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Scientific Update™

Atherosclerosis: From Lipids to Coronary Heart Disease

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A Discussion and Analysis based in part on a Program presented at the XIV International Symposium on Atherosclerosis

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Few developments in medical history have had the impact that the introduction of statins has had on cardiovascular therapeutics over the last two decades. This impact will, undoubtedly, be magnified many times over during the decades ahead as the population at risk of cardiovascular disease (CVD) increases globally and many more people worldwide have access to these medications. This issue of *Cardiology Scientific Update* reviews some of the latest developments in the field of statin therapeutics and anticipates some of the newer lipid-modifying therapies on the horizon.

Advances in dyslipidemia therapy

The introduction of the HMG co-enzyme A reductase inhibitors (statins) approximately two decades ago led to one of the few true "revolutions" in medical therapeutics. This event is comparable – with little fear of exaggeration because of the realized and future impact on the prevention of vascular disease – to the discovery of antibiotics or the introduction of vaccines.

Prior to the introduction of the statins, the therapeutic options for managing dyslipidemia were limited by their relatively poor efficacy; eg, often low-density lipoprotein cholesterol (LDL-C) reductions were <20% at maximum doses and there was inadequate tolerability. Clinical trials were often inconclusive, negative, or showed a reduction only in the composite endpoints of cardiovascular events, not in overall mortality. At that time, only surgical procedures (eg, ileal bypass) were able to accomplish large reductions in LDL-C levels. The Program on the Surgical Control of the Hyperlipidemias (POSCH) reported a reduction in cardiovascular mortality and morbidity, but the differences did not reach statistical significance after a mean follow up of 14.7 years. Only after a 5-year post-trial follow-up, however, did the differences become significant and there was a borderline reduction in total mortality.[1-4] Consequently, the "lipid hypothesis," derived from solid epidemiological research, remained unproven and subject to seemingly endless debate until the advent of statin therapy resulted in LDL-C reductions of a magnitude sufficient to achieve – safely and in large populations – a significant decrease in total mortality.[5]

Subsequently, progressively more potent statins were introduced, culminating in drugs that can routinely achieve, at usual therapeutic doses, reductions of >50% in LDL-C.[6,7] With one notable exception, cerivastatin, these drugs are able to achieve their remarkable lipid effects and significantly reduce cardiovascular events with an outstanding record of safety and tolerability.[8]

The discovery that these drugs also have effects that are independent of their lipid-lowering properties has generated great academic interest. These "pleiotropic" effects are believed to be due to the consequences of inhibition of HMG-CoA reductase, the rate-limiting enzyme in the biosynthesis of cholesterol, and how this affects other metabolites on that pathway.[9,10] The fact that these pleiotropic effects occur with the statins, and that they affect a number of pathways and mechanisms with potentially great biological consequences, has been documented conclusively by a rather voluminous and constantly expanding body of research. What is arguably less clear, and the subject of ongoing debate, is whether these pleiotropic effects (that may differ among the individual members of the statin class) are clinically relevant, especially with respect to the prevention of cardiovascular events. Of note, a recent meta-analysis argued that the prevention of cardiovascular events is directly proportional

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to the reduction in LDL-C levels and unrelated to the specific drug that is employed. As well, the pleiotropic effects of the statins do not appear to contribute an additional cardiovascular risk reduction benefit beyond that expected from the degree of LDL-C lowering.[11] If this is the case, the more recently introduced and more potent statins (eg, atorvastatin and rosuvastatin) would be preferable as monotherapy to the older ones to achieve the greatest reduction in cardiovascular events.

This is particularly relevant in view of the anticipated changes to the Canadian Dyslipidemia Guidelines that will implement a new and more stringent LDL-C target of ≤2.0 mmol/L for patients at high risk of cardiovascular events. Total cholesterol TC/HDL ratio is a secondary target set at <4.0. If, at present, there is still a substantial proportion of patients who have not achieved the recommended targets, the situation will only become more problematic when the more ambitious targets are recommended. These new targets are based on excellent large clinical trials demonstrating that there are additional benefits with more aggressive LDL-C reductions. It will, therefore, be incumbent upon clinicians to adopt the new targets as efficiently and as quickly as possible.

