# How to Achieve Regression of Atherosclerosis

BRIAN TOMLINSON, MIAO HU, VALIANT WL MAK, TANYA TW CHU

Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong

**TOMLINSON ET AL.:** ***How to Achieve Regression of Atherosclerosis.*** *Coronary artery disease and stroke are the leading causes of death in most developed countries and the prevalence of these diseases is increasing rapidly in developing countries. Atherosclerosis is a dynamic process that in most patients shows a gradual progression with episodes of more rapid deterioration usually related to thrombotic episodes. Many of the early trials of lipid lowering agents showed only very small degrees of angiographic regression despite impressive reductions in cardiovascular events. The development of noninvasive imaging techniques to study atherosclerotic changes in the arterial wall, such as computed tomographic imaging of coronary calcium, intravascular ultrasound of the coronary arteries, multidetector computed tomographic angiography, B mode ultrasound of the carotid arteries, and magnetic resonance imaging of the carotid arteries has facilitated studies of lesion progression and provided evidence that aggressive pharmacological interventions, particularly those of lipid-altering therapies, can reduce the rate of progression or in some cases actually produce regression of atheromatous lesions. A multimodality approach to the management of all the risk factors in patients with coronary artery disease is likely to produce the best results, but the evidence for lowering low-density lipoprotein cholesterol with intensive statin therapy is currently the most convincing. The lipid responses to statins vary widely between individuals because of a combination of phenotypic and genotypic factors, which are also likely to affect outcomes measured by the various imaging techniques as well as cardiovascular events, so there may be considerable scope for the individualization of treatments to achieve greater benefits when more pharmacogenetic data are available. (J HK Coll Cardiol 2008;16(Suppl 1):A52-A61)*

*Atherosclerosis, coronary artery disease, imaging techniques, individualized therapy, statins*

**摘要**

冠脈疾病和中風在大部分發達國家是主要死亡原因，其發病率在發展中國家也迅速增加。動脈粥樣硬化是一個動態過程，大部分患者中表現爲逐漸進展期和與血栓形成有關的迅速惡化期。許多早期關於降血脂藥物的研究表明儘管其能降低心血管事件發生率但血管造影顯示的改善不明顯。諸如冠脈鈣化CT成像，冠脈血管內超聲，多控測器CT血管造影，頸動脈 B 超和磁共振成像等無創技術的進展促進了對粥樣硬化病變進程的研究，證明藥物干預，尤其是血脂調節能延緩疾病進展甚至修復粥樣硬化病變。針對冠脈疾病所有危險因素的多形式綜合防治可能效果最佳，但目前研究顯示加強他汀類藥物從而降低低密度脂蛋白膽固醇含量的療法效果顯著。脂質對他汀類藥物的反應個體差異很大，這可能由於表現型與基因型的不同，此兩者也可能影響各種成像技術測量結果以及心血管事件發生率。因此在更多遺傳藥理學資料的基礎上，個體化治療能改善粥樣硬化的療效。

關鍵詞：動脈粥樣硬化　冠狀動脈疾病　成像技術　個體化治療　他汀類

Address for reprints: Prof. Brian Tomlinson
Division of Clinical Pharmacology, Department of Medicine and Therapeutics, The Prince of Wales Hospital, Shatin, New Territories, Hong Kong

Tel: (852) 2632 3139; Fax: (852) 2632 3139

Received October 9, 2008; revision accepted October 21, 2008

## Introduction

It has only been in recent years that regression of atheromatous plaques in humans has been considered a real possibility. Earlier concepts of the pathology of advanced atheromatous lesions in humans and in animal models considered that they contain components that might not regress, such as necrosis, calcification and fibrosis. Many of the early trials of lipid lowering agents showed only very small degrees of angiographic regression, despite large reductions in clinical events giving rise to the so-called 'angiographic paradox' but meta-analysis of trials of statin therapy showed that the LDL-cholesterol level on therapy and the percentage reduction in LDL-cholesterol both were good predictors of angiographic benefit.[1] The notion that lipid-rich, vulnerable plaques have a central role in acute coronary syndromes and the predominant benefit derived from statins in reduction of cardiovascular events was through stabilisation of lipid-laden plaques, rather than regression of atherosclerosis was also developed.[2] This was shown in human carotid plaques removed during carotid endarterectomy where 3 months of pravastatin treatment had a plaque-stabilising effect decreasing lipids, lipid oxidation, and inflammation, and increasing collagen content compared to no lipid-lowering therapy.[3]

