Statins and primary prevention: Is all the evidence in?

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Cardiovascular diseases (CVDs), including ischemic heart disease (IHD) and stroke, are the leading cause of death in North America, accounting for 37% of deaths in Canada (1); they are now also the leading cause of death in adults worldwide (2). To reduce the large health, social and economic burden of CVDs in North America, the key modifiable risk factors contributing to CVDs have been investigated continually over the past several decades. The most significant modifiable risk factor that has been identified is dyslipidemia. In the landmark INTERHEART study (3), which investigated the contribution of modifiable risk factors to IHD worldwide, including in North America, dyslipidemia accounted for approximately 50% of IHD incidents worldwide. Moreover, most of the evidence accumulated in epidemiological studies focusing on dyslipidemias thus far has strongly and consistently implicated serum low-density lipoprotein cholesterol (LDL-C) levels as the key modifiable risk factor in CVD. More specifically, a strong, linear correlation between serum LDL-C levels and the risk of developing CVDs has been shown in the majority of populations studied globally, including in North America (4,5).

Serum LDL-C lowering using statins

Lifestyle factors, including the dietary content of cholesterol and saturated fat, as well as the level of exercise, contribute to average LDL-C levels in populations, and lifestyle modifications should be included in any therapy to reduce LDL-C. Approximately one in 40 individuals exhibits dyslipidemia on the basis of inherited mutations affecting the production or clearance of LDL particles. These individuals may or may not respond to dietary restriction of cholesterol and fats, or to increased exercise. Biochemically significant decreases in LDL-C, together with statistically and clinically significant decreases in coronary artery disease (CAD) and all-cause mortality, were not observed until the advent of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, or statins, more than two decades ago (6). More recently, intensive lifestyle modifications, either with diet alone (ie, incorporating the low-fat Ornish diet) or with diet and moderate exercise, have been found to produce large reductions in LDL-C (up to 37%) and significant reductions in the extent of atherosclerosis development (7). These studies, however, have generally been carried out in relatively small numbers of individuals, in contrast to the landmark statin trials, and should be repeated with larger study populations to make more conclusive and specific recommendations about lifestyle interventions. LDL-C reduction with statin therapy alone reduces heart attacks by up to 40% in five-year statin trials, regardless of the presence of other risk factors (8). Moreover, analysis of the different large-scale, randomized, placebo-controlled statin trials showed that the decrease in coronary events was best predicted by the absolute decrease in plasma LDL-C concentrations (8).

The mechanism of action of statins leading to a reduction in serum LDL-C is a multistep process. Statins inhibit cellular HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis in all cells (9). In the liver, this depletes hepatocytes of cholesterol, which then leads to an upregulation of the transcription factor sterol regulatory element-binding protein 2 in a feedback loop (10). The sterol regulatory element-binding protein 2 then increases the levels of hepatic

LDL receptor messenger RNA and protein, resulting in an overall upregulation of hepatic LDL receptors at the cell surface, which then mediates the uptake of LDL particles from the circulation, thereby lowering serum LDL-C levels (10,11).

The current debate in the medical community on the use of statins in primary prevention populations

From a public health perspective, the estimated 50% to 70% decrease in cardiac mortality in the latter three decades of the 20th century in western countries can be attributed to population-wide declines in the major CAD risk factors, including serum cholesterol concentrations (12). However, the available data highlight a halt in the decline in CAD incidence since 1990, paralleling the halt in the decline in population-wide serum cholesterol levels (United States data) (13). The current public CVD burden remains high and is expected to increase further with increasing rates of obesity and diabetes. The calculated lifetime risk for developing symptomatic CAD by the age of 40 years is approximately 49% for men and 32% for women (12,14). This, in addition to the currently available epidemiological data, suggests that more aggressive therapy is warranted in the primary prevention of CAD in high-risk patients.