Despite the excellent safety and tolerability profile of the statins, there is a small minority of patients who cannot tolerate the statin doses necessary to achieve therapeutic targets. These doses are equivalent to those used in recent clinical trials, especially those that demonstrated the benefits of more aggressive reductions in LDL-C. However, there are new developments that promise to narrow the treatment gap and allow more patients to reach their targets. This includes the discovery and introduction of a new drug class that inhibits cholesterol absorption by blocking a specific intestinal sterol transporter, recently identified as Niemann-Pick C1-Like 1 protein (NPC1L1). The first example (and the only one presently available for clinical use) is ezetimibe.[12] Although ezetimibe on its own achieves only modest reductions in LDL-C levels in many patients; when it is used in combination with a statin – even at low doses – there is a remarkable effect and the reduction in LDL-C is often equivalent to that seen with maximal doses of the statin.[13]

In addition, recent discoveries have established that there are individual variations in the activity of the intestinal cholesterol transporter that impact the response to ezetimibe.[14,15] Individuals who are "hyperabsorbers," ie, those with high activity of the cholesterol transporter, often exhibit a much more marked response to ezetimibe, suggesting that a pharmacogenomic approach or the future development of a simple test to identify "hyperabsorbers" may more precisely select the individuals who are most likely to benefit. Additionally, there is a group of patients that, while tolerating the maximal recommended doses of a statin, do not reach target on monotherapy. In these patients, the addition of ezetimibe greatly potentiates the effect of the statin. While the inability to reach target on monotherapy is seen much less frequently with the newer and more potent statins such as rosuvastatin, it is precisely in combination with these statins that the most striking reductions in LDL-C levels are observed, even in patients who are refractory to other drugs or combinations of drugs.

The Canadian Dyslipidemia Guidelines recommend, as a first step, lowering LDL levels to reach targets that are determined based on the risk of fatal and nonfatal coronary heart disease events. These are calculated according the modified Framingham risk engine. A secondary goal is reducing the total cholesterol/HDL-C ratio to specific target levels that are also determined according to baseline risk. While the statins, alone or in combination, can have a powerful effect on the numerator of the ratio by reducing LDL-C, their effects on the denominator are modest at best.

It appears that there are differences in the abilities of the individual statins to raise HDL-C, particularly at higher doses. For instance, when comparing only the most potent statins, rosuvastatin appears to be more consistent in its HDL-C-raising properties than atorvastatin, particularly, as mentioned, at higher doses. These differences notwithstanding, the effects of the statins are often small and, especially in some patients with markedly reduced HDL-C levels, insufficient to decrease the ratio to recommended levels.

A number of approaches to increasing HDL are being studied, eg, IV administration of apolipoprotein A-1 mutants[16] that reduce coronary atheroma after several intermittent infusions, development of oral and intravenous apo A-1 mimetic peptides that are active in reverse cholesterol transport, and the development of new drugs.[17,18]

The next generation of PPAR-alpha agonists will be more potent at raising HDL-C levels than the limited number of fibrates currently available and dual PPAR-alpha/PPAR-gamma agonists are being investigated for the atherogenic dyslipidemia observed in many diabetics that is typically characterized by low HDL-C levels. A new class of drugs, the cholesteryl ester transfer protein (CETP) inhibitors, is also on the horizon. CETP promotes the transfer of cholesteryl esters from antiatherogenic HDL to proatherogenic apolipoprotein B-containing lipoproteins, including very-low-density lipoprotein (VLDL), VLDL remnants, intermediate density lipoprotein (IDL), and LDL-C. As well, CETP promotes HDL catabolism. Its inhibition decreases the fractional catabolic rate of HDL and increases its circulating levels. The first representative of this class is torcetrapib, which can raise HDL-C levels up to 90%. Clinical trials are ongoing and it is too early to determine whether this manner of increasing HDL-C levels will have an impact on cardiovascular events. An additional CETP inhibitor, JTT-705, is also in early clinical trials.[17,18]

Statin safety in perspective

The results of numerous clinical trials involving tens of thousands of patients and the experience of clinical practice, which involves tens of millions of prescriptions all over the world, have demonstrated that statins are generally well tolerated and their clinically relevant adverse effects occur at low

frequency. The only notable exception has been cerivastatin, which was associated with an unusually high incidence of cases of rhabdomyolysis, some of them fatal.