The increasing evidence from several large clinical outcome trials has clearly shown that aggressive LDL-cholesterol reduction with statins reduces hard end points of cardiovascular events.[4] The development of new imaging techniques has also been able to show that aggressive lipid lowering slows the progression of atherosclerosis. Arterial lumen size may not be a very accurate measure of atheromatous plaque and lesion remodeling may confound the effects of therapeutic interventions. Autopsy studies had shown that atherosclerotic human coronary arteries enlarged in relation to plaque area and the cross-sectional area of the lumen was preserved until the lesion occupied at least 40% of the internal elastic lamina area.[5] Furthermore, vulnerable plaques may be relatively small but may easily rupture and result in acute thrombotic events of unstable angina, acute myocardial infarction, and sudden cardiac death.[6] The development of noninvasive imaging techniques to study atherosclerotic changes in the arterial wall, such as computed tomographic (CT) imaging of coronary calcium, intravascular ultrasound (IVUS), multidetector CT angiography, B mode ultrasound of the carotid arteries, and MRI of the carotid arteries has facilitated studies of lesion progression and provided extremely useful information for clinical trials.[7, 8]

## Screening Guidelines

Some of these noninvasive imaging techniques have been included in guidelines for screening asymptomatic individuals who are considered high risk by the traditional risk factor-based approach. The Screening for Heart Attack Prevention and Education (SHAPE) Task Force proposed the First SHAPE Guideline to detect and treat individuals with subclinical atherosclerosis using 2 noninvasive imaging techniques: coronary artery calcium scoring using computed tomography and carotid intima media thickness and plaque using B-mode ultrasonography.[9] The National Cholesterol Education Program and the American Heart Association also suggested that noninvasive screening tests may be an option for advanced risk assessment in appropriately selected individuals, specifically in those who are at intermediate or indeterminate risk.[10, 11]

## Electron-Beam Tomography of Coronary Artery Calcium

A retrospective study showed that aggressive LDL-cholesterol lowering with statins correlated significantly with reduction in coronary calcium-volume score by electron-beam CT, indicating that even coronary artery calcifications can shrink with appropriate treatment.[12] In the BELLES (Beyond Endorsed Lipid Lowering with EBT Scanning) study in 615 hypercholesterolaemic postmenopausal women randomized to intensive (atorvastatin 80 mg/day) and moderate (pravastatin 40 mg/day) lipid-lowering therapy using sequential electron-beam tomography (EBT) scanning to quantify changes in coronary artery calcium (CAC) as a measure of atherosclerosis burden

only 475 completed the study and despite greater reductions in LDL-cholesterol in the intensive statin therapy it did not result in less progression of coronary calcification over 1 year.[13]

## Coronary Artery Intravascular Ultrasound

The IVUS technique allows tomographic assessment of lumen area, plaque size, distribution, and composition and it was recognized that it was likely to be particularly useful in atherosclerosis regression-progression trials with lipid lowering or other therapies which might reduce atheroma burden.[14, 15] Serial changes in plaque progression and lumen reduction as assessed with IVUS were compared with 3 established risk scores for primary prevention, PROCAM, SCORE, and Framingham, in 56 patients with established atherosclerosis and there was a positive linear relationship between the estimated risk of clinical events derived from all 3 established risk-score algorithms and the extent of plaque progression measured by serial IVUS.[16] The main lipid-modifying studies using IVUS are summarised in Table 1.

The first large study to use this technique to examine the changes in coronary atheroma with statin treatments was the REVERSAL (Reversing Atherosclerosis with Aggressive Lipid Lowering) study,[17] which was only able to demonstrate a lack of progression of coronary atheroma with high-dose (80 mg) atorvastatin, which reduced LDL-cholesterol to a mean of 79 mg/dL compared to a level of 110 mg/dL with pravastatin 40 mg. In the pravastatin treated group there was progression of coronary atherosclerosis (change in atheroma volume compared with baseline 2.7%; 95% confidence interval [CI], 0.2% to 4.7%; p =0.001). Analysis of the groups receiving atorvastatin and pravastatin combined, indicated that a reduction in LDL-cholesterol >50% was needed to obtain regression of coronary atheroma volume and changes in CRP also

**Table 1. Summary of intravascular ultrasound trials in patients with coronary disease receiving lipid-altering treatment**

