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# Plaque stability and plaque regression: new insights

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Patients with prior cardiovascular disease and/or diabetes are at the highest risk of a myocardial infarction or stroke. Thus, the majority of morbid cardiovascular events arise in the large population of patients with qualifying risk factors, according to standard risk factor scoring techniques. Angiography studies suggest that a substantial proportion of myocardial infarctions arise in vessels without severe atherosclerotic stenosis on initial examination. The rupture of the fibrous cap of the mature atherosclerotic plaque usually initiates intra-arterial thrombosis and is rendered more likely by additional factors such as inflammation, hyperglycaemic spikes, and mechanical or shear stress in the artery wall. The vulnerability of plaques to rupture is therefore an important determinant of outcome, and treatment strategies in patients with cardiovascular disease should address this issue. Continuing improvements in cardiac-imaging techniques raise the possibility of routine assessment of plaque stability in the future, which will facilitate the identification of vulnerable plaques and the delivery of appropriate treatment. Recent evidence from a large observational study suggests that low HDL-cholesterol not only drives atherosclerosis progression but also increases plaque vulnerability. Correcting low HDL-cholesterol, for example, with nicotinic acid or a fibrate, appears a rational strategy for addressing the continuing burden of atherothrombotic disease.

## Introduction

Preventing the progression of atherosclerosis or inducing regression of atherosclerotic plaques is central to strategies aimed at improving cardiovascular prognosis.<sup>1,2</sup> However, the extent of atherosclerosis is not the only factor determining the risk of an adverse cardiovascular outcome. The mature atherosclerotic plaque is covered by a thin, fibrous cap that shields the thrombogenic lipid core from the bloodstream, and rupture of this cap is believed to be the terminal event that precipitates the intravascular thrombosis that heralds the onset of a myocardial infarction or stroke.<sup>3</sup>

Increasing levels of the atheroprotective lipoprotein, HDL-cholesterol, may not only contribute to the inhibition of atherogenesis but may also exert numerous other potentially beneficial actions including stabilization of the

atherosclerotic plaque.<sup>4</sup> This review describes the pathophysiology of coronary heart disease and considers the potential contribution of elevating HDL-cholesterol to cardiovascular protection through reduced atherosclerotic progression and increased plaque stability.

## Development and progression of coronary heart disease

### Epidemiology of sudden cardiac death

Patient populations with evidence of prior coronary disease are at high risk of subsequent coronary events, and cardiovascular management guidelines recommend intensive intervention against coronary risk factors in this population.<sup>1,2</sup> However, it is important to understand that although the highest incidence of coronary events occurs in such patients, the greatest number of cardiovascular events overall occurs in the much larger

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general population with qualifying risk factors, but without a history of manifest ischaemic events or diagnosed organ damage. Conversely, the absolute number of cardiac deaths derives from this much greater fraction in the overall population.<sup>5</sup>

These considerations are clinically important, as interventions in the highest-risk groups may provide highly significant risk reductions, but actually address only a fraction of the overall burden of cardiovascular risk in the population. Consistent with these observations, angiographic measurement of coronary luminal stenosis has proved a poor predictor of progression to myocardial infarction. In one study, angiograms were reviewed before and after the development of myocardial infarction. Only 22% of one group of patients ( $n = 23$ ) had stenosis  $>70\%$  on the initial, pre-infarction angiogram in the coronary artery that subsequently occluded.<sup>6</sup> A further study in 92 patients showed that 78% of coronary artery segments that gave rise to subsequent myocardial infarction did not display clinically significant stenosis on angiography.<sup>7</sup> These and other similar findings<sup>8–10</sup> demonstrate that coronary thrombosis often arises from coronary arteries without severe atherosclerotic disease.