Rosuvastatin is the newest and most potent statin available in clinical practice. Few other medications in therapeutic history have been subjected to as strong and intensive scrutiny as rosuvastatin. This was due, in part, to the fact that it was the only statin introduced after the serious adverse events associated with cerivastatin, as well as the very high usage of this medication class. These efforts included the development, supported by the manufacturer of rosuvastatin, of a pioneering international rosuvastatin pharmaco-epidemiology program that is following the "real-life" use of statins in 100,000 patients treated with the drug in Canada, the Netherlands, the United Kingdom (UK), and the United States (US). This program includes 9 separate studies to rigorously assess the safety of rosuvastatin and other statins. Some are examining the characteristics and drug use patterns of new users of rosuvastatin compared with other statins and are using automated databases (eg, Saskatchewan Health database, the USA Managed Care Claims database, and the UK General Practice Research Database). Another group of studies is evaluating the safety of rosuvastatin and other statins by examining the rates of specific adverse events in cohorts of statin users and will determine risk factors for these events also using automated databases. Finally, an independent Prescription-Event Monitoring study will determine significant events with rosuvastatin treatment recorded by general practitioners. All of these studies are being conducted in renowned and well-recognized independent centres of excellence and will be completed and reported in the near future.[19]

Recently, the results of a rosuvastatin historical cohort study in >45,000 Dutch statin users were reported. This study was conducted during 2003-2004 and included incident users of rosuvastatin and other statins and a cohort of patients not prescribed statins from the PHARMO database of >2 million Dutch residents. Cases of hospitalization for myopathy, rhabdomyolysis, acute renal failure, or hepatic impairment were identified from these cohorts. In that 2-year period 10,147 incident rosuvastatin users, 37,396 incident users of other statins, and 99,935 patients without statin prescriptions were included. The total incidence of serious adverse events was very low: there were 26 validated outcome events in the 3 cohorts, including 1 case of myopathy in the "other statin" group and 1 case of rhabdomyolysis in the nontreated group. In all of the statin users, there were only 15 validated events in >45,000 person-years of follow-up (<1 per 3000 person-years). The number of validated cases of acute renal failure was proportionately higher in the 2 statin cohorts (3 events with rosuvastatin, 7 events with the other statins) compared to the nonuser cohort (3 cases), but there were no significant differences between rosuvastatin users and patients receiving other statins. There were no cases of hepatic impairment with rosuvastatin, 4 cases with other statins, and 7 cases in the control cohort. These differences were not statistically significant.

In summary, this study demonstrated that the incidence of severe adverse events is extremely low in patients taking statins compared to a control cohort. Additionally, the incidence of rhabdomyolysis, myopathy, acute renal failure, and hepatic impairment in rosuvastatin users was not increased compared to users of other statins.[20] These findings are in line with the results of similar studies in other countries and with the results of clinical trials demonstrating that serious adverse events are extremely infrequent in statin users and do not differ with currently available statins.

Another recent study conducted in the US compared the incidence rates of hospitalization associated with rhabdomyolysis, myopathy, renal or hepatic impairment, and in-hospital death in patients who were initiated on rosuvastatin compared to those taking other statins. This matched cohort study included patients who initiated statin therapy during the first 6 months of rosuvastatin availability and were from the administrative database of a large health insurer. The follow-up period was up to 18 months. A total of 11,249 eligible rosuvastatin initiators were matched to 37,282 initiators of other statins. There was 1 case of rhabdomyolysis in the rosuvastatin initiators and 2 cases in the initiators of other statins. There were 12 cases of renal dysfunction in rosuvastatin initiators and 42 events associated with other statins. In the case of hepatic dysfunction, there were 2 events with rosuvastatin and 8 for other statin initiators. There were no statistically significant differences between rosuvastatin and other statins in these parameters or in the other endpoints, such as myopathy or death. Reassuringly, the incidence of rhabdomyolysis and myopathy was extremely low among all statin initiators.[21]