| Variables | REVERSAL[17] (n=502) | ASTEROID[21] (n=349) | ILLUSTRATE[25] (n=910) | ACTIVATE[28] (n=408) |
|---|---|---|---|---|
| **Study medications** | Atorvastatin 80 mg vs. Pravastatin 40 mg | Rosuvastatin 40 mg | Atorvastatin vs. Atorvastatin + torcetrapib | Pactimibe 100 mg vs. placebo** |
| **Duration of study, month** | 18 | 24 | 24 | 18 |
| **Age, y** | 55.8 vs. 56.6 | 58.5 | 57 vs. 56.9 | 58.8 vs. 59.6 |
| **Male,%** | 71 vs. 73 | 70.2 | 70.5 vs. 70.4 | 65.8 vs. 71.6 |
| **Body mass index, kg/m$^2$** | 30.5 vs. 30.5 | 29.1 | 30.3 vs. 30.6 | 30.9 vs. 31.0 |
| **Mean baseline levels** | | | | |
| Total cholesterol, mg/dL | 231.8 vs. 232.6 | 204 | 157.5 vs. 157.7 | 173.4 vs. 171.5 |
| LDL-cholesterol, mg/dL | 150.2 vs. 150.2 | 130.4 | 84.3 vs. 83.1 | 96.0 vs. 94.8 |
| Triglyceride, mg/dL* | 197.2 vs. 197.7 | 135 | 123.9 vs. 122.0 | 144 vs. 150 |
| HDL-cholesterol, mg/dL | 42.3 vs. 42.9 | 43.1 | 45.2 vs. 46.0 | 44.6 vs. 42.4‡ |
| Percent atheroma volume, % | 38.4 vs. 39.5 | 39.6 | 37.1 vs. 37.0 | 39.8 vs. 39.3 |
| Total atheroma volume, mm$^3$ | 184.4 vs.194.5 | 212.2 | 198.7 vs. 196.1 | 198.1 vs. 196.5 |
| **Mean change from baseline** | | | | |
| Total cholesterol, % | -34.1 vs. -18.4† | -33.8 | 1.9 vs. 7.2† | NA |
| LDL-cholesterol, % | -6.3 vs. -25.2† | -53.2 | 6.6 vs. -13.3† | NA |
| Triglyceride, %* | -20.0 vs. -6.8† | -14.5 | -8.2 vs. -14.3† | NA |
| HDL-cholesterol, % | 2.9 vs. 5.6 | 14.7 | -2.2 vs. 58.6† | NA |
| Percent atheroma volume, % | 0.5 vs. 1.9† | -0.98 | 0.19 vs. 0.12 | 0.69 vs. 0.59 |
| Total atheroma volume, mm$^3$ | -0.4 vs. 5.1‡ | -14.7 | -6.3 vs. -9.4‡ | -1.3 vs. -5.6‡ |

*Data was presented as median except for REVERSAL trial; **212 (79.1) and 204 (76.7) patients in placebo group and pactimibe group using statins respectively; †: p<0.001 between 2 treatment groups ; ‡: p<0.05 between 2 groups; NA: data not available

predicted regression in REVERSAL.[17] In the clinical study of the same dosing strategy after acute coronary syndromes, the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction 22) trial, there was a marked reduction in adverse cardiovascular events with atorvastatin compared to pravastatin with a 16% (95% CI; 5 to 26%; p=0.005) reduction in the hazard ratio in favor of atorvastatin, supporting the theory of stabilisation of lipid-laden plaques without major regression of atherosclerosis with intensive statin therapy.[18]

More recently in the ASTEROID (A Study To Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial of 2 years treatment with rosuvastatin 40 mg daily, mean LDL-cholesterol levels decreased by 53% (from 130 to 61 mg/dL) and mean high-density lipoprotein (HDL) cholesterol levels increased by 15% (from 43 to 49 mg/dL) and there was a decrease in mean percent atheroma volume (from 39.6% to 38.6%) and mean atheroma volume in the most diseased 10-mm subsegment (from 65 to 59 $mm^3$).[19] A post-hoc analysis of data from REVERSAL, ASTEROID and 2 other IVUS studies showed in univariate analysis that mean levels and treatment-mediated changes in LDL-cholesterol, total cholesterol, non-HDL cholesterol, apolipoprotein B, and ratio of apolipoprotein B to apolipoprotein A-I were significantly correlated with the rate of atherosclerotic progression, whereas treatment-mediated changes in HDL-cholesterol were inversely correlated with atheroma progression.[20] Mean levels of LDL-cholesterol and increases in HDL-cholesterol remained independent predictors of atheroma regression in multivariate analysis. Substantial atheroma regression was seen in patients with on treatment levels of LDL-cholesterol less than the mean (87.5 mg/dL) and increases of HDL-cholesterol greater than the mean (7.5%).

Quantitative coronary angiography in the patients in the ASTEROID trial also showed evidence of lesion regression by decreasing percent diameter stenosis and improving minimum lumen diameter.[21] It was concluded that aggressive lowering of LDL-cholesterol and a moderate increase in HDL-cholesterol with rosuvastatin 40 mg resulted in regression of coronary atherosclerosis. The ASTEROID trial did not have any control group and the ongoing SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin) study will remedy this by comparing the effects of rosuvastatin 40 mg or atorvastatin 80 mg treatment for 2 years on atherosclerotic disease as measured by IVUS in patients with coronary disease undergoing angiography.[22]

