Should cholesterol-lowering medications be available in Canada without a prescription?

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S Rashid. Should cholesterol-lowering medications be available in Canada without a prescription? *Can J Cardiol* 2007;23(3):189-193.

Cardiovascular disease (CVD) presents an enormous and growing burden on the Canadian health care system. Elevated serum low-density lipoprotein cholesterol levels are an established, major risk factor in the development of premature CVD. There is strong evidence that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, significantly lower both low-density lipoprotein cholesterol levels and CVD risk. However, there is currently a treatment gap, in that a large segment of the population who should be receiving statins due to elevated serum cholesterol levels are not. Individuals at moderate risk of developing CVD represent one large population segment that is currently being undertreated. This group may be a candidate for receiving over-the-counter (OTC) or behind-the-counter (BTC) statins, which may be a suitable primary prevention strategy. Nonetheless, it must be noted that hypercholesterolemia is a complex, chronic condition that must be carefully managed and requires close consultation with a health care practitioner. The advantages and disadvantages of OTC or BTC statin usage must therefore be carefully weighed before any potential introduction of OTC or BTC statins in Canada.

Key Words: Cardiovascular disease; Cholesterol; HMG-CoA reductase inhibitor; Lipid; Statin

The enormous economic and health burden posed by cardiovascular disease (CVD) in Canada, as in all industrialized countries, is growing in epidemic proportions. Challenges include the increasing size of the elderly population (20% of all Canadians will be older than 65 years of age by the year 2011) (1), as well as growing numbers of obese individuals characterized by hypertension and other features of the metabolic syndrome, both of which are major risk factors for CVD.

Analysis of the trends in CVD rates and associated risk factors shows a key role of population serum lipid levels in the growing CVD burden (taken from American data [2]). More specifically, the trends in serum cholesterol levels have mimicked the trends of coronary artery disease (CAD) (the primary cause of the high CVD mortality rates) over the past few decades (2). CAD incidence rates have remained stable since 1990 (3) – which translates into increased CAD numbers in the population (12.5 million Americans) (2). Similarly, population-wide American studies, including data from the National Health and Nutrition Examination Survey (NHANES), have demonstrated a halt in declining mean serum cholesterol levels (observed between 1970 and 1990) during the 1990s (2,4,5). This indicates that better strategies must be developed to achieve more optimal lipid levels in the population.

Les hypocholestérolémiants devraient-ils être offerts sans ordonnance au Canada ?

Les maladies cardiovasculaires (MCV) présentent un fardeau énorme et croissant pour le système de santé canadien. Des taux sériques élevés de cholestérol à lipoprotéines de basse densité (C-LDL) sont un facteur de risque important et établi de MCV précoce. D'après des données probantes solides, les inhibiteurs de la réductase de la coenzyme A 3-hydroxy-3-méthylglutaryl, ou statines, réduisent considérablement les taux de C-LDL et de MCV. Cependant, il existe une lacune de traitement, car un important segment de la population qui devrait prendre des statines à cause de taux sériques élevés de cholestérol n'en reçoit pas. Les personnes à risque modéré de MCV représentent un important segment de la population actuellement sous-traitée. Ce groupe pourrait être candidat à recevoir des statines en vente libre ou sur ordonnance, ce qui pourrait constituer une stratégie de prévention primaire efficace. Néanmoins, il faut souligner que l'hypercholestérolémie est un trouble chronique complexe qu'il faut prendre en charge attentivement et qui exige le suivi étroit d'un praticien. Les avantages et les inconvénients liés à l'usage des statines en vente libre et sur ordonnance doivent être soupesés attentivement avant d'envisager l'adoption des statines en vente libre ou sur ordonnance au Canada.

According to the vast majority of medical practitioners, more optimal population lipid levels can be achieved through increased statin use. This is not surprising, because the class of drugs known as the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, have long been shown to potentially lower low-density lipoprotein cholesterol (LDL-C) levels, thereby significantly reducing atherosclerotic events in primary and secondary intervention trials. The statins, however, are underused. Patients at particular risk of developing CAD, such as elderly patients, are not receiving appropriate statin therapy. Given the enormous social and economic burden imposed by CVD, there is currently intense interest in narrowing this treatment gap.

