Prevention of Cardiovascular Ischemic Events
High-Risk and Secondary Prevention

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Atherosclerosis is a chronic disease involving the coronary, carotid, and aorto-femoral vascular beds that represents the major cause of death worldwide. Coronary artery disease (CAD) is the major cause of morbidity and mortality in the world. Efforts at preventing the clinical manifestations of atherosclerosis have yielded impressive results in the past 3 decades and constitute the major focus of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and the Joint Task Force of European and other Societies on Coronary Prevention. The primary prevention of CAD represents one of the most important aspects of preventive medicine today. The secondary prevention of CAD has become the major focus of healthcare teams dealing with cardiovascular medicine. Secondary prevention was initially designated for patients who had a myocardial infarction. More recently, the term has been used to encompass patients with objective evidence of coronary artery, cerebrovascular, or peripheral disease. With the realization that patients with diabetes had a prognosis at least as grave as patients with CAD, the term secondary prevention has yielded its place for a more comprehensive strategy aimed at treating patients at high risk of CAD. These include patients with multiple risk factors, a 10-year risk of cardiovascular event >20%, diabetes (especially those with one additional cardiovascular risk factor), atherosclerotic vascular disease, and a previous myocardial infarction. This population thus represents the top stratum of cardiovascular risk and has a prognosis equivalent to or worse than post-myocardial infarction patients. Over the past 15 years, clinical practice guidelines have been adapted to take into account novel information derived from large-scale intervention studies (Figure 1). Current strategies, in terms of public health and targeted therapy, are aimed at identifying global cardiovascular risk in an individual and treating all risk factors, starting initially by therapeutic lifestyle changes. These include a diet restricted in calories to reach a leaner body weight (a body mass index <25, a waist circumference <105 cm in men and <90 in women), physical exercise, smoking cessation, and blood pressure control. As knowledge is gained from clinical studies and trials, practice guidelines integrate this novel data and change in time (Figure 1); global risk stratification, rather than single cardiovascular risk modification is the standard of care. In high risk subjects, the aim is to lower plasma low-density lipoprotein cholesterol (LDL-C) to <2.6 mmol/L (100 mg/dL). Current guidelines are similar in Canada, but European guidelines suggest that high-risk patients should lower their LDL-C to <3.0 mmol/L. The use of antithrombotic medication, especially aspirin (80 to 325 mg/d) is now well established. Meta-analysis of clinical trials using aspirin have shown a 25% reduction in combined cardiovascular endpoints. The recent Clopidogrel in Unstable angina and Recurrent Events (CURE) trial has shown that the addition of clopidogrel 75 mg is associated with a 16% reduction in cardiovascular events above that obtained with aspirin. The use of inhibitors of the angiotensin converting enzyme in the Health Outcome and Prevention Evaluation (HOPE) study was associated with a significant decrease in mortality in older subjects at high risk of developing CAD.

The following review will discuss current recommendations for secondary and high-risk prevention of cardiovascular diseases.

Historical Aspects
The hypothesis that human atherosclerosis was not an absolute consequence of aging and could be reversed was put forth over 30 years ago. The pioneering work of Malinow in non-human primates and subsequently in humans heralded the era of clinical trials aimed at stopping the progression of atherosclerosis and in promoting its regression.

Regression Studies
A landmark study, the Cholesterol Lowering Atherosclerosis Study (CLAS), ushered in a decade of “regression studies,” wherein a treatment aimed at lowering plasma lipids was compared with conventional therapy on the angiographic progression of CAD. Angiographic progression of CAD was taken as a surrogate endpoint for clinical events. Post-hoc analysis of regression studies estimated that an average cholesterol reduction of 44% was required to prevent angiographic progression of CAD. A discrepancy was soon observed between the small effect noted on angiography and...
the marked decrease in clinical events. It became clear that angiography did not allow visualization of the atherosclerotic plaque, but rather showed luminal obstruction. The advent of intravascular ultrasonography and a better understanding of arterial remodeling in atherosclerosis have yielded considerable information on the pathogenesis of CAD and acute coronary syndromes. This technique has shown the presence of considerable plaque burden in the presence of angiographically normal coronary segments.17 Remodeling allows the coronary arteries to maintain patency despite a large plaque burden. Visualization of the lipid core and fibrous cap may have prognostic significance and can be used as an index of treatment success aimed at stabilizing the plaque.