Rosuvastatin and ezetimibe combination: the biggest LDL-C reduction ever

The results of the **EX**amination of **P**otential **L**ipid-modifying effects **O**f **R**osuvastatin in combination with **E**zetimibe versus **R**osuvastatin alone (EXPLORER) study were recently reported at the XIV International Symposium on Atherosclerosis in Rome, Italy, by Dr. Christie Ballantyne, the lead investigator. EXPLORER assessed whether the addition of ezetimibe, a cholesterol absorption inhibitor, further improved the marked lipid-modifying effects of rosuvastatin, the most potent statin currently available. The study compared, as its primary endpoint, the effect of rosuvastatin 40 mg and a combination of rosuvastatin 40 mg and ezetimibe 10 mg on the achievement of lipid targets, defined as the 2001 NCEP ATP III LDL-C goal, in patients with hypercholesterolemia and CHD or CHD risk equivalents.

The investigators conducted the study motivated by the fact that, even when patients are treated with lipid-lowering drugs, many are still not achieving their targets. For example, in a study of 2829 high-risk patients, less than half reached the goal (ie, LDL-C <2.5 mmol/L) with the recommended dose of their initial statin. Even among patients who were subsequently uptitrated, over two-thirds still failed to reach the treatment goal.[22]

The secondary objectives were to compare the effect of rosuvastatin and rosuvastatin plus ezetimibe on lipid and lipoprotein levels, high-sensitivity C-reactive protein, the percentage of patients reaching NCEP ATP III non-HDL cholesterol and European LDL-C and total cholesterol goals, and safety.

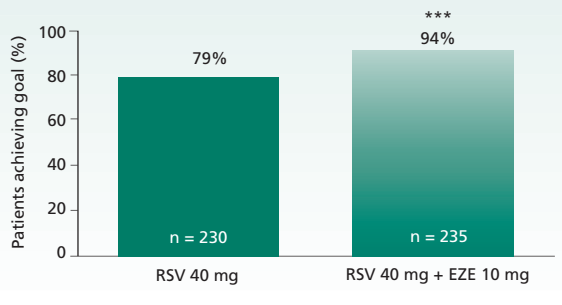
Patient selection

EXPLORER was a 6-week, open-label, randomized, multicentre, parallel-group study conducted in 58 centres in the US, Europe, and South Africa. After a 6-week dietary lead-in period, eligible patients were randomized 1:1 to receive either rosuvastatin 40 mg or rosuvastatin 40 mg plus ezetimibe 10 mg daily for another 6-week period. The study included: men or women aged ≥18 years with hypercholesterolemia and a history of CHD or clinical evidence of atherosclerotic disease, or considered CHD risk-equivalent, defined as a 10-year risk score >20% according to the Framingham risk estimate. In statin-naïve patients, the eligible levels of fasting LDL-C were ≥4.1 to < 6.5 mmol/L. A total of 469 patients were randomized.

Results

For the primary endpoint (Figure 1), significantly more patients (94%) achieved the 2001 NCEP ATP III LDL-C goal of 2.6 mmol/L following treatment with rosuvastatin plus ezetimibe compared with the similarly excellent result with rosuvastatin alone (79%, p<0.001). For the secondary endpoint (Figure 2) indicating the percentage of patients achieving the 2003 European LDL-C goal, the results were 94% for the combination compared with 74% for rosuvastatin alone (p<0.001). In terms of the change observed in lipids and lipoproteins at 6 weeks, the most striking result was the reduction in LDL-C. Rosuvastatin alone achieved a reduction of 57.1%, while the combination reduced LDL-C by a remarkable 69.8%. This is highest LDL-C reduction ever demonstrated in a major trial of lipid-lowering drugs. Ezetimibe did not attenuate the HDL-C raising effect of rosuvastatin (8.5% increase for rosuvastatin alone versus 10.8% for the combination, p = NS).

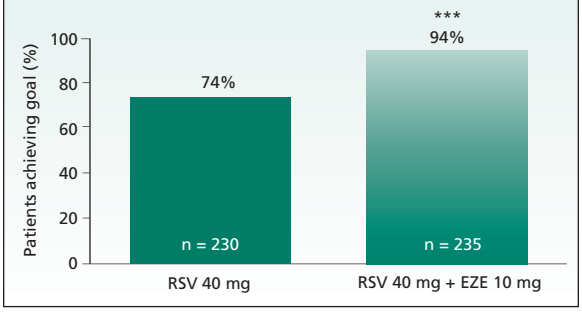
Figure 1: EXPLORER – Primary Endpoint. Patients (%) achieving NCEP ATP III LDL-C goal at 6 weeks



