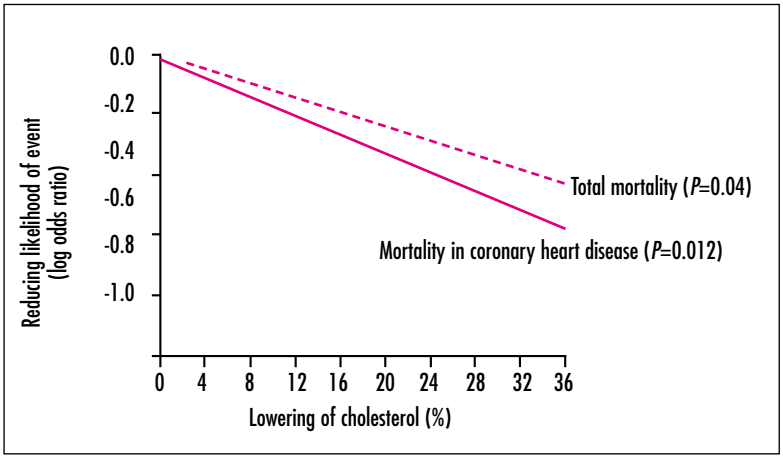
Total lipid management and residual risk: beyond statin therapy

Reducing cholesterol with statins has been clearly shown to reduce the risk of cardiovascular disease, but despite statin therapy there remains a considerable residual risk of cardiovascular disease. This article reviews the evidence supporting the management of lipids beyond cholesterol reduction with statin therapy alone.

Despite major advances in pharmacological and surgical treatments cardiovascular disease, in particular coronary heart disease, remains the leading cause of death in the industrialized world (Verschuuren et al, 1995). The disease burden is set to continue increasing associated with the rapid increase in coronary heart disease risk factors such as type 2 diabetes and obesity (Kannel and Larson, 1993). The evidence that incrementally lower cholesterol levels are better in terms of cardiovascular disease risk comes both from epidemiological studies and randomized clinical trials. Every major clinical endpoint trial of lipid-lowering therapy (Cheng and Leiter, 2006) (*Figure 1*) has demonstrated that lower low density lipoprotein cholesterol levels are associated with a reduced risk of cardiovascular event.

Analysis of the relationship between low density lipoprotein cholesterol levels and major coronary events in studies such as 4S after only 1 year of treatment suggests that event rates are lower for each lower tertile of low density lipoprotein cholesterol, while event rates may be reduced for each increasing tertile of low density lipoprotein cholesterol reduction (Scandinavian Simvastatin Survival Study, 1994). Such observations suggest that there may be no threshold for low density lipoprotein cholesterol reduction beyond which additional cardiovascular benefit may not be achieved. Indeed, O'Keefe et al (2004) suggested that the optimum low density lipoprotein cholesterol levels should be in the range of 1.3–1.8 mmol/litre, which was the typical level of our hunter-gatherer forefathers who showed no evidence of atherosclerosis, even in individuals living to their seventh or eighth decade of life.

Figure 1. Cholesterol reduction and the risk of vascular events. Data from 38 primary or secondary prevention studies with more than 98 000 patients. Adapted from Gould et al (1998).



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Despite the clear epidemiological association between cholesterol level and cardiovascular risk, many individuals who develop vascular disease do not have particularly elevated cholesterol levels. Population-based studies have consistently shown that high density lipoprotein cholesterol levels are a strong independent inverse predictor of cardiovascular events. In the Framingham heart study low levels of high density lipoprotein cholesterol was a more potent risk factor for coronary heart disease than was low density lipoprotein cholesterol level (Gordon et al, 1977). Epidemiological studies clearly demonstrate that the ratio of total cholesterol or low density lipoprotein cholesterol to high density lipoprotein cholesterol is the strongest determinant of cardiovascular risk (Stamler et al, 1993).

The reduction of total and low density lipoprotein cholesterol is currently the primary goal of lipid-lowering therapy with respect to cardiovascular risk reduction. The reduction of cholesterol whether by diet, drugs or other means is associated with a reduced risk of cardiovascular disease (*Figure 1*) (Cheng and Leiter, 2006) and since lipoproteins are only one element of cardiovascular risk, which is determined overall by the presence of other risk factors, the absolute benefit of cholesterol reduction is a function of baseline cardiovascular risk.