The importance of increases in plasma HDL-cholesterol has been shown in some animal models of atherosclerosis in which infusion of native HDL-cholesterol or lipid-free apolipoprotein A-1 (apo A-1) reduced plaque size.[23] Furthermore, weekly infusions of the recombinant mutant apolipoprotein apo A-1 Milano for 5 weeks resulted in modest plaque regression determined by IVUS in patients after an acute coronary event.[24] The approach to increase HDL-cholesterol was pursued in the ILLUSTRATE trial with torcetrapib, an inhibitor of cholesteryl ester transfer protein (CETP) and in the IVUS study in patients with coronary disease, compared with atorvastatin monotherapy, torcetrapib-atorvastatin combination therapy resulted in an approximate 61% relative increase in HDL-cholesterol and a 20% relative decrease in LDL-cholesterol, but there was no significant difference in the change in atheroma volume for the most diseased vessel segment between the two treatment groups.[25] This lack of benefit seems to be associated with an increase in systolic blood pressure of 4.6 mmHg and an increase in circulating aldosterone which could have negated the beneficial effects on lipids. Likewise, the clinical trial to investigate whether torcetrapib might reduce major cardiovascular events in patients at high cardiovascular risk (ILLUMINATE) was terminated prematurely because of an increased risk of death and cardiac events in patients receiving torcetrapib.[26]

Another negative IVUS study was the ACTIVATE (Acyl-CoA: Cholesterol Acyltransferase Intravascular Atherosclerosis Treatment Evaluation) Study with the ACAT inhibitor pactimibe, which has beneficial effects on foam cell formation and other antiatherosclerotic effects in animal models.[27] Pactimibe (100 mg per day) in addition to usual care for secondary prevention, including statins, if indicated, did not improve the primary efficacy variable (percent atheroma volume)

and adversely affected two major secondary IVUS efficacy measures and it was concluded that this treatment may actually promote atherogenesis in humans.[28]

## Carotid Intima-Media Thickness

Carotid intima-media thickness (CIMT) is related to most of the conventional cardiovascular risk factors. In subjects in the Atherosclerosis Risk in Communities (ARIC) study and a group of patients with coronary heart disease (CHD), carotid thickness showed approximately linear positive associations with fasting plasma LDL-cholesterol and apolipoprotein B (apoB) and negative associations with HDL-cholesterol and apoA-I levels.[29] CIMT was shown to predict not only stroke but also CHD events in studies such as the Rotterdam study,[30] the Cholesterol Lowering Atherosclerosis Study,[31] and the Cardiovascular Health Study.[32] In the follow up from the ARIC study, greater CIMT was associated with increased risk of CHD and future ischaemic stroke incidence.[33, 34]

A number of studies have shown that the progression in CIMT can be influenced by modification of the cardiovascular risk factors. The main lipid-modifying studies using CIMT endpoints are summarised in Table 2. In the ASAP (aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia) study, aggressive LDL-cholesterol reduction with atorvastatin 80 mg resulted in a decrease in CIMT of -0.031 mm (95% CI; -0.007 to -0.055; p=0.0017), whereas with conventional LDL-cholesterol lowering with simvastatin 40 mg it increased by 0.036 mm (95% CI; 0.014-0.058; p=0.0005).[35] In the ARBITER (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol) trial comparing the effects of atorvastatin 80 mg daily and pravastatin 40 mg daily on CIMT in patients that met National Cholesterol Education Program (NCEP) II criteria for lipid-lowering therapy, atorvastatin induced progressive CIMT regression over 12 months (change in CIMT, -0.034± 0.021 mm), whereas CIMT was stable in the pravastatin group (change of 0.025±0.017 mm; p=0.03).[36] A further study in patients with CHD and low levels of HDL-cholesterol (ARBITER 2) compared the addition of placebo or extended-release niacin to statin therapy. HDL-cholesterol increased by a mean of 21% in the niacin group and mean CIMT increased significantly in the placebo group (0.044±0.100 mm; p<0.001) and was unchanged in the niacin group (0.014±0.104 mm; p=0.23), but the overall difference in CIMT progression between the niacin and placebo groups was not statistically significant at 1 year (p=0.08).[37] Some participants from the ARBITER 2 study were enrolled in ARBITER 3 and took extended-release niacin 1000 mg daily for another 12 months.[38] The changes in CIMT suggested regression in atherosclerosis occurred over 24 months related to increases in HDL-cholesterol.

The study with torcetrapib on CIMT in patients with heterozygous familial hypercholesterolemia (RADIANCE 1 study) showed that the use of torcetrapib with atorvastatin, as compared with atorvastatin alone, produced a large increase in HDL-cholesterol levels and substantial decreases in LDL-cholesterol and triglyceride levels but failed to reduce progression of atherosclerosis, as assessed by a combined measure of CIMT, and was associated with progression of disease in the common carotid segment.[39] Similar findings were reported in another study comparing the combination of torcetrapib with atorvastatin to atorvastatin alone in patients with mixed dyslipidaemia (RADIANCE 2 study).[40] This lack of benefit of torcetrapib on CIMT appears to related to the increases in blood pressure and aldosterone as in the other studies with torcetrapib.

