Combination of statin and ezetimibe for the treatment of dyslipidemias and the prevention of coronary artery disease

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The prevention of coronary artery disease (CAD) involves therapeutic lifestyle changes such as smoking cessation, diet, weight reduction and exercise. In patients with established CAD or atherosclerosis in other vascular beds, or in patients at high risk of developing CAD, lowering serum total and low-density lipoprotein cholesterol (LDL-C) has been associated with a reduction in cardiovascular morbidity and mortality, and total mortality. Recently, large-scale studies have shown that lowering the LDL-C to less than 2.0 mmol/L is associated with a reduction of major cardiac events in patients with established CAD. Therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has had a major impact on preventive cardiology. Not all patients reach recommended LDL-C targets on currently available statins. Ezetimibe is a selective inhibitor of intestinal cholesterol absorption that results in an additional 15% to 25% reduction of LDL-C. The recommended dosage is 10 mg once daily; it is safe and well tolerated. Elevations in transaminase and creatine kinase occur in approximately 1% of subjects. Ezetimibe is suggested for patients who do not reach recommended LDL-C targets on an optimal dosage of statins alone. While the effects of ezetimibe on atherosclerosis have not been ascertained, clinical trials have consistently shown that the reduction in serum cholesterol correlates with a decrease in major cardiovascular events, irrespective of the method used to reduce cholesterol.

Key Words: Hypercholesterolemia; Lipid-lowering drugs; Selective inhibitors of cholesterol absorption

Over the past two decades, the primary prevention and treatment (secondary prevention) of coronary artery disease (CAD) has been dramatically altered with the advent of effective lipid-lowering agents, especially 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins. Clinical practice guidelines in the United States (US) and Canada have increasingly set lower low-density lipoprotein cholesterol (LDL-C) targets for optimal therapy in terms of cardiovascular morbidity and mortality (1,2). Consequently, tracking surveys have shown that many patients, especially those in the highest tier of cardiovascular risk, do not reach recommended guidelines (3,4); however, care must be taken when interpreting such studies. Although the recommended LDL-C target for very high-risk individuals in the US is now less than 1.8 mmol/L (based on the

La combinaison d'une statine et d'ézetimibe dans le traitement des dyslipidémies et la prévention de la coronaropathie

La prévention de la coronaropathie comprend de saines habitudes de vie, telles que l'abandon du tabac, la diète, la perte de poids et l'exercice. Chez les patients atteints d'une coronaropathie établie, d'athérosclérose des autres vaisseaux ou à risque élevé de coronaropathie, la réduction de la cholestérolémie sérique totale et, surtout, des lipoprotéines de basse densité (C-LDL), s'associe à une réduction de la morbidité et de la mortalité cardiovasculaires, ainsi que de la mortalité totale. D'importantes études cliniques ont récemment démontré qu'une réduction du C-LDL à moins de 2,0 mmol/L entraîne une diminution des événements cardiaques majeurs en prévention secondaire. Le traitement aux inhibiteurs de la 3-hydroxy-3-méthylglutaryl coenzyme A réductase (statines) a eu des répercussions majeures en cardiologie préventive. Toutefois, les patients n'atteignent pas tous les cibles thérapeutiques recommandées avec les statines disponibles. L'ézetimibe est un inhibiteur sélectif de l'absorption intestinale du cholestérol et entraîne une baisse additionnelle de 15 % à 25 % du C-LDL. La dose recommandée est de 10 mg par jour. Le médicament est sécuritaire et bien toléré. Une élévation des transaminases et de la créatine-kinase est observée chez environ 1 % des sujets. On propose l'ézetimibe pour les patients n'atteignant pas les valeurs cibles de C-LDL sur une dose optimale de statines seules. Même si les effets de l'ézetimibe sur l'athérosclérose n'ont pas été explorés, les études cliniques ont systématiquement démontré que la réduction de la cholestérolémie sérique est mise en corrélation avec une diminution des événements cardiaques, quel que soit le mode de réduction du cholestérol.

Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction [PROVE-IT TIMI-22] and Treating to New Targets [TNT] studies [5,6]), one should keep in mind that this figure was the mean level achieved at the completion of the trials. Assuming a normal distribution of LDL-C across the study subjects, one-half would be expected to have an on-trial LDL-C above this level.