Although there is a consensus in the medical community that statin therapy should be used as a secondary prevention strategy in individuals with a prior coronary event, initiating statin therapy as a primary prevention strategy is more controversial. Because of the high baseline risk of patients with a prior CAD event, intervention of these patients in relatively low numbers results in substantial reductions in CAD morbidity and mortality rates, despite any attendant adverse effects. The cost-benefit ratio is therefore favourable for this strategy and can be justified, it is thought, from a public health perspective. However, there are several problems with applying this strategy only to secondary prevention patients. Treating individuals once atherosclerosis is advanced results in substantial numbers of patients dying immediately or within weeks of their initial CAD event, or surviving, but with debilitating cardiac damage. More specifically, 59% of men and 45% of women die within five years of the start of heart failure related to CAD (12). Also, if treatment is limited to this high-risk secondary prevention group, the population burden of CVDs will continue to remain high. It has been estimated that this group comprises less than 10% of the total primary plus secondary prevention Canadian population at high risk of CVDs (12,15).

Thus, the idea that primary prevention interventions are required to maximize the health and minimize the economic burden of CVD on the population is growing. Generally, statin therapy in primary prevention has been limited to groups at high risk of CVD, including individuals with diabetes, hypertension, or those at high global risk of developing CVD (4). However, again, this group only comprises a small percentage of the total population CVD burden (approximately 10% when combined with the high-risk secondary prevention group) (12,15). Moreover, the latest Adult Treatment Panel Guidelines (ATP III) (16) recommend that both the high-risk (individuals with established CAD and those with diabetes or hypertension) and moderate-risk CVD groups be targets for cholesterol-lowering therapy. Together, it has been

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estimated that these groups comprise approximately 16% of the population in Canada (12,15) and, if treated, should make a greater dent in the population burden of CVDs. In addition, it has been argued that because of their high numbers, statin intervention even in the low-risk proportion of the population should result in a substantial decrease in clinical disease incidence.

The established guidelines, such as the most recent ATP III recommendations (16) and the Canadian Cardiovascular Society position statement on treatment of dyslipidemia (12), are based mainly on large randomly controlled clinical studies using statin intervention in the prevention of secondary CAD end points (17). These landmark studies have definitively shown significant decreases in all-cause mortality and secondary prevention of CAD end points, with nonsignificant changes in adverse effects. The results of these trials have been extrapolated to primary prevention groups (17); however, clear evidence that the favourable cost-benefit analysis in the larger secondary prevention statin trials can be extended to primary prevention groups is still lacking.

Statins are still not used as aggressively as recommended by the guidelines in high-risk primary prevention populations, let alone those in lower-risk groups (13,18). One major reason is the issue of adverse effects, which may result in significant numbers of total affected individuals in clinics, due to the large numbers in the overall primary prevention group. Furthermore, because of a lower baseline CVD risk in primary prevention groups in general relative to secondary prevention populations, overall mortality benefits are much more difficult to demonstrate. In some earlier primary prevention statin trials, including the Coronary Primary Prevention Trial, for example, a significant decrease in CAD mortality was observed, while decreases in all-cause mortality were not seen, attributed to the modest cholesterol-lowering achieved and the relatively small sample sizes (6). Another reason for the reluctance to aggressively treat primary prevention groups is the economic cost of drug intervention in large numbers of individuals. An accurately quantified cost-benefit analysis of statin use in the primary prevention of CAD is thus needed to guide public policy and justify drug intervention more clearly in this group.

Meta-analyses of studies examining primary prevention of CVDs with statins

Such a timely cost-benefit analysis in the primary prevention of CAD has been carried out in the meta-analysis by Moride et al (pages 293-300 of this issue of *The Canadian Journal of Cardiology*). The authors, whom, it is noted, were paid honoraria by Pfizer Canada Inc to facilitate the research, carried out their meta-analysis in a broad range of primary prevention groups on the eight randomized and controlled statin studies with a prestudy-defined primary prevention group. A prior comprehensive Cholesterol Treatment Trialists' (CTT) study included primary prevention subjects in their meta-analysis (8), and this study was discussed in the Moride et al paper. However, the CTT group performed their analyses by combining the data on secondary and primary prevention cohorts (8), while Moride et al carried out their analysis using only primary prevention patients, using very specific, carefully justified definitions of cost in terms of serious adverse effects (SAEs) and benefits.