In the METEOR (Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin) study in 984 middle-aged asymptomatic subjects with low CHD risk (Framingham risk score <10%), modest CIMT thickening (1.2 to <3.5 mm), and elevated LDL-cholesterol (mean, 154 mg/dL), rosuvastatin 40 mg daily resulted in statistically significant reductions in the rate of progression of maximum CIMT over 2 years vs. placebo.[41] The change in maximum CIMT for the 12 carotid sites was -0.0014 mm/year (95% CI; -0.0041 to 0.0014) for the rosuvastatin group vs. 0.0131 mm/year (95% CI; 0.0087 to 0.0174) for the placebo group (p<0.001). In another small trial, the ACADIM (the Asymptomatic Carotid Atherosclerotic

**Table 2. Summary of Carotid Intima-Media Thickness trials in patients with lipid-modifying treatments**

| Variables | ASAP[35] (n=325) | ARBITER[36] (n=161) | ARBITER 2[37] (n=167) | METEOR[42] (n=984) |
|---|---|---|---|---|
| **Subjects** | FH | Patients eligible for lipid lowering therapy | CHD patients on background statin therapy | Individuals with moderately elevated cholesterol and low risk of cardiovascular disease |
| **Study medications** | Atorvastatin 80 mg vs. simvastatin 40 mg | Atorvastatin 80 mg vs. pravastatin 40 mg | Niacin 1000 mg vs. placebo | Rosuvastatin 40 mg vs. placebo |
| **Duration of study, month** | 24 | 12 | 12 | 24 |
| **Age, y** | 48 | 58 vs. 61 | 67 vs. 68 | 57 vs. 57 |
| **Male,%** | NA | 68.4 vs. 74.4 | 89.7 vs. 92.5 | 60 vs. 59 |
| **Body mass index, kg/m$^2$** | 26 | NA | NA | 27.1 vs. 27.5 |
| **Mean baseline levels** | | | | |
| Total cholesterol, mg/dL | 386 vs. 397 | 229 vs. 234 | 154 vs. 161 | 229 vs. 230 |
| LDL-cholesterol, mg/dL | 309 vs. 322 | 148 vs. 155 | 87 vs. 91 | 155 vs. 154 |
| Triglyceride, mg/dL | 166 vs. 164 | 203 vs. 211 | 154 vs. 172 | 126 vs. 134 |
| HDL-cholesterol, mg/dL | 46 vs. 45 | 49 vs. 49 | 39 vs. 40 | 50 vs. 49 |
| Carotid intima-media thickness, mm | 0.93 vs. 0.92 | 0.625 vs. 0.615 | 0.893 vs. 0.868 | 0.76 vs. 0.76 |
| **Mean change from baseline** | | | | |
| Total cholesterol, % | -41.8 vs. -33.6† | NA | NA | -33.7 vs. 0.3† |
| LDL-cholesterol, % | 50.5 vs. -41.2† | -48.5 vs. -27.2† | NA | -48.8 vs. -0.3† |
| Triglyceride, % | -29.2 vs. -17.7† | NA | NA | -15.7 vs. 10.1† |
| HDL-cholesterol, % | 13.2 vs. 13.4 | NA | +21% vs. no change | 8.0 vs. 2.8† |
| Carotid intima-media thickness, mm | -0.031 vs. 0.036† | -0.034 vs. 0.025‡ | 0.014 vs. 0.044 | 0.0004 vs. 0.088† |

| Variables | RADIANCE 1[39] (n=850) | RADIANCE 2[40] (N=752) | ENHANCE[43] (n=720) |
|---|---|---|---|
| **Subjects** | FH | Mixed dyslipidaemia | FH |
| **Study medications** | Atorvastatin vs. Atorvastatin + torcetrapib 60 mg | Atorvastatin + placebo vs. Atorvastatin + torcetrapib 60 mg | Simvastatin 80 mg + placebo vs. Simrvastatin + ezetimibe 10 mg |
| **Duration of study, month** | 24 | 24 | 24 |
| **Age, y** | 45.2 vs. 46.8 | 56.5 vs. 57.9 | 45.7 vs. 46.1 |
| **Male,%** | 51.1 vs. 47.6 | 65 vs. 63 | 49.3 vs. 53.5 |
| **Body mass index, kg/m$^2$** | 26.7 vs. 26.7 | 30.0 vs. 30.0 | 26.7 vs. 27.4‡ |
| **Mean baseline levels** | | | |
| Total cholesterol, mg/dL | 213.5 vs. 213.0 | 184 vs. 185 | 400.0 vs. 400.0 |
| LDL-cholesterol, mg/dL | 138.9 vs. 138.4 | 101 vs. 101 | 317.8 vs. 319.0 |
| Triglyceride, mg/dL | 97.4 vs. 97.4* | 166 vs. 167 | 160 vs. 157* |
| HDL-cholesterol, mg/dL | 51.8 vs. 52.9 | 48 vs. 48 | 47.4 vs. 46.7 |
| Carotid intima-media thickness, mm | 0.72 vs. 0.71 | 0.83 vs. 0.83 | 0.65 vs. 0.67 |
| **Mean change from baseline** | | | |
| Total cholesterol, % | 5.1 vs. 3.8 | 2.3 vs. 5.9† | -31.9 vs. -45.3† |
| LDL-cholesterol, % | 6.3 vs. -14.4† | 4.4 vs. -13.3† | -39.1 vs. -55.6† |
| Triglyceride, % | 2.1 vs. -7.7†* | 1.5 vs. -12.6† | -23.2 vs. -29.8†* |
| HDL-cholesterol, % | 2.5 vs. 54.4† | -1.8 vs. 61.6† | 7.8 vs. 10.2 |
| Carotid intima-media thickness, mm | -0.0014 vs. 0.038 (per year)† | 0.008 vs. 0.0013 (per year)† | 0.0024 vs. 0.0019 |