In the past 20 years, clinical trials examined the effect of lowering total cholesterol (TC) and LDL-C on cardiovascular end points, cardiovascular morbidity and total mortality. These have been reviewed elsewhere (7). The landmark Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) used cholestyramine to lower TC levels and resulted in a reduction of cardiovascular end points (8). Bile acid sequestrants were initially used for the treatment of severe

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TABLE 1
Currently available drugs for the treatment of dyslipidemias

Generic name	Trade name	Recommended dose range
Statins		
Atorvastatin	Lipitor*	10 mg–80 mg
Fluvastatin	Lescol†	20 mg–80 mg
Lovastatin	Mevacor‡	20 mg–80 mg
Pravastatin	Pravachol§	10 mg–40 mg
Rosuvastatin	Crestor¶	10 mg–40 mg
Simvastatin	Zocor‡	10 mg–80 mg
Bile acid sequestrants		
Cholestyramine	Generic	6 g–24 g
Colestipol	Colestid*	5 g–30 g
Cholesterol absorption inhibitors		
Ezetimibe	Ezetrol†	10 mg
Fibrates		
Bezafibrate	Bezalip**	400 mg
Fenofibrate	Lipidil††	67 mg–200 mg
Gemfibrozil	Lopid*	600 mg–1200 mg
Niacin		
Nicotinic acid	Generic or Niaspan††	1 g–3 g

*Pfizer Canada Inc, Canada; †Novartis Pharmaceuticals Canada Inc, Canada; ‡Merck Frosst/Schering Pharmaceuticals, Canada; §Bristol-Myers Squibb Canada, Canada; ¶AstraZeneca Canada Inc, Canada; **Hoffman-La Roche Limited, Canada; ††Fournier Pharma Inc, Canada; ††Oryx Pharmaceuticals Inc, Canada

hypercholesterolemia. This was the first large-scale trial of cholesterol-lowering therapies for the prevention of CAD. A trial of ileal bypass surgery (to limit ileal absorption of cholesterol) showed that lowering of serum cholesterol by decreasing its absorption resulted in decreased cardiovascular events in patients with severe hypercholesterolemia, albeit at a cost of noncardiac morbidity (9).

More recently, the advent of statins has made the management of hypercholesterolemia much easier for clinicians and patients alike. Statins are potent inhibitors of the rate-limiting enzyme involved in sterol synthesis, HMG-CoA reductase. There are currently six statins available on the market. A seventh statin, cerivastatin, was removed from the market in 2003 because of concerns of development of rhabdomyolysis, a rare, but serious and potentially fatal, side effect. Since their introduction in clinical practice in the mid-1980s, the use of statins has grown rapidly. Multiple clinical trials have shown the ability of statins to markedly reduce serum levels of TC, LDL-C, triglycerides (TGs) and apolipoprotein B (Apo B). This effect on serum lipids and lipoprotein lipids has dramatically changed the relative risk of cardiovascular morbidity and mortality and on total mortality (6,10–13). The effect of statins on high-density lipoprotein cholesterol (HDL-C) is usually modest (5% to 10% increase). Fibrates are peroxisome proliferator-activated receptor alpha-type agonists and have multiple metabolic effects, primarily reducing TGs and decreasing TC and LDL-C (10% to 15%) (14). The drug niacin is especially used to raise HDL-C, often in combination with other lipid-lowering agents; niacin also lowers TGs and LDL-C (15). Ezetimibe represents a novel class of lipid-lowering agents that selectively inhibits intestinal cholesterol absorption. Table 1 shows the currently available drugs for the treatment of dyslipidemias.

EZETIMIBE

Ezetimibe was initially identified as a potential inhibitor of acyl coenzyme A:cholesterol acyltransferase. Animal studies have shown that ezetimibe causes a decrease in dietary cholesterol absorption (16,17). Currently, ezetimibe is approved by Health Canada to treat an elevated serum cholesterol level when dietary and lifestyle changes (weight reduction and exercise) are insufficient to reach the treatment target. In Canada, provincial formularies regulate its use. It is marketed under the commercial name Ezetrol (Merck Frosst/Schering Pharmaceuticals, Canada) and is prescribed at 10 mg taken once daily, with or without meals.