### Pathophysiology of atherogenesis

Atherogenesis arises through a complex interplay of humoral and molecular factors.<sup>11–13</sup> Typically, activation of the arterial endothelium is an early step in atherosclerosis and may arise from a number of cardiometabolic derangements, including oxidative stress (e.g. from smoking or formation of advanced glycation end-products in the setting of hyperglycaemia), mechanical stress due to high blood pressure, or reduced endothelial function secondary to insulin resistance. The activated endothelium expresses adhesion molecules, such as E-selectin, which bind monocytes loosely to the endothelial surface. The chemotactic factor, monocyte chemoattractant protein-1, mediates tight binding of monocytes and infiltration into the vessel wall where they take up lipids avidly (especially oxidized LDL) and differentiate into macrophages under the influence of macrophage colony-stimulating factor and other chemokines. These macrophages, in turn, become foam cells, and then break down to form fatty streaks, thus providing the beginnings of the lipid core of the mature atherosclerotic plaque.

Typically, this accumulation of lipids drives the growth of the atherosclerotic plaque for about three decades.<sup>14</sup> However, the inflammatory cells that invade the arterial wall during atherogenesis also secrete a range of inflammatory substances and growth factors, which profoundly influence the properties of the arterial wall. Thus, from about the fourth decade of atherosclerosis onwards, proliferation of smooth muscle cells and deposition of collagen contribute increasingly to the overall formation of the plaque.<sup>14</sup> The contents of the plaque are contained within a collagen-rich fibrous cap, which stabilizes the plaque and prevents access of its thrombogenic core to the bloodstream. This cap is itself continually remodelled, with simultaneous removal and replacement of collagen.<sup>3,15</sup> Clearly, any reduction in the strength of the

fibrous cap during this process may increase the likelihood of plaque rupture, believed to be the most common precipitating event for coronary thrombosis and myocardial infarction, and an important cause of unstable angina pectoris where coronary occlusion is incomplete.<sup>3</sup> The likelihood of myocardial infarction therefore depends on a complex balance between the composition (stability) of the plaque and the presence of external stimuli, such as inflammation, mechanical or shear stresses, and hyperglycaemic episodes, which may by themselves or in combination induce plaque rupture.<sup>15</sup>

### Intervening in patients at risk of adverse cardiovascular outcomes

#### The metabolic syndrome as a marker of increased atherothrombotic risk

Atherosclerosis and thrombosis contribute importantly to the development of a myocardial infarction, as discussed earlier, and the term 'atherothrombotic' describes this process more accurately than either component alone.<sup>13,16</sup> In recent years, the concept of the metabolic syndrome (sometimes referred to as the insulin resistance syndrome) has been developed as a practical tool for identifying patients at risk of an atherothrombotic event. The most-used criteria for the diagnosis of the metabolic syndrome, proposed by the US National Cholesterol Education Program/Adult treatment Panel III (NCEP/ATPIII)<sup>2</sup> and by the International Diabetes Federation (IDF),<sup>17</sup> each depend on the presence of three of five cardiovascular risk factors, based on abdominal obesity (high waist circumference), low HDL-cholesterol, hypertriglyceridaemia, high blood pressure, and hyperglycaemia (high waist circumference is mandatory for diagnosis according to the IDF criteria). However, it is well recognized that a cluster of other cardiovascular risk factors related to thrombosis are also associated with the metabolic syndrome, including impaired endogenous fibrinolysis secondary to increased levels of plasminogen activator inhibitor-1, and increases in circulating fibrinogen, and liquid phase coagulation factors such as factor VII, von Willebrand factor, etc.<sup>16,18</sup>

The atherothrombotic disturbances associated with the metabolic syndrome are likely to markedly increase the risk of intravascular occlusion at the site of a vulnerable plaque and may account for a substantial proportion of the excess cardiovascular risk associated with the metabolic syndrome. Establishing adequate control of these risk factors therefore remains a principal goal of therapy to prevent or delay the onset of established cardiovascular disease.<sup>19</sup> Controlling cardiovascular risk factors is often more difficult in diabetic than in non-diabetic patients, highlighting the need for intensive intervention in this population.<sup>20</sup>

#### Quantifying myocardial perfusion disturbances

The standard method for identifying coronary impairment has been the appearance of adverse ECG changes

during an exercise test. This test is relatively simple to perform, but is relatively unspecific and may be confounded by pathophysiological variables.<sup>21,22</sup> Recent advances in echocardiography or myocardial perfusion-imaging techniques have enabled the detection of defects in regional myocardial perfusion. So, associations with atherothrombotic lesions can be studied directly and non-invasively in patients simultaneously subjected to myocardial stress through exercise or administration of a vasodilator drug.<sup>23,24</sup> Although a detailed review of this area is beyond the scope of this review, a brief description of the principal techniques involved is provided subsequently.