Angiographic regression studies showed that lowering of plasma cholesterol and increasing of high-density lipoprotein (HDL) cholesterol with a statin, fibrate derivative, or combination therapy prevented angiographic progression and promoted regression of CAD.18 This has paved the way for studies that examined cardiac mortality and morbidity. The advent of inhibitors of hydroxymethylglutaryl coenzyme A reductase (statins) ushered in an era of renewed interest in regression of CAD in man. These agents are powerful inhibitors of the rate-limiting step of cholesterol synthesis and markedly reduce plasma levels of total, LDL, non–HDL-cholesterol, the cholesterol/HDL-C ratio, and apolipoprotein B (apoB). They also reduce plasma triglyceride levels and have a modest raising effect on HDL-C.

**Lipid-Lowering Studies**

The publication of the Scandinavian Simvastatin Survival Study (4S),19 the Cholesterol And Recurrent Events (CARE) trial,20 and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial21 marked a turning point in clinical practice. Strong evidence from 4S supported the concept that in patients with established CAD and an elevated LDL-C (240 mg/dL; ≈6.2 mmol/L), 20 to 40 mg of simvastatin reduced total and cardiac mortality and markedly reduced cardiovascular events. The CARE and LIPID trials addressed the issue of treating patients with “average” plasma levels of LDL-C (≈3.5 mmol/L and ≈4.0 mmol/L, respectively) (Figure 2). These studies extended the observations from the 4S and confirmed that lowering total cholesterol and especially LDL-C decreased cardiovascular mortality and morbidity. Controversy arose from sub-group analysis of the CARE and LIPID trials, as well as an analysis of trials using pravastatin.22 Post-hoc analysis of the data suggested that there was no further benefit in terms of reduction in major cardiac events when the LDL-C was <125 mg/dL (3.2 mmol/L). This controversy influenced the NCEP II and III levels of LDL-C for initiation of drug therapy.4 A careful review shows that this issue cannot be unambiguously resolved on the basis of the published data; confidence intervals permit several possible interpretations.23 The suggestion was made that statins may have effects on atherothrombosis distinct from those related to the lowering of LDL-C levels. These pleiotropic effects24 involve a broad range of biological effects that seem not to be related to the effects of the drug on plasma levels of LDL-C. Whether these effects have true biological significance is very difficult to assess clinically. One on-going trial, the PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) trial, will attempt to lay the matter to rest by comparing the effects of pravastatin 40 mg to that of atorvastatin 80 mg on cardiovascular events. In addition, the PROVE-IT trial will examine the effect of gatifloxacin on the treatment of chlamydia pneumonia in preventing future cardiovascular events.

The Heart Prevention Study (HPS)25 randomized 20 556 high-risk patients (previous myocardial infarction, established CAD or atherosclerotic vascular disease, diabetes, or hypertension) aged 40 to 80 years with a total cholesterol 135 mg/dL (≈3.5 mmol/L) to either simvastatin 40 mg or placebo for 5 years. Patients were also randomized to a cocktail of antioxidant vitamins (vitamins E, C, and beta-carotene). The vitamin arm proved ineffective in the prevention of cardiovascular disease. Simvastatin use was associated with a 24% reduction (intention-to-treat analysis) in major cardiac endpoints and a 12% reduction in total mortality, regardless of baseline cholesterol or LDL-C levels, age, gender, or the presence of diabetes. The implications of the HPS are far-reaching; simvastatin at a dose of 40 mg proved safe and effective in preventing cardiovascular morbidity and mortality in high-risk patients over a broad range of clinical conditions. The HPS did not confirm the “threshold” effect of pravastatin observed in the CARE trial and showed that
benefit was derived even when LDL-C levels are 100 mg/dL (<2.6 mmol/L), which is the NCEP ATP III treatment target.