Ezetimibe is usually used in combination with a statin for the reduction of elevated TC, LDL-C, Apo B and TG levels in patients with hypercholesterolemia. It has also been used in combination with fibrates, but clinical experience with this combination is limited.

Ezetimibe is indicated for patients with genetic lipoprotein disorders, especially familial hypercholesterolemia, where baseline TC and LDL-C exceed the 95th percentile for an age- and sex-matched population. It has replaced, in many cases, the use of bile acid sequestrants such as cholestyramine and colestipol. In homozygous familial hypercholesterolemia, ezetimibe is often added to a statin in conjunction with extracorporeal LDL-C removal either by filtration, apheresis, immunoabsorption or precipitation techniques. It is also used in the rare disorder sitosterolemia, which is caused by mutations in the genes coding for the ATP-binding cassette transporters ABCG5 or ABCG8. In sitosterolemia, ezetimibe prevents the absorption of plant sterols (especially sitosterol), and, thus, its accumulation in the body that would otherwise lead to severe and very premature atherosclerosis (18).

Pharmacological and pharmacokinetic properties

The mechanism of action of ezetimibe is different from that of other lipid-lowering agents, including statins, fibric acid derivatives, plant sterols (phytosterols) and bile acid sequestrants. Bile acid sequestrants, by virtue of their molecular structure, bind cholesterol noncovalently in the intestine and prevent its absorption in a relatively nonselective manner. Ezetimibe is the first of a new class of lipid-lowering drugs that selectively inhibits the absorption of cholesterol and related phytosterols.

Ezetimibe localizes at the epithelial brush border of the small intestine and inhibits the absorption of cholesterol and phytosterols without affecting the absorption of TGs and fat-soluble vitamins (16,17,19). The likely molecular target for ezetimibe is the Niemann-Pick C1 Like 1 (NPC1L1), a membrane-associated protein. The precise role of NPC1L1 is unknown, but the protein contains a sterol-sensing domain and may be part of a complex that transports sterols across the intestinal epithelial cells (20).

Unlike statins, ezetimibe does not inhibit hepatic cholesterol synthesis and, unlike bile acid sequestrants, ezetimibe does not increase bile secretion. By decreasing cholesterol delivery to the liver, ezetimibe causes an increase in liver expression of LDL receptors, resulting in an increase in the removal of LDL-C from serum (21–23).

The mode of action of ezetimibe is independent of, but complementary to, that of statins, and controls cholesterol synthesis in the liver by inhibiting the activity of HMG-CoA reductase. HMG-CoA reductase is responsible for converting

HMG-CoA to mevalonic acid, the rate-limiting step of cholesterol synthesis (24).

Pharmacokinetics

Ezetimibe is absorbed rapidly and undergoes extensive glucuronidation in the liver. Ezetimibe and ezetimibe-glucuronide are transported through the entero-hepatic circulation and are delivered to the intestinal epithelial cell brush border, the site of pharmacological action. Ezetimibe is rapidly absorbed and reaches a peak serum concentration in 4 h to 12 h; the serum half-life is approximately 22 h. Ezetimibe is extensively protein bound (99.7%), as is its glucuronidated metabolite (88% to 92%). Most of the drug is excreted in the feces (more than 78%) (25).

Dosage and administration

The recommended dosage is 10 mg/day taken orally, with or without food, and is considered safe for adults and children 10 years and older. No dosage adjustment is required for elderly patients. Although bioavailability appears to be increased with severe renal impairment, no dosage adjustment is necessary for patients with renal failure. Similarly, no dosage adjustment is necessary for subjects with mild hepatic impairment (Child-Pugh score 5 to 6). However, the use of ezetimibe is not recommended for patients with moderate to severe hepatic impairment (Child-Pugh score 7 to 15). There is no further significant effect of increased dosage of ezetimibe above 10 mg/day.

Drug interactions

No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolized via the cytochrome P450 oxidase (CYP) system (CYP 1A2, 2C8/9, 2D6, and 3A4 isoenzymes), and by N-acetyltransferase such as caffeine, dextromethorphan, tolbutamide and intravenous midazolam. Ezetimibe does not induce or inhibit CYP isoenzymes. The concomitant use of ezetimibe and cyclosporine in transplant subjects should be closely monitored as the concentration of ezetimibe (as reflected by the area under the curve) can increase three- to fourfold.