NCEP ATP III goal: <100 mg/dL (2.6 mmol/L)
NCEP ATP = National Cholesterol Education Program Adult Treatment Panel; LDL-C = low-density lipoprotein cholesterol
RSV = rosuvastatin; EZE = ezetimibe.
*** p<0.001 vs rosuvastatin

Ballantyne CM et al. [Presented at the ISA 2006]

Figure 2: EXPLORER – Efficacy. Patients (%) achieving 2003 European LDL-C goal at 6 weeks



2003 European LDL-C goals: <2.5 or 3.0 mmol/L (97 or 115 mg/dL), depending on risk category
LDL-C = low-density lipoprotein cholesterol; RSV = rosuvastatin; EZE = ezetimibe; *** p<0.001 vs rosuvastatin

Ballantyne CM et al. [Presented at the ISA 2006]

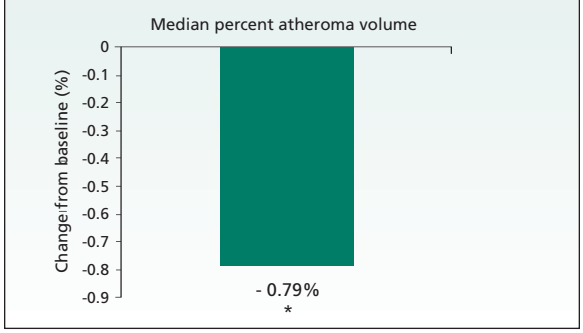
What is the ideal target for LDL-C? Insights using intravascular ultrasound

The statins comprise one of the most comprehensively evaluated therapies in medical history and many large clinical trials have demonstrated their beneficial effects in preventing cardiovascular events. However, ideal target levels for LDL-C are not known and modern guidelines have gradually shifted toward lower targets based on the most recently reported clinical trials. This is certainly the case for the Canadian Dyslipidemia Guidelines that are widely expected to lower the target for high-risk patients from 2.5 mmol/L to 2.0 mmol/L in the updated 2006 version.

As well as clinical outcome trials, several imaging studies have assessed the effects of lipid-lowering therapy on atherosclerosis progression. Initial studies employed quantitative coronary angiography and carotid ultrasound and yielded promising results, despite the limitations of these techniques and the more modest LDL-C reductions achieved with the older statins that were used in most of the studies. More recently, intravascular ultrasound (IVUS) has been recognized as the predominant imaging technique for evaluating the progression of coronary atherosclerosis. IVUS is likely to retain its dominant position until noninvasive techniques can be further refined.

Until recently, IVUS studies were able to demonstrate only a slowing or arresting of atherosclerotic progression after statin use. None of the major clinical studies provided convincing evidence that lipid-lowering with a statin actually resulted in regression of atherosclerosis.[23] This changed

Figure 3: ASTEROID – Endpoint analysis: change in median percentage atheroma volume[24]



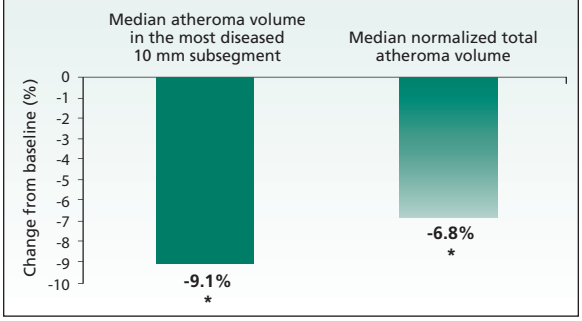
*p<0.001 for difference from baseline values. Wilcoxon signed rank test

recently with the results of ASTEROID (A Study To evaluate the Effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden).[24] ASTEROID used IVUS to evaluate the effect of rosuvastatin on atherosclerotic disease in patients with coronary artery disease and investigated whether rosuvastatin induced regression of the volume of coronary artery atheroma.