The Veteran’s Administration HDL Intervention Trial (VA-HIT) examined subjects with CAD and a low HDL-C level with or without elevated triglycerides and a relatively low LDL-C level. The baseline total cholesterol (4.5±0.6 mmol/L), LDL-C (2.9±0.6 mmol/L), HDL-C (0.83±0.1 mmol/L), and triglyceride (1.8±0.8 mmol/L) levels (mean±SD) showed that this group would not normally have been treated with lipid-lowering therapy according to guidelines in place at the time. The drug used was gemfibrozil, a fibric acid derivative at a dose of 1200 mg/d; it reduced plasma triglycerides by 31%, raised HDL-C by 6%, and did not alter LDL-C levels. There was a significant decrease in the primary endpoints of combined major cardiovascular events by 22%.

The absolute gain in reduction of cardiovascular events seems not to be linear across the range of total (or LDL) cholesterol levels. As shown in Figure 3, a greater absolute reduction in major cardiovascular events is seen in studies with a higher baseline total cholesterol level.

Unresolved Issues

Consensus statements and recommendations evolve in time as novel information from basic research and clinical trials filter in the practice of medicine. In the early 1980s, epidemiological studies and clinical trials such as the Lipid Research Clinics Primary Prevention Trial (LRC-CPPT), the Coronary Drug Project (CDP), and the Helsinki study shaped early recommendations on the prevention of coronary artery disease and influenced the first publication of the NCEP in 1988. Regression studies and pooled epidemiological analyses shaped NCEP II (1993), and the large clinical trials of primary and secondary prevention, as well as the concept of global risk assessment and the developing epidemic of the metabolic syndrome, led to the publication of NCEP III (2001). The HPS is raising issues beyond current guidelines like the NCEP ATP III. Information from on-going trials will shed some light on the following issues.

Threshold LDL-C Level to Initiate Treatment

This debate has provoked much confusion. On the basis of currently available data, proponents of a threshold effect point to the results obtained from the CARE and Pravastatin pooled trial results to suggest that little benefit is gained by initiating a statin (pravastatin) when the LDL-C is <120 mg/dL (3.2 mmol/L). The 4S did not show an attenuation of the beneficial effect of simvastatin at lower LDL-C levels. Baseline LDL-C values in 4S were higher than in the CARE and LIPID trials (Figure 1). The HPS showed that the benefit of simvastatin was similar in a sub-set of patients with baseline LDL-C <100 mg/dL (2.6 mmol/L). There were 6793 patients in HPS with LDL-C <120 mg/dL (3.0 mmol/L), which was more than the entire CARE cohort. The issue of threshold can therefore be put to rest.

Is Lower Better?

The Treat to New Targets (TNT) study examines a LDL-C target of 100 mg/dL (2.6 mmol/L) versus 75 mg/dL (=1.9 mmol/L) in over 10 000 patients with CAD using atorvastatin 10 mg versus 80 mg; the Study of Effectiveness of Additional Reduction in Cholesterol and Homocysteine (SEARCH) has randomized 12 000 patients to simvastatin 20 versus 80 mg/d, in combination with folate and vitamin B 12 to lower homocysteine, or double placebo. The Incremental Decrease in Events with Aggressive LDL lowering (IDEAL) study will use the strategy used in the 4S study versus atorvastatin 80 mg per day in 8888 patients. The PROVE-IT trial will examine the effect of pravastatin 40 mg versus atorvastatin 80 mg, as well as gatifloxacin in the prevention of recurrent events. Extrapolation from existing data supports the concept that a lower target level of LDL-C may bring additional benefit. Secondary aims of therapy now highlight the importance of particles other than LDLs. The NCEP III recommends using non-HDL-C as a target, especially in patients with the metabolic syndrome. ApoB as a therapeutic goal is also recommended on the basis of the fact that total apoB best reflects the sum of circulation atherogenic particles.

Are Follow-Up Lipid Measurements Indicated or Useful?

