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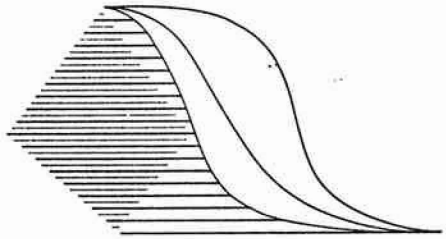

APPRAISING THE EVIDENCE: EFFECTIVENESS OF CHOLESTEROL TESTING AND TREATMENT IN PRIMARY PREVENTION

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1.0 Background

In the U.S. last year, $2.5 Billion was spent for the purchase of cholesterol lowering drugs. Cholesterol lowering drugs were the third most purchased after anti-ulcerant and calcium blocking agents. Over the past decades, there has been a lot of interest in using these drugs for the primary prevention of coronary heart disease. However, successes with drugs like niacin, colestipol, clofibrate, and gemfibrozil have been limited. First, because of the poor tolerability of many these drugs. Drugs like niacin may produce significant gastro-intestinal malaise that seriously affect their acceptability to patients.[1] Second, because of the finding of even more serious side effects especially with clofibrate and gemfibrozil. Clinical trials of these drugs have found them to produce significant increases in non-coronary heart disease (CHD) mortality. Increases which offset any benefits on the incidence of myocardial infarction (MI). [2-3]

The publication of a new trial at the end of 1995, the West of Scotland Coronary Prevention Study Group (WOSCOPS),[4] seemed to offer the much awaited evidence supporting a more extensive use of cholesterol lowering drugs in primary prevention. The WOSCOPS trial evaluated a new drug; pravastatin. The trial reported a significant reduction in the incidence of myocardial infarction and cardiovascular deaths. This study has since been used to justify both the testing and treatment of individuals without established coronary artery disease.

2.0 Purpose

The purpose of this presentation is: i) to examine and discuss specific issues regarding the generalizability of the WOSCOPS trial; and, ii) to discuss the effectiveness of the cholesterol testing strategies to identify patients who may benefit from pravastatin.

3.0 The WOSCOPS trial

The West of Scotland trial is a double-blind trial which randomized 6,595 participants to pravastatin or placebo and followed them for an average of 4.9 years. The primary clinical endpoint was combined non-fatal myocardial infarction and CHD death. Participants were recruited from coronary screening clinics through the West of Scotland district.

After 5 years of treatment, the study reported absolute treatment effect ranging in size from 0.7% for cardiovascular deaths to 2.5% for the primary combined clinical endpoint. These findings were statistically significant for $p<0.01$.

Extrapolation and application of these findings to other populations, first require examination of three main issues regarding the generalizability of this trial.

4.0 Generalizability of the trial

4.1 Risk level

The population of the West of Scotland district is known for having the highest world-wide risk of death from ischemic heart disease. The mean ischemic heart disease mortality rate for that population is estimated at 4.6 deaths per 1000 population per year. From this population, the investigators selected middle-aged men with average cholesterol level > 7.0 mmol/l. Based on data from the British Heart Study, this would correspond to the top 20th percentile of the total cholesterol distribution.[5] In addition, the study did not exclude patients with stable angina. In fact, 16% of the study sample is comprised of individuals with established coronary heart disease.

In order for the results to be generalizable, these characteristics of the West of Scotland study sample first need to be contrasted with the incidence of ischemic heart disease in the Canadian population. In the general Canadian population, the mortality rate from ischemic heart disease is around 1.93 death per 1000 per year.[6] Almost two and a half times less than that observed in the West of Scotland study. In fact, the incidence of ischemic heart disease mortality in the West of

Scotland study sample is closer to that of individuals with established coronary heart disease. Meta-analyses of cholesterol lowering drugs have suggested that the benefit-risk ratio is likely to be positive only in groups with an incidence of CHD death ≥ 3 deaths per 100 per year.[7] They further suggested that this risk level was compatible with individuals with established coronary heart disease, not with primary prevention population. Generalization of the WOSCOPS results to true primary prevention population would therefore involve using pravastatin in groups at a risk level lower than the 3% CHD deaths and may actually lead to a negative benefit-risk ratio.