Clinical efficacy

Currently, the Canadian recommendations for the management of dyslipidemia and the prevention of cardiovascular disease recognize three risk factor categories (low, intermediate and high). These categories are based on Framingham risk calculations and two treatment targets: LDL-C and the TC to HDL-C ratio (2). Individuals are categorized and targets are established for LDL-C and the TC to HDL-C ratio based on risk categories: high risk (CAD, cerebrovascular disease or peripheral arterial disease, chronic kidney disease, diabetes, 10-year risk of CAD of 20% or higher), intermediate risk (10-year risk between 11% and 19%) and low risk (10-year risk of 10% or lower) (26). The 2003 Canadian recommendations suggested LDL-C targets of less than 4.5 mmol/L in low-risk subjects (less than 5.0 mmol/L in very low-risk individuals), less than 3.5 mmol/L in intermediate-risk subjects and less than 2.5 mmol/L in high-risk subjects. The second goal of treatment is a TC to HDL-C ratio of less than 4.0 in high-risk subjects (2). The management of dyslipidemias for the prevention of cardiovascular disease must include therapeutic lifestyle changes (diet, exercise, smoking cessation, weight loss) and, if necessary, medication, to reach target levels. Because clinical studies have shown that reducing TC and

TABLE 2

Major clinical trials of total and low-density lipoprotein (LDL-C) cholesterol lowering for the prevention of coronary artery disease-related death and nonfatal myocardial infarction

Trial	Placebo*		Statin	
	Event rate† (% of patients)	LDL-C (mmol/L)	Event rate† (% of patients)	LDL-C (mmol/L)
4S (10)	28.0	4.9	19.4	3.2
LIPID (12)	15.9	3.9	12.3	2.9
CARE (11)	13.2	3.5	10.2	2.5
HPS (13)	11.8	3.3	8.7	2.3
TNT (6)	8.3	2.6	6.7	2.0
IDEAL‡ (37)	10.4	2.6	9.3	2.1

*The Treating to New Targets (TNT) trial did not have a placebo arm – all patients were on atorvastatin 10 mg/day at baseline; †Event rate adjusted for five years; ‡The Incremental Decrease in Endpoints through Aggressive Lipid lowering (IDEAL) study compared simvastatin 20 mg to 40 mg with atorvastatin 80 mg. 4S Scandinavian Simvastatin Survival Study; CARE Cholesterol and Recurrent Events; HPS Heart Protection Study; LIPID Long-term Intervention with Pravastatin in Ischemic Disease; MI Myocardial infarction

LDL-C decreases cardiovascular morbidity and mortality, and total mortality in high-risk subjects, the primary goal of treatment is the reduction of LDL-C. The effects of TG reduction were recently examined in the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) with the fibric acid derivative gemfibrozil; while encouraging, the reduction in hard cardiovascular end points is not as strong as that seen in statin trials (27). The effects of fenofibrates in diabetic subjects will be examined in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial (14). Recently, two studies have addressed the issue of achieving a lower LDL-C goal than previously recommended in the Third Report of the National Cholesterol Education Program (NCEP III) or the 2003 Canadian guidelines. The PROVE-IT TIMI 22 study examined over 4172 subjects with acute coronary syndrome. The use of 80 mg of atorvastatin was superior to 40 mg of pravastatin in reducing cardiovascular end points (5). The TNT study compared atorvastatin (10 mg versus 80 mg) in 10,000 patients with established CAD. The 80 mg dose proved superior to the 10 mg dose in preventing cardiovascular end points (6). Based on these studies, current therapeutic guidelines in the US (1), Canada and Europe recommend a more intensive treatment of lipoprotein disorders in high-risk subjects. The revised NCEP III recommendations suggest an LDL-C target of less than 1.8 mmol/L in these subjects (1). There is a growing consensus in Canada to reach an LDL-C target of less than 2.0 mmol/L in high-risk subjects. This recommendation is based on the available clinical trial evidence of the effect of lowering LDL-C on cardiovascular end points of CAD deaths and nonfatal acute myocardial infarctions. Table 2 summarizes these major studies.