The NCEP ATP III and most consensus conferences recommend a targeted approach for dyslipidemias in the treatment of high-risk individuals. This implies initial screening visits for baseline parameters and the exclusion of secondary causes of dyslipidemias and possible confounding variables, such as diet, cigarette smoking, and alcohol intake that may alter the lipid profile. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study examined the effect of early initiation of atorvastatin 80 mg versus placebo within 24 to 96 hours of an acute coronary syndrome in 3086 patients. The study showed a 16% reduction in coronary events at 16 weeks. Most of the benefit in MIRACL was due to a decrease in worsening of angina that required hospitalization. This study showed that a high-dose statin before discharge in high risk-individuals reduced cardiac events in the short-term and is also safe. The HPS used a single dose of simvastatin (40 mg) for 5 years. Side effects over the follow-up period were comparable to placebo. No untoward effects were reported in patients with LDL-C levels <100 mg/dL (2.6 mmol/L). The issues raised are...
several-fold. In high-risk patients, should baseline lipid levels be determined before initiation of therapy or should therapy be titrated after? How often should follow-up lipid profiles be performed and what should be measured (total cholesterol, direct LDL-C, lipid profile, apoB)? Lastly, are target levels meaningful in the high-risk category?

Many such questions may never be answered by a clinical trial. However, the NCEP III recommendations should serve as a minimum standard of care. The use of higher dose statin, the equivalent of simvastatin 40 mg/dL, has proven to be safe and to decrease mortality. In experienced hands, higher dose statins (simvastatin 80 mg, atorvastatin 80 mg, and rosuvastatin 80 mg) have proven to be safe and effective, but have an elevated risk of myositis and rhabdomyolysis. On the latter point, data from the Food and Drug Administration shows that for statins other than cerivastatin, the reported incidence of fatal rhabdomyolysis is <0.2 cases/million patients. In comparison, the major cardiovascular event rate in this category of risk is >20%/10 years (or 20 000/million); the risk-benefit ratio favors statin use. In high-risk patients, therefore, a statin at an equivalent dose of simvastatin 40 mg/d can be safely initiated. Titration to <100 mg/dL (2.6 mmol/L) within 6 to 12 weeks seems appropriate. A safe lower LDL-C limit has not been established.

**Should C-Reactive Protein Be Measured and What Should an Elevated Level Trigger?**

C-reactive protein (CRP) is an acute-phase reactant produced by the liver in response to an inflammatory stimulus. Consistent and reproducible data have been generated from prospective studies showing that high-sensitivity CRP (hsCRP) is an independent cardiovascular risk factor that is statistically superior to LDL-C in the prediction of risk. In addition, retrospective data from large-scale treatment studies show that statins lower hsCRP, and this seems to be a class effect. More importantly, subjects with an elevated hsCRP benefit from a statin even when the LDL-C is low. At the present time, recommendations for or against the routine measurement of hsCRP for the prevention of cardiovascular disease cannot be made. In high-risk subjects, treatment with a statin is a strong recommendation. The most likely use of hsCRP will be in the moderate-risk category, where current algorithms for risk prediction may be imprecise, especially in subjects with the metabolic syndrome. Such an approach will need to be tested prospectively.

**What Is the Appropriate Treatment of Patients With Predominantly a Low HDL-C?**

The treatment of high-risk individuals (as defined in NCEP ATP III) with a low-HDL-C is still a matter of some controversy. The VA-HIT has examined this issue directly and provides evidence that the fibric acid derivative gemfibrozil reduces cardiac events independently of effects on LDL-C levels. The HDL Atherosclerosis Treatment Study (HATS) examined 163 patients with a low HDL-C level (<35 mg/dL [0.91 mmol/L] for men and <40 mg/dL [1.03 mmol/L] for women) and an LDL-C level <145 mg/dL (3.75 mmol/L) with angiographically documented CAD. After treatment for 3 years on low dose (10 to 20 mg, although up-titration to 80 mg was permitted) simvastatin alone or with niacin with or without antioxidants, the combination simvastatin/niacin increased HDL-C by 26% and reduced major cardiovascular events by 90%. The HPS study showed a similar benefit to simvastatin 40 mg/d in subjects with baseline LDL-C <100 mg/dL (2.6 mmol/L), similar to that obtained in subjects with higher baseline LDL-C levels.

In this sub-set of high-risk patients, therefore, the current evidence indicates that a high dose of a statin (equivalent to simvastatin 40 mg/d), the combination of lower-dose statin with niacin (2 to 4 g/d), and gemfibrozil 1200 mg/d are appropriate choices on the basis of published data. Whether all fibrates share equal cardioprotective effect has not yet been determined. The Bezafibrate Infarction Prevention (BIP) trial yielded inconclusive results despite a large study size, in part because of the large number of on-trial patients who received lipid-lowering medication off protocol. The Diabetes Atherosclerosis Intervention Study (DAIS) examined the effect of fenofibrate on angiographic progression of CAD in 418 patients with type 2 diabetes. The lipid inclusion criteria included a low HDL-C level and an elevated triglyceride level. Although the study did not meet statistical significance for the primary endpoint, a beneficial change in minimal luminal diameter, other angiographic parameters improved on fenofibrate and a reduction in clinical events was noted compared with placebo.