High density lipoprotein cholesterol exerts numerous biological effects which may protect from atherogenesis (*Figure 2*), including reverse cholesterol ester transport, anti-inflammatory and antioxidant properties, and may also attenuate endothelial dysfunction. Endothelial injury is an early event in the process of atherogenesis facilitating the passage of cholesterol-containing (Apo B) lipoprotein particles into the arterial intima (*Figure 3*). Lipid enrichment of such particles results in the

genesis of smaller, denser particles which more readily undergo oxidation once within the arterial intima (*Figure 3*). These lipoprotein particles undergo phagocytosis by macrophages resulting in foam cell formation and the genesis of a local inflammatory diathesis. Continuing penetration of the arterial intima propagates this process, resulting in formation of further inflammatory cytokines, adhesion molecules and foam cells and thus the genesis of an atherosclerotic plaque. This process facilitates growth factor and metalloproteinase generation, promoting matrix degeneration within the arterial wall, which results in the destabilization of the atherosclerotic plaque, leading to rupture and surface thrombus formation resulting in an acute cardiovascular event.

Based on our understanding of the pathogenesis of such unstable atherosclerotic plaques, it is clear that the biological properties of high density lipoprotein cholesterol particles can attenuate this process at various stages. The potential clinical importance of this biological process is underlined by observations from the INTERHEART study in which the ratio of Apo B to Apo A-I (the main transport lipoprotein for high density lipoprotein) was found to be the single most important determinant of risk for first myocardial infarction across over 10 000 subjects from varying geographical locations and ethnic origin (Yusuf et al, 2004). Indeed the Apo A-I moiety of high density lipoprotein cholesterol is increasingly recognized as an important factor in modulating atherogenesis, with infusions of recombinant apo A-I Milano/phospholipid complexes appearing to reduce atheroma volume as measured by intravascular ultrasound and result in rapid reversal in endothelial dysfunction (Nissen et al, 2003; Nicholls et al, 2006).

Plasma triglyceride is also becoming increasingly recognized as an independent cardiovascular risk factor (Assmann, 2001). Fasting hypertriglyceridaemia (>1.7 mmol/litre) is associated with the generation of triglyceride-rich lipoprotein particles with enhanced atherogenic properties, in particular an augmented potential to both penetrate the arterial endothelium and undergo oxidative modification within the arterial wall. In support of this concept triglyceride enrichment of very low density lipoprotein and intermediate density lipoprotein particles in the Monitored Atherosclerosis Regression Study was shown to strongly associate with atherosclerotic disease progression (Hodis and Mack, 1998).

At plasma triglyceride levels >1.7 mmol/litre there are adverse changes in the quality of both low density lipoprotein and high density lipoprotein particles. With increasing triglyceride concentrations plasma residence time of triglyceride-rich lipoproteins increases, resulting in increased interchange of triglyceride from chylomicrons and very low density lipoprotein into low density lipoprotein and high density lipoprotein particles, while cholesterol esters travel in the opposite direction, through the action of cholesterol ester-transfer protein. The triglyceride enrichment of low density lipoprotein results in the generation of increased numbers of small dense more atherogenic low density lipoprotein particles which, along with high density lipoprotein particles with altered biological properties rendering their function less cardioprotective in nature, promotes a proatherogenic diathesis.

Indeed in a study of patients with unstable angina, elevated plasma triglyceride and reduced high density lipoprotein cholesterol and Apo A-I levels were highly significant predictors of progression to coronary events (Bolibar et al, 2000). Low density lipoprotein cholesterol levels were of marginal significance and the risk of events increased substantially with increasing tertiles of triglyceride and decreasing Apo A-I levels.

This apparent independence of high density lipoprotein cholesterol and low density lipoprotein cholesterol as determinants of cardiovascular risk is critically important as it suggests that simultaneous therapeutic changes in each of these variables may have additive effects on risk reduction.

Figure 2. Anti-atherogenic effects of high density lipoprotein cholesterol.