Effect on cholesterol, TG and lipoprotein lipids

Ezetimibe was effective when used as monotherapy to reduce LDL-C and improve all key lipid parameters, providing a safe and effective complement or alternative to statins in subjects who do not reach therapeutic goals on statin monotherapy. Two studies (19,28) with a sufficient number of subjects evaluated the efficacy and safety of ezetimibe (10 mg) monotherapy in patients with mild to moderate hypercholesterolemia. Dujovne et al (28) and Knopp et al (19) enrolled 892 and 827 patients, respectively. After 12 weeks of treatment, the

decrease in LDL-C with ezetimibe monotherapy compared with placebo was approximately 17% and 18%, respectively. The effect was noted after two weeks of treatment and persisted throughout the study.

In practice, ezetimibe is most likely to be used for patients already on a statin who require additional therapy to reach treatment goals. Some patients already on a maximum dose of a statin, particularly those with familial hypercholesterolemia, require additional LDL-C lowering; ezetimibe has largely replaced bile acid sequestrants in these patients. In most cases, patients or their physicians prefer not to use the maximal dose of statins because of concerns of potential toxicity and other side effects. Ezetimibe can be coadministered with any statin and will provide a mean LDL-C reduction of 18% to 25%. In a study by Gagne et al (29), only 19% of selected patients reached treatment goals on statin monotherapy and the addition of ezetimibe brought this figure to 72%.

Feldman et al (30) examined 710 patients over a 23-week period, comparing ezetimibe coadministered with simvastatin versus simvastatin monotherapy at all dose ranges of simvastatin. The combination of 10 mg ezetimibe with simvastatin at doses of 10 mg, 20 mg, 40 mg and 80 mg resulted in an additional mean decrease of LDL-C of 14% the dose range of simvastatin.

In a direct comparison of atorvastatin and the combination of simvastatin and ezetimibe, Ballantyne et al (31) evaluated 788 patients over four periods of six weeks. The coadministration of ezetimibe and simvastatin had significantly greater efficacy in decreasing levels of LDL-C, non-HDL cholesterol, Apo B and TC than atorvastatin monotherapy did across the entire dose range. The combination of 10 mg ezetimibe and 40 mg simvastatin resulted in a 55.6% reduction of LDL-C, compared with 52.5% reduction on 80 mg atorvastatin alone.

Goldberg et al (32) examined the efficacy and safety of ezetimibe coadministered with simvastatin in 887 patients with primary hypercholesterolemia and found that a significant proportion of subjects in the combined treatment group were able to achieve LDL-C target levels compared with those treated in monotherapy. Seventy-one per cent of patients treated with the ezetimibe-simvastatin combination achieved a 50% or greater reduction of LDL-C compared with 21% of patients in the simvastatin monotherapy group.

Coadministration of ezetimibe with a statin was also found to be beneficial in hypercholesterolemic patients with diabetes mellitus or metabolic syndrome (33). The combination was associated with significant reductions in LDL-C, ranging from 22% to 27%, with little or no change observed in patients treated with placebo in addition to their statins. Significantly more patients in the ezetimibe group achieved their LDL-C targets at the end of the study than those in the placebo group (33). The treatment period for the studies were relatively short (approximately 12 weeks). Long-term treatment (12 months) examining the long-term safety and tolerability of ezetimibe in patients with primary hypercholesterolemia treated with simvastatin found the combination therapy to be well tolerated, with a safety profile comparable to simvastatin monotherapy (34).

In a clinical study of 3030 patients with elevated LDL-C (based on NCEP III criteria), Pearson et al (35) examined the effect of adding 10 mg of ezetimibe to the patients' current statin therapies for six weeks (40% atorvastatin, 29% simvastatin, 22% pravastatin, 10% other statins). Patients were

randomly assigned 2:1 to either ongoing statin plus 10 mg ezetimibe, or ongoing statin plus placebo. The mean age of participants was 62 years, and three-quarters had CAD or were at CAD-equivalent risk. The addition of ezetimibe to statin therapy further decreased LDL-C by approximately 25%. The combination of statin and ezetimibe allowed 71% of patients to reach NCEP LDL-C targets, compared with 21% on statin monotherapy.

When evaluating the lipid-lowering effects of statins, a rule of thumb indicates that each doubling of a statin dose reduces LDL-C by approximately 6% (on average). Thus, three doublings of simvastatin or atorvastatin (from 10 mg to 80 mg) will reduce LDL-C by approximately 18%. Addition of ezetimibe to the lowest dose of a statin will accomplish the same effect.