4.3 Understanding the risk level

Not only are the WOSCOPS participants at a higher risk for IHD, but the reasons explaining this greater risk are not fully understood. The reported incidence of CHD risk factors in the WOSCOP study sample is not significantly different from the incidence of the same risk factors in a Canadian population.[6] Only differences in the number of smokers were documented but these were likely due to differences in case definition. The MONICA study (WHO) suggests that known risk factors explained at most 23% of the deaths from IHD.[8] Until we obtain a better understanding of the factors at play in the WOSCOPS study sample, the reproducibility of these results may not be possible.

4.3 Gender issues

While few women were included in secondary prevention trials of cholesterol lowering drugs, the data on primary prevention of coronary heart disease in women is even sketchier. The study sample of the WOSCOPS trial included only men and therefore provided no additional evidence in women. To date, the few primary prevention trials that have included women, have found no significant reductions in coronary heart disease morbidity or mortality from cholesterol lowering drugs, including hormone replacement therapy.[9] In addition, women have been shown to differ from men in terms of their risk for CHD. It was estimated that in women, the risk of CHD is significantly lower than that of men of the same age.[10] Although women have increasingly demanded and been provided with cholesterol testing and lowering interventions, the WOSCOPS

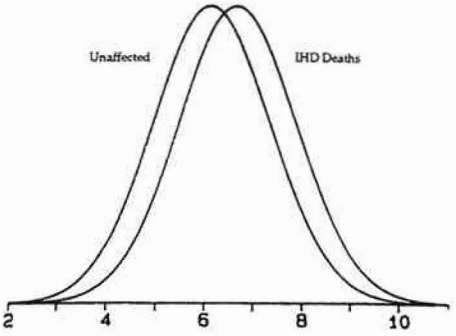
study provides no evidence to support these measures. The effectiveness of cholesterol lowering intervention in women still remains to be demonstrated. The lower level of CHD risk in women is an important factor to consider in the benefit-risk ratio.

5.0 Identifying patients for treatment

Even if the generalizability of the West of Scotland trial was not an issue, the matter of identifying patients that could benefit from pravastatin would be. To date, despite the serious issues around generalizability, policy-makers and guideline-developers have relied on the results of the WOSCOPS trials and have implemented testing strategy to identify candidates for treatment. In the U.S. for example, the recommendations of the U.S. Preventive Task Force and American College of Physicians support testing of all middle-aged men and women without established coronary heart disease.[11-12] In Canada, groups like the Canadian Working Group and the Saskatchewan Health Services Utilization and Research Commission have also relied on the WOSCOP to support cholesterol testing in middle-aged men and women without established coronary heart disease.[13-14]

However, these guidelines ignore the fact that in primary prevention population, total cholesterol is a poor predictor of CHD. Figure 1 illustrates the distribution of total cholesterol levels in men with and without CHD. The figure emphasize the great amount of overlap between the two distributions.[5] This amount of overlap results in a large number of false positive tests. A large number of men will test positive although they will not develop CHD. A review of the sensitivity, specificity and predictive value of lipid tests revealed that in a primary prevention population, the positive predictive value for total cholesterol tests above 6.1 mmol/l ranges from 1.6% (for an incidence CHD of 1.2% over 8 years) to 7.7% (for an incidence of CVD of 6.3% over 14 years).[15]

Figure 1: Distribution of total cholesterol levels in men with and without IHD



In a Canadian setting, if we assume a total cholesterol sensitivity of 65%, a specificity of 80% and a positive predictive value as high as 16%, in a group of 100,000 men followed for 30 years, implementation of the U.S. Preventive Task Force, American College of Physicians or Saskatchewan's guidelines would lead to:

- 22,555 men testing positive for high cholesterol;
- 84% of these would be false positive;
- 18,864 men would be treated though not at risk for MI or CHD death; and,
- the incidence of MI and CHD death would be reduced from 5.7% to 5.6% over 30 years.

5.0 Conclusion

The generalizability of the WOSCOPS trial needs further examination before the study is used as to evidence to support cholesterol lowering and cholesterol testing in primary prevention. Even if the generalizability was ever established, the identification of patients eligible for treatment would still be an issue. Given the poor predictive value of cholesterol testing and the small absolute treatment effect obtained with pravastatin, in a true primary prevention population, the effectiveness and cost-effectiveness of cholesterol testing and treatment program needs careful examination.

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