ECG-gated single-photon emission computed tomography (SPECT) is a particularly powerful diagnostic tool, as it allows simultaneous measurement of myocardial perfusion and left ventricular (LV) ejection fraction.<sup>24,25</sup> These techniques have been found to provide useful additional prognostic information to standard cardiovascular risk assessments on the basis of risk factor scoring. A new generation of hybrid scanners can now combine the anatomical and functional information from SPECT and CT scanning.

Positron emission tomography allows simultaneous measurement of myocardial perfusion and myocardial metabolism by the use of specific tracers for each. A recent study applied this technique to 28 patients with diabetes and ischaemic LV dysfunction and who were managed with medical therapy (i.e. no revascularization).<sup>26</sup> Seventeen patients died during a follow-up period of 4.3 years. Patients were stratified according to whether a mismatch was present between LV perfusion and metabolism. The presence of such a mismatch was highly predictive of mortality [risk ratio 3.98 (95% CI 1.33–11.91);  $P = 0.013$ ].

Electron beam computed tomography measures the amount of calcium within the coronary arteries. As calcification of the coronaries accompanies atherosclerosis, this technique provides a quantitative index of the extent of atherosclerosis, which appears to be prognostic and can be used to monitor the atherosclerotic process over time.<sup>27–29</sup> These imaging techniques permit visualization of atherosclerosis and promise to contribute importantly to cardiovascular risk stratification, including patients with diabetes and/or less advanced atherosclerosis, for whom conventional risk scoring may underestimate the true cardiovascular risk. In future, advances in tracer technology in combination with these imaging modalities may allow us to distinguish between stable and unstable plaques, for example, by quantitative assessment of inflammatory processes occurring within the coronary artery wall.

## HDL and plaque stability

### Antiatherogenic mechanisms of HDL

HDL provides the principal means by which excess cholesterol can be removed from peripheral tissues, including the foam cells of the evolving atherosclerotic plaque,

and returned to the liver for catabolism or recycling.<sup>30</sup> At the molecular level, HDL inhibits atherosclerosis at multiple sites, including reduced adhesion of inflammatory cells to the endothelium and their migration into the arterial intima, reduced inflammation within the artery wall, and inhibition of LDL oxidation.<sup>30</sup> The promotion of reverse cholesterol transport by HDL implies a beneficial effect on atheroma volume, whereas the anti-inflammatory effects of HDL may promote plaque stability and reduced risk of plaque rupture.

This aspect of HDL action was evaluated in the Tromsø study, a 7-year, prospective, population-based observational study of carotid plaque progression measured using ultrasound in 1952 subjects with evidence of carotid atherosclerosis at baseline.<sup>31</sup> Patients were stratified into quintiles for a range of cardiovascular risk factors, of which only HDL-cholesterol, age, smoking, and systolic blood pressure were significantly related to atherosclerosis progression in a multivariate analysis, whereas total cholesterol or triglycerides were not. Subjects with HDL-cholesterol in the highest quintile had markedly lower progression of atherosclerosis compared with patients in the other quintiles (Figure 1). Denser plaques that became more echogenic on ultrasound examination during follow-up grew less quickly than plaques that tended to remain more echolucent (Figure 2).