†: p<0.01 between 2 groups; ‡: p<0.05 between 2 groups; *Data was presented as Median; NA: data not available

Disease in Manfredonia) Study, treatment with rosuvastatin (10 mg/day) for only 16 weeks in 66 subjects with hypercholesterolemia and carotid atherosclerosis at baseline significantly reduced the CIMT of both common carotid arteries as well as improving lipid and lipoprotein levels.[42]

Thus, aggressive reduction of LDL-cholesterol with statins appears effective in reducing CIMT over a relatively short period of time. However, in the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) study in 720 patients with familial hypercholesterolemia treated with 80 mg of simvastatin either with placebo or with 10 mg of ezetimibe for 24 months, there was no significant difference in changes in CIMT between the two treatments despite additional reductions with the combination treatment of 16.5%, 6.6% and 25.7% for LDL-cholesterol, triglycerides and C-reactive protein, respectively.[43] Whilst at first sight this may not appear to support the concept that lower levels of LDL-cholesterol will result in greater benefits, it should be noted that the patients in this study had smaller baseline values for CIMT than in most previous studies and they had been treated aggressively with statins for some years previously and many of them had taken part in the earlier aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP).[35]

## High-Resolution Magnetic Resonance Imaging

The role of magnetic resonance imaging (MRI) for detection and monitoring of the development and progression of atherothrombosis responsible for ischemic events has been reviewed recently.[7,44] It appears particularly useful to characterize carotid atherosclerotic plaque and identify vulnerable lesions.[45] In hypercholesterolemic patients with moderate carotid stenosis, noninvasive MRI was able to determine the distribution of lesions and lesion types reproducibly and showed a wide range of lesion types, including advanced lesions.[46]

The ORION (Outcome of Rosuvastatin treatment on carotid artery atheroma: a magnetic resonance Imaging ObservatioN) trial used high-resolution magnetic resonance imaging (MRI) to evaluate the effect of low-dose (5 mg) and high-dose (40/80 mg) rosuvastatin for 2 years on carotid artery atherosclerosis in 43 patients with fasting LDL-cholesterol ≥100 and <250 mg/dL and 16% to 79% carotid stenosis by duplex ultrasound.[47] LDL-cholesterol was significantly reduced by 59.9±3.3% in the high-dose group and by 38.2±2.4% in the low-dose group (both $p<0.001$) and HDL-cholesterol increased by 10.1±2.0% in the high-dose group ($p<0.001$) with no significant change from baseline in the low-dose group (2.2±3.2%; $p=0.05$). At 24 months, the overall plaque burden remained unchanged for both dosage groups, but in all patients with a lipid-rich necrotic core (LRNC) at baseline, the mean proportion of the vessel wall composed of LRNC (%LRNC) decreased by 41.4% ($p=0.005$).

## Statin Pharmacogenetics

It is worth noting that the clinical efficacy, in terms of LDL-cholesterol lowering, and the safety of statin treatment varies considerably from person to person because of a combination of phenotypic and genotypic factors.[48-50] These factors are also likely to effect outcomes measured by the various imaging techniques as well as cardiovascular events so there may be considerable scope for the individualization of treatments when more pharmacogenetic and pharmacogenomic data are available to predict these responses. A recent study using the genome-wide scan for genetic markers of simvastatin-related myopathy found that a common variant in the hepatocyte uptake transporter organic anion-transporting polypeptide 1B1 (OATP1B1), encoded by the gene *SLCO1B1*, was associated with increased risk of myopathy, and this polymorphisms may be useful in the future for the choice of drug and dosage to achieve maximum efficacy and safety.[51] Rosuvastatin shows increased systemic exposure in Asians compared with Caucasians and regulatory authorities including the FDA have

recommended starting with lower doses (5 mg) in 'Asian' patients.[52] The OATP1B1 uptake transporter does influence hepatic uptake of rosuvastatin but the higher systemic exposure did not appear to be related to the common polymorphisms and haplotypes in *SLCO1B1* in a study examining the ethnic differences in disposition of rosuvastatin in Singapore.[53] In that study there was considerable overlap in the measures of rosuvastatin systemic exposure between different ethnic groups so a number of other genotypic or phenotypic factors are likely to be involved in determining efficacy and safety.

