: Classification of First-Line Treatment for Non-Persistent Patients Aged 66

	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
N	9,057	7,474	7,148	6,699	6,255	6,154	6,507	6,364	6,267	9,409
Diuretics	54%	49%	43%	41%	38%	36%	35%	33%	33%	30%
Diuretics Plus	5%	4%	4%	4%	3%	3%	3%	3%	3%	4%
Beta-Blockers	15%	14%	13%	13%	13%	12%	13%	13%	15%	16%
ACE-Inhibitors	5%	8%	12%	14%	16%	18%	20%	21%	20%	21%
CCB	14%	18%	20%	20%	22%	22%	21%	19%	16%	11%
Other	6%	5%	5%	5%	5%	6%	5%	7%	11%	13%
ND Combo	2%	2%	3%	3%	3%	3%	3%	4%	3%	4%

CCB = calcium-channel blockers.
ND = Combination of non-diuretic drugs.

Appendix G: Regression Analysis for Trends in First-Line Treatments for Persistent Patients

Table 16: Regression Analysis for Trends in First-Line Treatments for Persistent Patients

	Total	DIR	DIR+	BET	ACE	CCB	OTH	NDC
R^2	0.52	0.75	0.54	0.62	0.89	0.53	0.78	0.65
Constant	2092.7*	695.4*	219.2*	374.9*	154.5*	451.8*	91.3*	105.5*
	(132.0)	(42.4)	(17.3)	(25.8)	(29.8)	(30.7)	(13.2)	(10.9)
Q1 Dummy	240.2$^+$	103.2$^+$	23.9	49.5$^+$	39.2	16.7	-2.5	10.2
	(122.7)	(39.4)	(16.1)	(24.0)	(27.7)	(28.5)	(12.3)	(10.1)
Q2 Dummy	-8.6	45.8	-3.9	-3.9	11.3	-20.8	-15.8	-21.2$^+$
	(123.3)	(39.6)	(16.1)	(24.1)	(27.8)	(28.6)	(12.3)	(10.1)
Q3 Dummy	-292.8$^+$	-20.5	-31.0	-47.9$^+$	-82.3*	-72.0*	-10.6	-28.6*
	(122.3)	(39.3)	(16.0)	(23.9)	(27.6)	(28.4)	(12.2)	(10.1)
Quarterly Growth 86-93	-6.0	-16.3*	-3.8*	-4.8*	16.1*	2.8$^+$	-1.8*	1.8*
	(6.1)	(2.0)	(0.8)	(1.2)	(1.4)	(1.4)	(0.6)	(0.5)
Quarterly Growth 94-96	77.9*	35.5*	6.5	21.6*	9.5	-16.3*	19.0*	2.1
	(26.2)	(8.4)	(3.4)	(5.1)	(5.9)	(6.1)	(2.6)	(2.2)
94-96 Dummy	-2542.1*	-1498.9*	-291.0$^+$	-797.2*	139.7	530.7*	-623.0*	-2.4
	(926.4)	(297.8)	(121.3)	(180.9)	(209.1)	(215.0)	(92.7)	(76.1)
Slope Change F(1,37)	9.7*	35.9*	8.5*	25.5*	1.2	9.4*	60.4*	0.0

*Significant at p=0.01
$^+$ Significant at p=0.05
Standard errors are in parentheses.

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