**Is There Evidence That Raising HDL-C Is Beneficial for Cardiovascular Prevention and Should There Be an HDL-C Goal?**

The independent effect of HDL-C on clinical outcome can be performed after careful statistical manipulation of the data. Results from the large clinical intervention studies are shown in the Table; also shown are results from the BIP, DAIS, and HATS trials that have specifically addressed patients with a low HDL-C as an entry criterion. Statins have produced a modest (5% to 10%) increase in HDL-C levels compared with placebo and fibrates. The results with fibrates have been less consistent. Only with gemfibrozil and simvastatin (in the 4S) was the increase in HDL associated with a decrease in cardiovascular events (in the 4S, this association lost statistical significance when corrected for in a multiple regression analysis). NCEP ATP III has selected an HDL-C level of <40 mg/dL (1.03 mmol/L) as a categorical risk factor. Although this is reasonable despite the continuous and graded relationship between HDL-C and cardiovascular risk, the contentious issue is whether efforts should be made to increase plasma HDL-C beyond this level or use another marker of artherosgenous lipoproteins as a treatment goal. The NCEP has targeted non–HDL-C, whereas the Canadian guidelines have focused on the total cholesterol/HDL-C ratio. Targeting HDL as a therapeutic goal may be inappropriate in light of the lack of evidence that raising HDL-C by medications prevents CAD and the paucity of effective medications except niacin to raise HDL-C. Establishing an HDL-C goal might have implications in clinical practice toward expanded use of niacin and a potential increase in side-effects. The
lifestyle changes known to increase HDL-C levels (smoking cessation, proper diet, weight reduction, exercise, and moderate alcohol intake) stand in their own merit in terms of preventing cardiac events.

Other Effects of Statins
Statins inhibit hydroxymethylglutaryl coenzyme A reductase by preventing the formation of mevalonate, the rate-limiting step of sterol synthesis. In the cholesterol synthetic pathway, intermediate molecules of dimethylallyl pyrophosphate are metabolized by prenyl transferase into geranyl pyrophosphate and subsequently into farnesyl pyrophosphate. This step occurs before the formation of squalenes. The intermediates geranylgeranyl and farnesyl are used for protein prenylation, a mechanism by which a lipid moiety is attached to a protein, allowing anchoring into the plasma membrane and enhancing its biological activity. This is the case for the guanidine triphosphate-binding proteins Rho A, Rac, and Ras. Such a mechanism has been postulated to be one of the mechanisms by which statins increase HDL-C, by preventing the geranylgeranylation of Rho A and phosphorylation of peroxisome proliferation activator receptor-α, which mediates apo AI transcriptional regulation. This mechanism may also mediate many of the effects of statins not related to a reduction in LDL-C levels. Atherosclerosis is an inflammatory disease. Statins have been shown to decrease CRP, induce apoptosis in smooth muscle cells, alter collagen content of atherosclerotic plaques, alter endothelial function, and decrease the inflammatory component of plaques. Some argue that statins possess other effects independent from their effect on hydroxymethylglutaryl coenzyme A reductase. In clinical practice, the it is difficult to assess role of these effects and to determine if differences exist in terms of clinical efficacy between statins for a given percent reduction in LDL-C. This controversy will be partially addressed by the PROVE-IT trial, which compares pravastatin 40 mg to atorvastatin 80 mg in patients with CAD.