NARROWING THE TREATMENT GAP

The difference between the levels of detection and management of hypercholesterolemia recommended by the United States (US) National Cholesterol Education Program (American data are used as an approximation of Canadian proportionate data) and those actually reached constitutes the treatment gap (2). The 10-year risk of myocardial infarction or CAD death and the distribution of hypercholesterolemia in American adults have been quantified using the National Cholesterol Education

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Received for publication April 6, 2006. Accepted July 16, 2006

Program Adult Treatment Panel III algorithm applied to the NHANES III database (2,6). It has been estimated from these data that 16% of adults, or 23 million people, are at moderate risk (10% to 20%) and another 3% (four million) are at high risk (greater than 20%) of myocardial infarction or CAD death. Of these, approximately 22 million require intervention with drug therapy. Unfortunately, only five million of these patients (20%) are actually on drug therapy. Therein lies the treatment gap.

In Canada, the Working Group on Hypercholesterolemia and Other Dyslipidemias has identified three risk categories, and their target LDL-C lipid levels are as follows: high-risk subjects, in whom the 10-year risk of CAD is greater than 20%, or those who have a history of diabetes mellitus or any atherosclerotic disease, have a target LDL-C level of less than 2.5 mmol/L; moderate-risk individuals, in whom the 10-year risk of CAD is 10% to 20%, have a target LDL-C level of less than 3.5 mmol/L; low-risk subjects, in whom the 10-year risk of CAD is less than 10%, have a target LDL-C level of less than 4.5 mmol/L (7).

Within the above group of patients, a sizable subgroup has been identified in whom cholesterol-lowering therapy is particularly underused – that is, individuals whose serum LDL-C levels are between 3.4 mmol/L to 4.4 mmol/L and who are at moderate risk of CAD (8). These individuals do not have diabetes, have not had an atherosclerotic event and are targets for primary prevention of CAD. The size of this group has been estimated at 18 million people, and this accounts for a significant portion of CVD cases; however, only four million of them are currently receiving lipid-lowering therapy (8). If this segment of the population were to be left untreated, it has been estimated that it would eventually constitute one-third of CAD cases (2).

It is agreed that both physicians and patients have a role in the treatment gap. While physicians rate highly in terms of initial screening of lipid levels, they frequently fail to diagnose, treat and control hypercholesterolemia (5,9). Physicians are essentially not prescribing statins to those who qualify for them. For example, in one study (10), 72,351 hypertensive patients were analyzed for the presence of hyperlipidemia and their cholesterol management. Of these patients, 38,116 were found to be dyslipidemic. Nonetheless, 52% of patients had not had a documented cholesterol measurement in the past year, 35% of the dyslipidemic patients had not been prescribed any antilipidemic medication, and only 15% were on a statin or another antilipidemic medication. The rates of hypercholesterolemia awareness and treatment documented in the above study are typical of the American population as a whole, as described in the NHANES 1999–2000 report (5).

Other causes of the treatment gap have been attributed to issues on the patient side. These include cost and access to treatment, as well as patient compliance. In Canada, where health care resources are limited in relation to those in the US, physician availability can represent an additional barrier to care. In Canada, the rate of general practitioners is approximately 180 per 100,000 population (11) (compared with in the US, where 279 physicians service 100,000 individuals [12]), and waiting times to see a physician may be prolonged, particularly in rural areas. Patient compliance is known to be poor in a large proportion of patients despite physician supervision (13). This is not surprising, considering that patients generally require one to two years of continuous lipid-lowering treatment to see a significant beneficial effect (13). A lack of

motivation and education regarding hypercholesterolemia and CAD risk likely contribute to the poor rate of patient compliance.

PROPOSALS FOR NONPRESCRIPTION STATIN USE

In the US, Merck sought approval from the US Food and Drug Administration (FDA) for several years for over-the-counter (OTC) sale of its statin, Mevacor – also known by its generic name, lovastatin. In January of 2005, however, Merck's second bid was turned down by the FDA. Lovastatin is a naturally derived fungal derivative and was the first statin to receive FDA approval in 1987. The FDA stated that many unresolved issues remained in the Merck bid for OTC use of lovastatin. This does not bode well for Bristol-Myers Squibb, who has submitted its own application for its lipid-lowering agent, pravastatin.

Merck proposed that a 20 mg/day dose of the drug be available OTC for individuals with LDL-C levels of between 3.4 mmol/L and 4.4 mmol/L, and one additional risk factor (obesity, sedentary lifestyle, high blood pressure or age) for CVD. Again, these are individuals who have a moderate 10-year risk of CVD. Presently, prescription lovastatin is dispensed to patients over a wide range of doses, from 10 mg/day to 80 mg/day, depending on their plasma LDL-C concentrations and CAD risk factors. Side effects of lovastatin, as with several other statins, have been described as mild (headache, nausea and constipation) to serious at the higher doses (myositis, rhabdomyolysis and hepatic dysfunction) in a small number of cases.