The primary objective of ASTEROID was to evaluate whether long-term treatment with rosuvastatin 40 mg in CAD patients resulted in regression of coronary artery atheroma burden, as evaluated by the percentage atheroma volume (PAV) in the entire segment length of the assessed artery and total atheroma volume (TAV) in the most severely diseased segment. The study included patients with CAD undergoing coronary angiography. Inclusion required at least 1 stenosis with >20% narrowing in luminal diameter. The target vessel for IVUS evaluation did not have >50% luminal narrowing throughout the target segment. All patients were statin-naïve and any baseline level of LDL-C was permitted; however, those with hypertriglyceridemia (≥5.7 mmol/L) or poorly-controlled diabetes (glycosylated hemoglobin levels ≥10%) were excluded. A total of 349 patients were enrolled and had IVUS assessments at baseline and after 24 months of intensive lipid-lowering with rosuvastatin 40 mg daily. The mean baseline total cholesterol level was 5.3 mmol/L and the LDL-C level was 3.4 mmol/L. With rosuvastatin therapy, the former declined by 34% and the latter by 53%, while HDL-C increased by 15%.

Compared with baseline, the change in the median percentage atheroma volume was -0.79% ($p<0.001$) with rosuvastatin therapy (Figure 3). Percentage atheroma volume is the most rigorous IVUS parameter of atherosclerosis progression and regression. This is the first ever demonstration of coronary atherosclerosis regression with statin therapy as demonstrated by IVUS. Previous studies, such as REVERSAL, demonstrated a halting of the process with atorvastatin; however, this effect was not observed in the group of patients randomized to a less potent statin. Analysis of the secondary endpoints revealed that the median atheroma

Figure 4: ASTEROID – Endpoint analysis: change in key IVUS parameters[24]



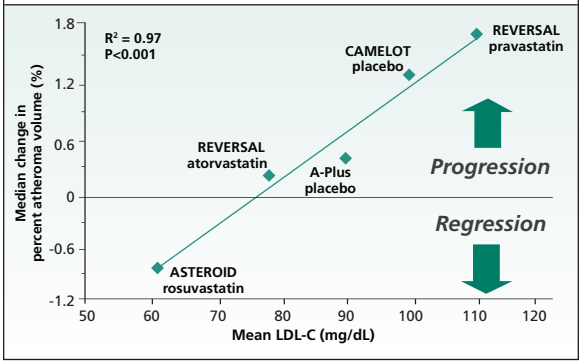
*p<0.001 for difference from baseline values. Wilcoxon signed rank test

volume in the most diseased subsegment declined by 9.1% and the median normalized total atheroma volume decreased by 6.8% ($p<0.001$ for both comparisons versus the baseline) (Figure 4). The total percentage of patients exhibiting regression by each of these IVUS parameters was 78% for the normalized total atheroma volume and the atheroma volume in the most diseased subsegment and 64% for the percent atheroma volume.

Rosuvastatin 40 mg was well tolerated with a safety profile consistent with the existing extensive safety database. The increases in ALT (>3 x upper limit of normal [ULN] on 2 consecutive visits) were low (0.2%) and there were no clinically significant increases in creatine kinase (CK) (defined as CK > 10 x ULN) observed in the core laboratory and no cases of rhabdomyolysis.

In summary, ASTEROID showed that regression of atherosclerosis can be achieved with intensive statin therapy using rosuvastatin 40 mg. This dose produced significant regression of atherosclerosis for all 3 IVUS measures. Furthermore, regression occurred in 4 of 5 patients and in virtually all of the subgroups evaluated, including men and women, older and younger patients, and in most subgroups defined by lipid levels. In comparison with other previously

Figure 5: Relationship between LDL-C levels and change in percent atheroma volume for several IVUS trials[24]



conducted IVUS trials, the analysis of results from ASTEROID confirmed the strong correlation between reduction in LDL-C and reduction in atheroma volume (Figure 5).

Conclusion

Great strides have been made in the prevention of CVD since the introduction of the statins, a truly revolutionary discovery in medical therapeutics. More promising results are likely to characterize the future as the introduction of new and more potent statins, such as rosuvastatin, allows us to achieve recommended targets in an increasing number of patients. As well, the potency of rosuvastatin has made it possible to demonstrate for the first time regression of coronary atherosclerosis by IVUS. For patients who are unable to reach the LDL-C target on monotherapy or cannot tolerate recommended statin doses, the combination of a statin with a cholesterol absorption inhibitor, such as ezetimibe, shows great promise, although we are still awaiting the results of cardiovascular outcome trials. The combination of high-dose rosuvastatin with ezetimibe has resulted in the greatest LDL-C reduction (70%) ever reported in a major clinical trial of lipid-lowering drugs. Additionally, ongoing efforts to influence the denominator of the total cholesterol/HDL ratio by apo A-1 or apo A-1 mimetic therapy, CETP inhibitors, or new PPAR agonists, are likely to lead to further gains in our ability to treat and prevent cardiovascular disease.