Combination Therapy
The combination of 2 or more lipid-lowering agents is appealing in patients with severe dyslipidemias who cannot achieve target levels on monotherapy or who develop intolerance to higher doses of medications. With the probability of increasing drug interaction, combination therapy should be administered with appropriate follow-up. In patients with severe LDL-C elevations, as seen in familial hypercholesterolemia, the addition of bile acid binding resins (colestipol or cholestyramine) or the use of ezetimibe, an intestinal inhibitor of cholesterol, marked decreases in LDL-C (by 60% or more) can be achieved. Patients with combined lipoprotein disorders often represent a therapeutic challenge. Many have components of the metabolic syndrome, and lifestyle changes prove frustratingly difficult to implement for a variety of reasons (lack of patient motivation, lack of resources, such as dietitians and exercise facilities, and prohibitive cost). In light of current knowledge, the priority of treatment remains the LDL-C level. Persistent hypertriglyceridemia, especially in the presence of low HDL-C, may respond to a combination statin/fibrate, bearing in mind that this combination has not yet been examined in large randomized trials and that the benefits should outweigh potential toxicity. The combination of statins and niacin has been shown in experienced hands to prove highly beneficial in small clinical trials.

The development of selective inhibitors of intestinal sterol absorption is a significant advance in the treatment of lipoprotein disorders. Ezetimibe is the first compound currently accepted for this use. The precise mechanism of action at the molecular level is not completely understood, but the drug seems to selectively prevent uptake of cholesterol by intestinal epithelial cells. It is indicated for patients with an elevated LDL-C level, and in combination with a moderate dose of a statin, it lowers LDL-C by up to 55% to 60%, an effect comparable to that of the maximal dose of statins.

New therapeutic modalities in the treatment of atherosclerosis by modulating lipoprotein metabolism include the development of inhibitors of cholesteryl ester transfer protein to increase HDL-C levels or modulation of the lecithin:cholesterol acyltransferase by preventing the formation of mevalonate, the rate-limiting step of sterol synthesis. In the cholesterol synthetic pathway, intermediate molecules of dimethylallyl pyrophosphate are metabolized by prenyl transferase into geranyl pyrophosphate and subsequently into farnesyl pyrophosphate. This step occurs before the formation of squalenes. The intermediates geranylgeranyl and farnesyl are used for protein prenylation, a mechanism by which a lipid moiety is attached to a protein, allowing anchoring into the plasma membrane and enhancing its biological activity. This is the case for the guanidine triphosphate-binding proteins Rho A, Rac, and Ras. Such a mechanism has been postulated to be one of the mechanisms by which statins increase HDL-C, by preventing the geranylgeranylation of Rho A and phosphorylation of peroxisome proliferation activator receptor-α, which mediates apo AI transcriptional regulation. This mechanism may also mediate many of the effects of statins not related to a reduction in LDL-C levels. Atherosclerosis is an inflammatory disease. Statins have been shown to decrease CRP, induce apoptosis in smooth muscle cells, alter collagen content of atherosclerotic plaques, alter endothelial function, and decrease the inflammatory component of plaques. Some argue that statins possess other effects independent from their effect on hydroxymethylglutaryl coenzyme A reductase. In clinical practice, the it is difficult to assess role of these effects and to determine if differences exist in terms of clinical efficacy between statins for a given percent reduction in LDL-C. This controversy will be partially addressed by the PROVE-IT trial, which compares pravastatin 40 mg to atorvastatin 80 mg in patients with CAD.

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terol acyl transferase, inhibitors of acyl:coenzyme A acetyl transferase to prevent the formation of cholesteryl esters in foam cells, inhibitors of microsomal triglyceride transfer protein to prevent hepatic secretion of apo B-containing lipoproteins, and inhibitors of bile acid transport and inhibitors of intestinal cholesterol absorption to decrease intestinal cholesterol uptake. These drugs are currently under evaluation, and their effect on human atherosclerosis has so far not been documented in clinical trials. Pharmacological modulation of HDL-C levels by something other than niacin has not led to results proportional to those achieved for LDL-C. Potential modulators of HDL-C levels include the scavenger receptor B-1 and the adenosine triphosphate binding cassette transporter A1 pathways.

Conclusions
In the past 3 decades, the lipid hypothesis has been confirmed. Decreasing plasma levels of LDL-C has led to a reduction in mortality in high-risk subjects. Despite these encouraging results, patients with established CAD and those at high risk for the development of CAD continue to have a worse prognosis than healthy subjects. Lifestyle changes and intensive and aggressive treatment of risk factors must be initiated and maintained in such individuals. Pharmacological modulation of the atherothrombotic processes may lead to improvements in outcomes.

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