The effect of ezetimibe on TGs is consistent across studies; it has little additional effect when added to a statin. As expected, ezetimibe decreased non-HDL cholesterol by 20% to 25%. Reducing the non-HDL cholesterol is a recommended target of therapy in NCEP III; the Canadian guidelines recommend reducing the TC to HDL-C ratio as a secondary target (1,2). Ezetimibe decreases Apo B levels by approximately 15% to 20%. Ezetimibe has little effect on HDL-C; a small 1% to 2% increase in HDL-C is reported in most large-scale studies.

Ezetimibe is effective when initiated concurrently with statin therapy. Pooled results indicate that ezetimibe-statin combination groups in each trial achieved statistically significant reductions of LDL-C (18% to 23%) compared with statin monotherapy. Ezetimibe plus a low-dose statin was significantly more effective than 10 mg, 20 mg or 40 mg of the statin alone and was as effective as 80 mg of the statin alone.

The effect of ezetimibe on the high-sensitivity C-reactive protein (hsCRP) was examined in several studies. Whereas all statins lower hsCRP, ezetimibe alone has no significant effect on hsCRP levels. In combination with a statin, however, ezetimibe further reduces hsCRP and this effect depends on baseline levels. When ezetimibe was added to simvastatin in subjects with a baseline hsCRP level higher than 3 mg/L, hsCRP levels decreased by 44%, compared with 32% with simvastatin alone (36).

Safety and tolerability

Ezetimibe was well tolerated in all clinical studies. The rate of discontinuation for side effects was not different from that of a placebo. Abdominal pain and diarrhea were reported in approximately 3% of patients (not significantly different from placebo); similarly, arthralgia was reported in 3.8% of patients (not significantly different from placebo). Elevations of hepatic transaminase more than three times the upper limit of normal are reported and may be seen in 1% of subjects on the statin-ezetimibe combination therapy. Elevations in creatine kinase are not seen more frequently than on statin monotherapy. It is recommended that hepatic transaminase and creatine kinase levels be measured before initiating therapy with ezetimibe (35).

Ezetimibe is contraindicated in pregnant and lactating women. No clinical data on exposed pregnancies are available for ezetimibe, and its effects on labour and delivery are unknown. All statins are contraindicated in pregnancy. Caution is recommended by the manufacturer when ezetimibe is prescribed to pregnant women. Studies in rats have demonstrated that ezetimibe is excreted in milk; however, it is not known whether ezetimibe is excreted in human breast milk.

Ezetimibe should not be prescribed to nursing mothers unless potential benefits justify potential risks to the infant. All statins are contraindicated in nursing women.

CONCLUSIONS

Ezetimibe is a safe and effective medication for the treatment of elevated LDL-C. Ezetimibe monotherapy produces a relatively modest LDL-C reduction. Clinicians must weigh the benefits of a 15% to 20% LDL-C reduction for individual patients in terms of reduction of cardiovascular risk, and not in terms of improvement of LDL-C levels. In patients with genetic forms of dyslipidemias, ezetimibe has been a very useful adjunct to elevated or maximal dosages of statins. The addition of ezetimibe to currently prescribed doses of statins enables the majority of patients to reach therapeutic targets. It also allows clinicians to decrease the current statin doses for patients with myalgias or other side effects while still reaching a significant LDL-C reduction. While the effects of ezetimibe on atherosclerosis have not been ascertained,

clinical trials have consistently shown that the reduction in serum cholesterol correlates with a decrease in major cardiovascular events, irrespective of the method used to reduce cholesterol.

The question of whether prescribing ezetimibe to a patient already taking a statin will reduce CAD to the same extent as the statin (to the same magnitude of LDL-C reduction) or whether it will provide further benefits for statin-treated patients can only be addressed by well designed, ongoing clinical trials.

CONFLICT OF INTEREST: Jacques Genest receives speaker's fees from AstraZeneca, Bristol-Myers Squibb, Merck Frosst/Schering Pharmaceuticals and Pfizer. He is on the advisory board of Aventis, AstraZeneca, Liponex, Merck Frosst/Schering Pharmaceuticals, Pfizer and Resverlogix. He is a consultant for, and receives royalties from, Novartis and Pfizer; however, in neither of these cases is the amount more than US\$10,000. He does not hold equities, shares or bonds in these companies.

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