Why then has the FDA declined Merck's application for OTC use of lovastatin? The FDA's decision not to provide regulatory approval for OTC lovastatin was not entirely unexpected, because there is no precedent for OTC drug use in the US for a chronic disease condition. Examples of drugs that have successfully made the switch from prescription to OTC use include smoking cessation aids and histamine H₂-receptor antagonists, both of which treat acute conditions (13). The general FDA conditions for OTC use of a drug are that the drug may be used safely and effectively, and that it has an easily understood label enabling self-treatment by the average person (13). The general criteria used in meeting these conditions include the following: the condition intended for drug treatment must be self-diagnosable, the condition must be sufficiently understandable to patients, so that the decision to initiate treatment is easily made, the success of the therapy can be monitored by patients and the dose and frequency of drug use can be appropriately determined by patients (13). In response to Merck's proposal, the FDA has indicated doubts that consumers would be able to determine whether they are appropriate candidates for cholesterol-lowering treatment. Furthermore, compliance to therapy was not demonstrated, and users had a relatively low compliance rate with follow-up cholesterol tests in Merck's studies on OTC use of lovastatin (13-15).

In contrast to the above FDA ruling in the US, in July 2004, British health authorities approved an application by Johnson & Johnson MSD Consumer Pharmaceuticals to remove the restriction on the prescription-only use of 10 mg simvastatin (commercially known as Zocor Heart-Pro). Simvastatin is licensed for primary prevention of CAD in moderate-risk patients (10% to 20% 10-year CAD risk) (12).

This particular cohort was targeted for statin use without a prescription because, again, it represents a significantly large population health burden in the United Kingdom (UK), and also because less intervention and monitoring is expected to be required than in those at high CAD risk.

Why the difference in rulings between the US and the UK? A different model is in place in the UK, in which the statin was not given approval for OTC use, but was instead reclassified from a prescription-only medicine to a pharmacy class (P) (behind-the-counter [BTC] medicine [12]). This third P class of drugs is not available in the US and requires intervention by a pharmacist. To enable monitoring of patient progress in LDL-C reduction, cholesterol testing is also available in the pharmacy (12). Finally, although studies have not been published to date regarding the efficacy of the UK status P statin system, a systematic data collection procedure is in place that should enable long-term monitoring of the progress of P class simvastatin use, if implemented.

POTENTIAL ADVANTAGES OF NONPRESCRIPTION STATINS IN CANADA

Studies are currently being conducted in Canada to determine whether statins should be introduced for consumer use without a prescription. Such an option clearly presents numerous potential benefits and risks to Canadian health care. Unfortunately, the data to support the validity of the benefits and concerns are limited to only a few studies (16), mostly in the US. The clearest potential benefit posed by statin use without a prescription (either OTC or BTC) is a reduction in the population's CAD burden. This is because OTC or BTC statins would remove some of the barriers to treatment and thus lead to broader, improved access to lipid-lowering therapy. Indeed, the Consumer Use Study of OTC Mevacor (CUSTOM) trial (17), which evaluated OTC lovastatin use in subjects with moderate or intermediate risk of developing CAD (calculated 10-year risk of CAD of 10% to 20%), found that after 26 weeks, median levels of LDL-C were reduced by 25%. It has been estimated that a mere 10% decline in population-wide LDL-C levels would decrease the incidence of CAD by 30% (American, European and Israeli data [18,19]), thereby markedly decreasing the rates of morbidity and mortality, as well as the associated heavy financial costs of CAD. The Canadian health care system may also save money in other ways. It is anticipated that some costs of prescription statins would be shifted to the consumer, who would still likely pay a relatively low drug price as manufacturers broaden their market. This is indeed what has occurred in the UK (12).

In terms of the safety of statins, there is little disagreement that statins have few adverse effects (15). They have a wide safety margin, have been used in many patients and their potential for abuse is low (13). Analyses from several primary prevention trials have showed a one in 10,000 incidence of rhabdomyolysis, for example (8). Extra care should be taken, however, in certain groups at increased risk of myopathy, such as the frail, elderly patients, and especially women and patients with diabetes complicated by chronic renal failure (6).

For the patient, OTC or BTC statins potentially represent greater self-empowerment. In general, awareness and self-education of health care issues and self-treatment is a cultural trend in consumers (7,20). In this spirit, consumers in North America have expressed a high level of interest in nonprescription statins, as indicated in the National Lipid

Association surveys (21). Consumers are already demonstrating a trend toward increased use of nonpharmaceutical lipid-lowering agents, such as nutraceuticals (eg, garlic, niacin, vitamin E) and grain-based products (psyllium, red yeast rice) (22). In fact, such products are the fastest growing segment of health products, with \$12 billion spent per year on self-medication for CAD prevention (22). Although these agents are believed to lower cholesterol, for many of them, there is a lack of evidence of a cholesterol-lowering effect. These products also have not undergone rigorous, large-scale clinical trials to test for safety and effectiveness, as with the statins. Instead, OTC or BTC statins are a better option for the consumer.