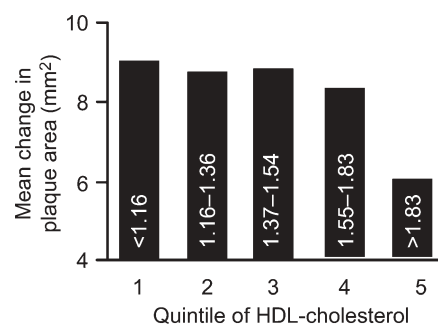


Figure 1 HDL and stabilization of carotid atherosclerotic plaques in the Tromsø study. Figures in columns are levels of HDL-cholesterol corresponding to each quintile (divide by 0.02586 to convert to mg/dL).<sup>31</sup> Reproduced with permission from Lippincott, Williams & Wilkins.

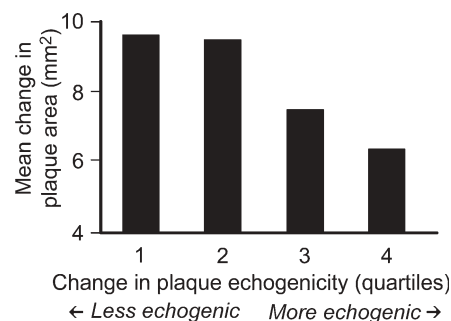


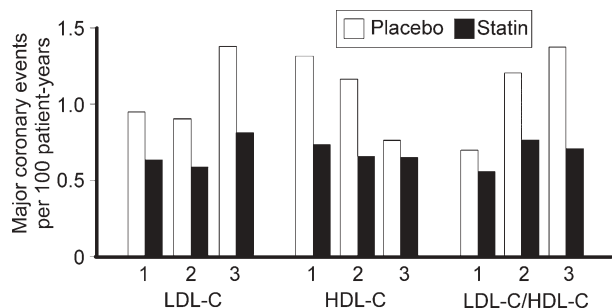
Figure 2 Relationship between echogenicity and stability of plaques in the Tromsø study.<sup>31</sup> Reproduced with permission from Lippincott, Williams & Wilkins.

The Tromsø study group had previously found that denser, more echogenic plaques were associated with higher levels of HDL-cholesterol.<sup>32</sup> The lipid core of an atherosclerotic plaque is echolucent on ultrasound, whereas the fibrous component is echodense. These findings were therefore consistent with enhanced removal of lipid from the atherosclerotic plaque in patients with higher levels of HDL, leading to the formation of denser, slower-growing plaques with a relatively higher proportion of fibrous material. Thus, higher levels of HDL tended to stabilize plaques and inhibit their growth. This important study provides evidence for antiatherogenic effects of HDL, relating to both inhibition of plaque growth and enhanced plaque stability. These findings are further extended by a recent population-based observational cohort study in the UK in 18 815 patients.<sup>33</sup>

### Effectiveness of interventions to increase HDL-cholesterol

Low HDL-cholesterol is an independent risk factor for atherothrombotic coronary events, and correction of low HDL-cholesterol reduced coronary event rates significantly in a number of randomized intervention trials (reviewed elsewhere).<sup>34,35</sup> The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) illustrates the benefits of intervening to correct the lipid profile in a patient population with low HDL-cholesterol at baseline.<sup>36</sup> Stratification for levels of lipids in this study (Figure 3) showed that the placebo event rate was highest for patients in the highest tertile for LDL-cholesterol and also for patients in the lowest tertile for HDL-cholesterol (or the highest tertile for the ratio of LDL-cholesterol to HDL-cholesterol).<sup>37</sup> Interestingly, patients with the lowest HDL-cholesterol appeared to derive greatest benefits from intervention with a statin (Figure 3), consistent with their higher overall cardiovascular risk.