To quantify adverse effects, the authors excluded serious cardiovascular events among SAEs, they argue, because these are efficacy outcomes dependent on baseline risk. In the paper, SAEs consist of non-CVD mortality, cancer and rhabdomyolysis. Moreover, their definition of benefits included the primary end points of the different studies and total CVD events, leaving out all-cause mortality. The rationale for their use of this definition is its greater utility from a public health perspective. It seems evident, however, that reduced total mortality in primary prevention patients treated with statins is also required to show utility from a public health perspective. Finally, to quantify the costs of statin treatment in primary prevention relative to benefits, for utility in population health, the authors used the numbers needed to treat (NNT) as a pragmatic and clearly understandable measure.

Overall, the results indicated that statins decrease LDL-C, CVD rate and CVD mortality significantly in primary prevention, with no

difference in SAEs, the rates of which were low between treatment and control arms. The most favourable NNTs were identified in populations with higher baseline risk (patients with diabetes, hypertension and high global CVD risk profiles). Moreover, the benefits of statins were independent of baseline cholesterol levels, with greater CVD benefit and greater magnitude of LDL-C lowering. We do not know from the paper, however, whether there were favourable NNTs in the primary prevention groups at varying levels of calculated risk, or only in those with diabetes or hypertension. The paper also did not address whether statin treatment is justified in primary prevention groups from a dollar-cost standpoint. Such information is still required to inform the public policy debate regarding primary prevention.

Other evidence to support LDL-C-lowering initiatives in primary prevention populations

Other recent findings support lowering LDL-C levels as a public health policy in primary prevention populations before advanced atherosclerosis develops. Cohen et al (19) have identified cohorts in both black and white populations that have a functional mutation in the serine protease gene, PCSK9. The resulting inactive protein results in decreased serum LDL-C levels in affected individuals (28% in blacks and 15% in whites), with concomitant very large reductions in CVD risk (88% and 50% reductions in the coronary event rate, respectively) (19). The resultant large reductions in CVD risk for the relatively modest decreases in LDL-C, as also indicated in some statin trials, underscores the importance of the length of time of treatment, as well as the potentially large reductions in CVD risk achievable in healthy populations if therapy is initiated early enough. Another indication for such a primary prevention public health policy arises from the fact that the lifetime CVD risk is quite high in 'healthy' men and women by the age of 40 years, even with 'normal' western LDL-C levels (12). This is in contrast to populations with much lower LDL-C levels (less than 70 mg/dL) due to diet and lifestyle who do not have the early indications of chronic disease seen in the young and the atherosclerosis seen in older people of western populations (5,20). Such protected populations also indicate the strong need for improved diet and exercise regimens implemented early in life in western populations as a means to lower lifetime CVD burden.

CONCLUSIONS

Current data, strengthened by Moride et al's meta-analysis, indicate that the enormous health, social and economic burden of CVD can be lessened with an optimal primary prevention strategy in place. In terms of which primary prevention groups to target for statin intervention, patients with diabetes or hypertension clearly seem to benefit, as Moride et al's analysis indicated. There is also a clear rationale for initiating chronic lipid-lowering therapies in primary CVD prevention patients with severe inherited dyslipidemias and a family history of premature vascular disease. However, a detailed analysis of the benefits relative to cost in other primary prevention subgroups, based on measures of CVD baseline risk (ie, the Framingham risk score), is still needed to support the use of chronic statin or other lipid-lowering therapy in these groups. Neither Moride et al nor the CTT have published such an analysis of primary prevention subgroups. Moreover, better methods of measuring atherosclerotic burden with less invasive imaging modalities, as well as evidence that those measures correlate definitively with CVD event rates, are needed to better assign risk and determine who to treat in the primary prevention population. Finally, optimal diet and exercise routines need to be reintroduced to primary prevention populations, starting at a young age, as basic public health policy.

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