In the DISCOVERY Asia study conducted at 70 centers in China, Hong Kong, Korea, Malaysia, Taiwan, and Thailand,[54] the starting dose of 10 mg rosuvastatin produced no adverse effects and the reduction in LDL-cholesterol was similar to that seen in other studies with rosuvastatin 10 mg mainly in Caucasians reviewed by Schuster[55] or in the STELLAR trial.[56]

## Conclusions

The development of these new imaging technologies has allowed the visualisation of arterial wall thicknesses, areas, and volumes and plaque composition and burden and enables the early detection of atherosclerosis, refinement of risk assessments, and monitoring of atherosclerosis progression/regression. A multimodality approach to the management of lipid risk factors in patients with coronary artery disease is likely to produce the best results, but the evidence for potent statins is still the most compelling at present. The results of several ongoing trials should help to clarify whether combinations of pharmacologic agents may be even more efficacious in the long-term management of patients at risk for atherosclerosis events. A pharmacogenetic approach may eventually allow the individualisation of treatments for even greater benefits.

## Acknowledgment

The preparation of this review was partially supported by a grant from the Research Grants Council of the Hong Kong Special Administrative Region, China (Project no. CUHK 4472/06M).

## References

1. Ballantyne CM, Herd JA, Dunn JK, et al. Effects of lipid lowering therapy on progression of coronary and carotid artery disease. Curr Opin Lipidol 1997;8:354-61.
2. Brown BG, Zhao XQ, Sacco DE, et al. Lipid lowering and plaque regression. New insights into prevention of plaque disruption and clinical events in coronary disease. Circulation 1993;87:1781-91.
3. Crisby M, Nordin-Fredriksson G, Shah PK, et al. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization. Circulation 2001;103:926-33.
4. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.
5. Glagov S, Weisenberg E, Zarins CK, et al. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371-5.
6. Fuster V, Moreno PR, Fayad ZA, et al. Atherothrombosis and high-risk plaque: part I: evolving concepts. J Am Coll Cardiol 2005;46:937-54.
7. Crouse JR 3rd. Thematic review series: patient-oriented research. Imaging atherosclerosis: state of the art. J Lipid Res 2006;47:1677-99.
8. Raggi P, Taylor A, Fayad Z, et al. Atherosclerotic plaque imaging: contemporary role in preventive cardiology. Arch Intern Med 2005;165:2345-53.
9. Naghavi M, Falk E, Hecht HS, et al. The First SHAPE (Screening for Heart Attack Prevention and Education) Guideline. Crit Pathw Cardiol 2006;5:187-90.
10. Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
11. Smith SC Jr., Greenland P, Grundy SM. AHA Conference Proceedings. Prevention conference V: Beyond secondary prevention: Identifying the high-risk patient for primary prevention: executive summary. American Heart Association. Circulation 2000;101:111-6.
12. Callister TQ, Raggi P, Cooil B, et al. Effect of HMG-CoA reductase inhibitors on coronary artery disease as assessed by electron-beam computed tomography. N Engl J Med 1998;339: 1972-8.
13. Raggi P, Davidson M, Callister TQ, et al. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering