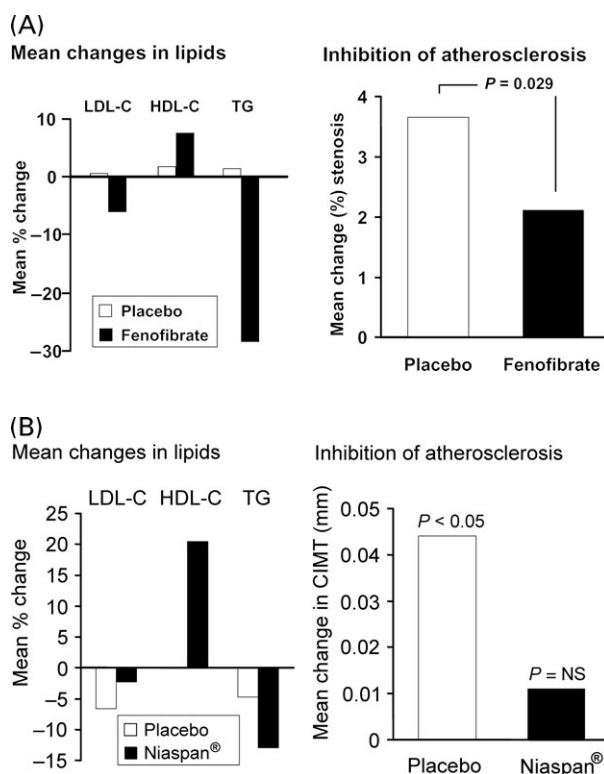
Two classes of agents are currently available for increasing levels of HDL-cholesterol: fibrates and nicotinic acid<sup>2</sup>; randomized trials have evaluated the effects of each class of agent on the lipid profile and on



**Figure 3** Relationship between levels of lipoprotein parameters at baseline and subsequent coronary event rates while receiving placebo or a statin in AFCAPS/TexCAPS.<sup>37</sup> Reproduced with permission from Lippincott, Williams & Wilkins.

progression of atherosclerosis.<sup>35</sup> Figure 4A shows the effects of fenofibrate on these treatment outcomes in the Diabetes Atherosclerosis Intervention Study (DAIS).<sup>38</sup> Treatment with the fibrate for at least 3 years increased HDL-cholesterol by ~8%, but the main effect of treatment was a reduction in triglycerides of ~30%. Indices of atherosclerosis progression on angiography were reduced, including the 42% reduction in per cent stenosis shown in Figure 4A.

Nicotinic acid is the most powerful agent currently available for increasing HDL-cholesterol.<sup>2</sup> The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 2) study<sup>39</sup> evaluated the anti-atherogenic effects of Niaspan<sup>®</sup>, a prolonged-release formulation of nicotinic acid with equivalent HDL-raising efficacy but superior tolerability relative to the immediate-release formulation,<sup>40</sup> in patients with low HDL-cholesterol who were already receiving a statin. As expected, a marked increase in HDL-cholesterol of ~20% was observed after treatment with Niaspan (Figure 4B). Carotid ultrasound measurements at baseline and after 1 year of treatment showed that significant progression of atherosclerosis was observed only in the statin-alone group.



**Figure 4** Effects of a fibrate or Niaspan on lipids and atherosclerosis progression in randomized trials. (A) The DAIS. Reprinted from The Diabetes Atherosclerosis Intervention Study.<sup>37</sup> Copyright (2001) with permission from Elsevier. (B) The ARBITER 2. Significance values are relative to baseline (NS, not significant). Left-hand panel drawn from data presented by Taylor *et al.*<sup>39</sup> and right-hand panel reproduced from Taylor *et al.*,<sup>39</sup> with permission from Lippincott, Williams & Wilkins.

## Conclusions

Identifying and managing patients with atherosclerotic plaques that are vulnerable to rupture and thrombosis will receive increasing emphasis in routine cardiovascular care in the future. Improvements in cardiac-imaging methodologies and therapeutic intervention strategies to stabilize plaques are likely to contribute to improved outcomes in these high-risk patients, in addition to interventions to slow or reverse the progression of atherosclerosis itself. We already have strong observational evidence that correcting low HDL-cholesterol is likely to achieve both reduced atherosclerosis burden and improved plaque stability, indicating a marked improvement in overall atherothrombotic risk.

**Conflict of interest:** D.T. is a member of the speakers bureau of Merck KGaA. B.S. has no conflict of interest to declare.

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