Moreover, because pharmaceutical companies provide educational support material directly to the consumer when drugs are switched from prescription to OTC or BTC status, it is conceivable that increased patient self-education and control will be the result. This, combined with a decrease in the delays in treatment caused by limited physician access, may lead to greater motivation and compliance in statin use. In support of this argument, a study in Sweden assessing 16 drugs that had been switched from prescription to OTC status found that this resulted in a 36% increase in drug sales (17,23). This, of course, does not necessarily indicate the percentage of drug purchases that were appropriate for the intended indication, but it does indicate a trend toward greater drug usage (16).

Finally, if BTC statins are introduced in Canada, paramedical personnel will need to expand their role in the Canadian health care system. They will need to be trained and educated in this role, as in the UK, to be able to provide expert advice and care to the consumer. In any case, this is a good opportunity for greater autonomy for paramedical personnel.

POTENTIAL DISADVANTAGES OF NONPRESCRIPTION STATINS IN CANADA

There are numerous concerns about switching statins (and other drugs) from prescription to nonprescription status. Most concerns relate to the ability and motivation of the patient to determine whether they are initial and ongoing candidates for statin therapy.

First, hypercholesterolemia is not a self-diagnosable condition. Patients would have to be able to interpret their risk factors as explained in the drug package labels and inserts, and be motivated to obtain their plasma cholesterol concentrations as provided to them by a health care professional. Patients must exercise good judgment and interpretive skills to successfully determine whether they are appropriate candidates for nonprescription statin use.

Fortunately, the results of National Lipid Association consumer surveys in the US indicate that 83% of consumers would consult their physicians before purchasing the drug (21). Furthermore, in the actual-use, retail, multicentre CUSTOM trial, the majority (76%) of lovastatin (20 mg) users were found to have accurately reported their plasma LDL-C concentrations, and 40% to 50% of users had LDL-C concentrations in the target range (3.4 mmol/L to 4.4 mmol/L) and 10-year low to moderate CAD risk (5% to 20%) (14). While the results of the CUSTOM trial indicate the need for improvement in the self-diagnosis and evaluation of patient cholesterol concentrations, they translate into approximately a 20% reduction in individual LDL-C concentrations and significant CAD risk reductions if applied to the general population (14). The results of both of the above studies should,

nonetheless, be interpreted with caution, because individuals who participated in the investigations were either invited from pre-existing independent data or recruited via advertising and were, thus, more highly motivated than the general population.

Besides accurate self-diagnosis of hypercholesterolemia, diligent and appropriate long-term self-management of the condition is required for significant CAD risk reduction with nonprescription statins. For successful long-term management of hypercholesterolemia, patients must obtain follow-up plasma cholesterol assessments, titrate their drug dose as needed in accordance with advice from health care professionals and chronically adhere to therapy. It is important to note that long-term management also requires adherence to a heart-healthy lifestyle (diet, exercise and cessation of smoking). The question overall is whether patients can understand and manage their hypercholesterolemia sufficiently to significantly reduce and maintain their plasma cholesterol levels in the target range. The CUSTOM trial addressed some of the above issues and found, overall, that 56% of 1059 users of lovastatin adhered to treatment over six months, which, while not ideal, is comparable with the percentages in observational studies of prescription statin therapy (14). Within the treatment period, the majority of users for whom data were available (70%) received at least one follow-up cholesterol test and made the appropriate decision in response to their cholesterol concentrations (75%) (14). In addition, 57% of lovastatin users reported an interaction with their physicians (14). In general, as with the issue of self-diagnosis of hypercholesterolemia, there is indeed room for improvement, but one can see the potential for benefit in public health with nonprescription statin treatment.

The final topic of major concern is the safety of nonprescription statin use. Statins have been found to have a wide safety margin when used appropriately, as noted in multiple large clinical trials (for example, rhabdomyolysis in one in 10,000 users) (8,13); however, the dose-related adverse effects can increase substantially when patients consume inappropriate doses at increased frequencies ('two pills are better than one'). The toxic effects observed in muscle and liver at higher statin doses can then take effect. The effects can further be prolonged if patients do not monitor liver or muscle function (as advised on prescription statin labels). Drug toxicity is especially a concern in elderly patients, who are the largest segment of prescription and nonprescription drug users. Elderly patients may be particularly sensitive to the toxic effects of a drug and may be using multiple medications simultaneously, which can increase toxic side effects of drugs.