References

1. Buchwald H, Moore RB, Matts JP, et al. The Program on the Surgical Control of the Hyperlipidemias: a status report. *Surgery* 1982;92:654-662.
2. Buchwald H, Varco RL, Boen JR, et al. Effective lipid modification by partial ileal bypass reduced long-term coronary heart disease mortality and morbidity: five-year posttrial follow-up report from the POSCH. Program on the Surgical Control of the Hyperlipidemias. *Arch Intern Med* 1998;158:1253-1261.
3. Buchwald H, Varco RL, Matts JP, et al. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH). *N Engl J Med* 1990;323: 946-955.
4. Moore RB, Buchwald H, Varco RL. The effect of partial ileal bypass on plasma lipoproteins. *Circulation* 1980;62:469-476.
5. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-1389.
6. Olsson AG, Istad H, Luurila O, et al. Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia. *Am Heart J* 2002;144:1044-1051.
7. Brown WV, Bays HE, Hassman DR, et al. Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: a randomized, double-blind, 52-week trial. *Am Heart J* 2002;144:1036-1043.
8. Law M, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol* 2006;97:52C-60C.
9. Ray KK, Cannon CP. The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes. *J Am Coll Cardiol* 2005;46:1425-1433.
10. Liao JK. Clinical implications for statin pleiotropy. *Curr Opin Lipidol* 2005;16:624-629.
11. Robinson JG, Smith B, Maheshwari N, et al. Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. *J Am Coll Cardiol* 2005;46:1855-1862.
12. Bruckert E, Giral P, Tellier P. Perspectives in cholesterol-lowering therapy: the role of ezetimibe, a new selective inhibitor of intestinal cholesterol absorption. *Circulation* 2003;107:3124-3128.
13. Stein E, Stender S, Mata P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. *Am Heart J* 2004;148:447-455.
14. Hegele RA, Guy J, Ban MR, et al. NPC1L1 haplotype is associated with inter-individual variation in plasma low-density lipoprotein response to ezetimibe. *Lipids Health Dis* 2005;4:16.
15. Simon JS, Karnoub MC, Devlin DJ, et al. Sequence variation in NPC1L1 and association with improved LDL-cholesterol lowering in response to ezetimibe treatment. *Genomics* 2005;86:648-656.
16. Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA* 2003;290:2292-2300.
17. Duffy D, Rader DJ. Emerging therapies targeting high-density lipoprotein metabolism and reverse cholesterol transport. *Circulation* 2006;113: 1140-1150.
18. Duffy D, Rader DJ. Drugs in development: targeting high-density lipoprotein metabolism and reverse cholesterol transport. Curr Opin Cardiol 2005;20:301-306.
19. Johansson S, Ming EE, Wallander MA, et al. Rosuvastatin safety: a comprehensive, international pharmacoepidemiology programme. *Pharmacoepidemiol Drug Saf* 2006;15:454-461.
20. Goettsch WG, Heintjes EM, Kastelein JJ, et al. Results from a rosuvastatin historical cohort study in more than 45,000 Dutch statin users, a PHARMO study. *Pharmacoepidemiol Drug Saf* 2006;15:435-443.
21. McAfee AT, Ming EE, Seeger JD, et al. The comparative safety of rosuvastatin: a retrospective matched cohort study in over 48,000 initiators of statin therapy. *Pharmacoepidemiol Drug Saf* 2006;15:444-453.
22. Foley KA, Simpson RJ, Jr., Crouse JR, III, et al. Effectiveness of statin titration on low-density lipoprotein cholesterol goal attainment in patients at high risk of atherogenic events. *Am J Cardiol* 2003;92:79-81.
23. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 2004;291:1071-1080.
24. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006;295:1556-1565.

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