with EBT Scanning (BELLES). Circulation 2005;112:563-71.
14. Nissen SE, Yock P. Intravascular ultrasound: novel pathophysiological insights and current clinical applications. Circulation 2001;103:604-16.
15. Schoenhagen P, Nissen SE. Intravascular ultrasonography: using imaging end points in coronary atherosclerosis trials. Cleve Clin J Med 2005;72:487-9, 493-6.
16. von Birgelen C, Hartmann M, Mintz GS, et al. Relationship between cardiovascular risk as predicted by established risk scores versus plaque progression as measured by serial intravascular ultrasound in left main coronary arteries. Circulation 2004;110:1579-85.
17. 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;291:1071-80.
18. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495-504.
19. 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;295:1556-65.
20. Nicholls SJ, Tuzcu EM, Sipahi I, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA 2007;297:499-508.
21. Ballantyne CM, Raichlen JS, Nicholls SJ, et al. Effect of rosuvastatin therapy on coronary artery stenoses assessed by quantitative coronary angiography: a study to evaluate the effect of rosuvastatin on intravascular ultrasound-derived coronary atheroma burden. Circulation 2008;117:2458-66.
22. Schuster H, Fox JC. Investigating cardiovascular risk reduction - the Rosuvastatin GALAXY Programme. Expert Opin Pharmacother 2004;5:1187-200.
23. Barter P, Kastelein J, Nunn A, et al. High density lipoproteins (HDLs) and atherosclerosis; the unanswered questions. Atherosclerosis 2003;168:195-211.
24. 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;290:2292-300.
25. Nissen SE, Tardif JC, Nicholls SJ, et al. Effect of torcetrapib on the progression of coronary atherosclerosis. N Engl J Med 2007;356:1304-16.
26. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007; 357:2109-22.
27. Nicholls SJ, Sipahi I, Schoenhagen P, et al. Intravascular ultrasound assessment of novel antiatherosclerotic therapies: rationale and design of the Acyl-CoA:Cholesterol Acyltransferase Intravascular Atherosclerosis Treatment Evaluation (ACTIVATE) Study. Am Heart J 2006;152:67-74.
28. Nissen SE, Tuzcu EM, Brewer HB, et al. Effect of ACAT inhibition on the progression of coronary atherosclerosis. N Engl J Med 2006;354:1253-63.
29. Sharrett AR, Patsch W, Sorlie PD, et al. Associations of lipoprotein cholesterols, apolipoproteins A-I and B, and triglycerides with carotid atherosclerosis and coronary heart disease. The Atherosclerosis Risk in Communities (ARIC) Study. Arterioscler Thromb 1994;14:1098-104.
30. Bots ML, Hoes AW, Koudstaal PJ, et al. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation 1997;96:1432-7.
31. Hodis HN, Mack WJ, LaBree L, et al. The role of carotid arterial intima-media thickness in predicting clinical coronary events. Ann Intern Med 1998;128:262-9.
32. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999;340:14-22.
33. Chambless LE, Folsom AR, Clegg LX, et al. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol 2000;151:478-87.
34. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol 1997; 146:483-94.
35. Smilde TJ, van Wissen S, Wollersheim H, et al. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. Lancet 2001;357: 577-81.
36. Taylor AJ, Kent SM, Flaherty PJ, et al. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. Circulation 2002;106:2055-60.
37. Taylor AJ, Sullenberger LE, Lee HJ, et al. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation 2004;110:3512-7.
38. Taylor AJ, Lee HJ, Sullenberger LE. The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. Curr Med Res Opin 2006; 22:2243-50.
39. Kastelein JJ, van Leuven SI, Burgess L, et al. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. N Engl J Med 2007;356:1620-30.
40. Bots ML, Visseren FL, Evans GW, et al. Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, double-blind trial. Lancet 2007;370: 153-60.
41. Crouse JR 3rd, Raichlen JS, Riley WA, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA 2007;297:1344-53.
42. Riccioni G, Bazzano LA, Bucciarelli T, et al. Rosuvastatin reduces intima-media thickness in hypercholesterolemic subjects with asymptomatic carotid artery disease: the Asymptomatic Carotid Atherosclerotic Disease in Manfredonia (ACADIM) Study. Expert Opin Pharmacother 2008;9:2403-8.
43. Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J

Med 2008;358:1431-43.
44. Fuster V, Fayad ZA, Moreno PR, et al. Atherothrombosis and high-risk plaque: Part II: approaches by noninvasive computed tomographic/magnetic resonance imaging. J Am Coll Cardiol 2005;46:1209-18.
45. Yuan C, Mitsumori LM, Beach KW, et al. Carotid atherosclerotic plaque: noninvasive MR characterization and identification of vulnerable lesions. Radiology 2001;221:285-99.
46. Chu B, Hatsukami TS, Polissar NL, et al. Determination of carotid artery atherosclerotic lesion type and distribution in hypercholesterolemic patients with moderate carotid stenosis using noninvasive magnetic resonance imaging. Stroke 2004; 35:2444-8.
47. Underhill HR, Yuan C, Zhao XQ, et al. Effect of rosuvastatin therapy on carotid plaque morphology and composition in moderately hypercholesterolemic patients: a high-resolution magnetic resonance imaging trial. Am Heart J 2008;155:584 e1-8.
48. Kajinami K, Takekoshi N, Brousseau ME, et al. Pharmacogenetics of HMG-CoA reductase inhibitors: exploring the potential for genotype-based individualization of coronary heart disease management. Atherosclerosis 2004;177:219-34.
49. Mangravite LM, Thorn CF, Krauss RM. Clinical implications of pharmacogenomics of statin treatment. Pharmacogenomics J 2006;6:360-74.
50. Schmitz G, Schmitz-Madry A, Ugocsai P. Pharmacogenetics and pharmacogenomics of cholesterol-lowering therapy. Curr Opin Lipidol 2007;18:164-73.
51. Link E, Parish S, Armitage J, et al. SLCO1B1 variants and statin-induced myopathy—agenomewide study. N Engl J Med 2008;359:789-99.
52. Grundy SM. The issue of statin safety: where do we stand? Circulation 2005;111:3016-9.
53. Lee E, Ryan S, Birmingham B, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther 2005;78:330-41.
54. Zhu JR, Tomlinson B, Ro YM, et al. A randomised study comparing the efficacy and safety of rosuvastatin with atorvastatin for achieving lipid goals in clinical practice in Asian patients at high risk of cardiovascular disease (DISCOVERY-Asia study). Curr Med Res Opin 2007;23:3055-68.
55. Schuster H. Rosuvastatin--a highly effective new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor: review of clinical trial data at 10-40 mg doses in dyslipidemic patients. Cardiology 2003;99:126-39.
56. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am J Cardiol 2003;92:152-60