In addition to the risks of adverse side effects, suboptimal therapy is another area of concern within the topic of overall drug safety. Patients at high CAD risk, with cholesterol concentrations above the intended nonprescription range, may choose nonprescription statins if they believe that the nonprescription drug is as effective and more convenient than one obtained by a physician. Indeed, in the CUSTOM trial, a substantial number of patients believed they qualified for OTC lovastatin therapy even though their plasma cholesterol levels were outside the indicated package label range (14). Such patients would then be receiving suboptimal treatment and delaying proper professional assistance for a serious condition.

CONCLUSIONS

Due to the enormous economic and social burden presented by present and future trends in CAD prevalence in Canada, this nation must make it a priority to improve population CAD outcomes. Furthermore, because the size of cohorts with no previous cardiac events is increasing rapidly in Canada (individuals with the metabolic syndrome, elderly patients), primary prevention must be an important component of such a resolution. Primary prevention strategies should focus on public education to increase awareness of CAD risk factors and appropriate lifestyle adjustments. Therapeutic lifestyle changes, including diet, weight management and physical activity, are primary recommendations for patients at moderate risk of CAD (15). However, trends in the structure of modern life (more calorie-rich convenient foods and sedentary lifestyles) indicate that lifestyle changes alone are unlikely to reduce the CAD and hypercholesterolemia health burden sufficiently. Emphasizing therapeutic lifestyle adjustments by physicians until now has still resulted in a \$18.5 billion health burden on the Canadian health care system because of CVD. Thus, educational campaigns to manage hypercholesterolemia need to emphasize the complementary natures of lifestyle and drug treatment (15). Emphasizing increased statin usage, along with therapeutic lifestyle changes, may decrease the overall health burden posed by CVD.

There is a consensus that increased statin use is needed. Multiple controlled clinical trials with statins have demonstrated a high degree of effectiveness and wide safety margins, and provide a strong argument for increased statin use. The current existence of a wide treatment gap, moreover, has led health care systems to debate the desirability and feasibility of nonprescription statins in North America.

Hypercholesterolemia is, however, a complex, chronic condition that requires close consultation with a health care practitioner. Indeed, multiple concerns and flaws in the consumer decision-making process for nonprescription statins have resulted in the US, the FDA recently rejecting an OTC statin application. Still, the trend in the general population of self-management of health conditions is increasing at a rapid pace. The effect has been an increase in the use of unreliable nonpharmaceutical cholesterol-lowering agents, such as herbs and cereals. Critics argue that this is not sufficient reason to justify the introduction of nonprescription statins and that there is no precedent for nonprescription drug treatment for CVD in North America. That would not be entirely correct, because acetylsalicylic acid and nonprescription antihypertension medications have been advertised, advised and used in this way in North America.

Possibly the best option in Canada is the introduction of BTC statins, as in the UK, where P class drugs do not require a prescription and are available only from pharmacists under a pharmacist's supervision. In terms of the logistics of implementing such a system, it is true that pharmacists in Canada currently do not have the expanded role that they do in the UK; nonetheless, pharmacist education and training programs may be put in place. Legislative action would likely be necessary to establish the UK pharmacist-based BTC control in Canada. There are many similarities between the Canadian and UK health care systems (centralization and controlled resource allocation) that may make the introduction of central lipid-monitoring clinics, for example, feasible.

In the UK, the sale of BTC statins shifted the cost burden from the National Health Service to the consumer (24); the cost of statins dropped as a result (less than US\$1.00/day) (8). In Canada, we would have to evaluate where the cost burden of BTC statins should be based.

In any case, various concerns of nonprescription statin use must be addressed. Safety is of particular concern and has not been systematically tested in certain patient groups (elderly patients and women) (25). Epidemiological research should thus be carried out in these cohorts to evaluate potential risks. If nonprescription statins are then implemented, systems should be put into place to increase the general awareness of

hypercholesterolemia, CAD risk and heart-healthy lifestyles. The goal is to enable patients to gain sufficient knowledge and comfort to manage their cholesterol therapy (26). To this effect, educational campaigns, consumer advertising, clear labels and support materials should all be included. In general, whatever decisions are made regarding nonprescription statin use in Canada, all options that meet the ultimate goal of reducing the population CAD burden should be seriously reviewed and considered.

ACKNOWLEDGEMENTS: Shiryia Rashid is supported by a Canadian Institutes of Health Research Fellowship.

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