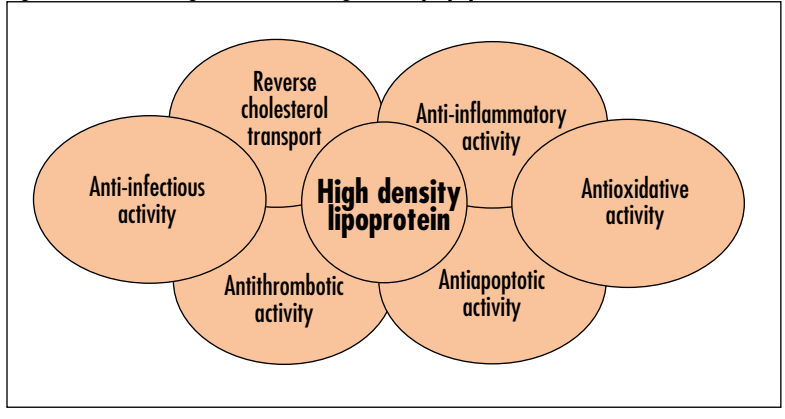
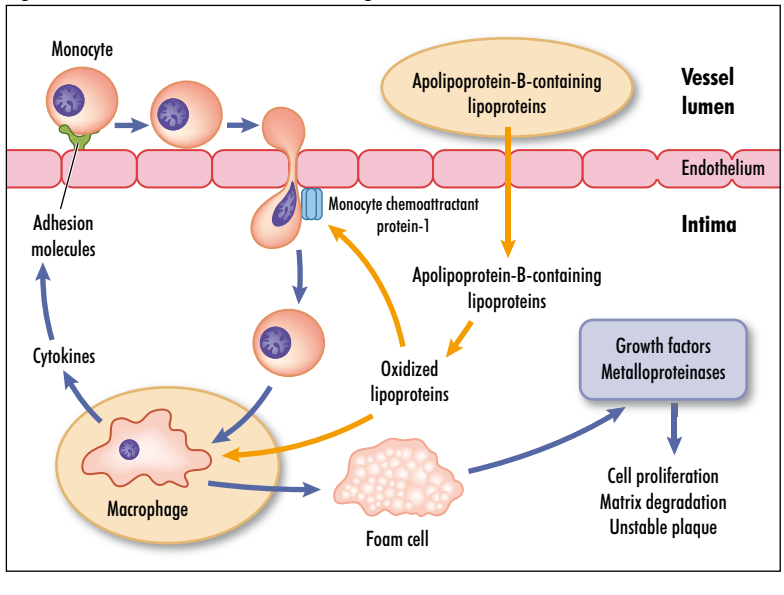


Figure 3. Mechanistic overview of atherogenesis. From Ross (1999).



Statins, cholesterol reduction and residual risk

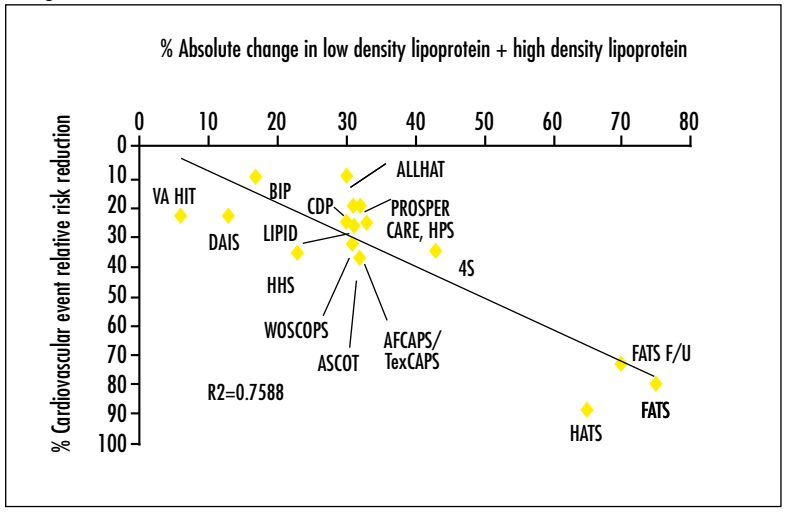
The most compelling evidence for cholesterol lowering comes from clinical trials using statins (HMG-CoA reductase inhibitors) (Baigent et al, 2005). The early major statin trials in people with established cardiovascular disease using simvastatin and pravastatin (4S, CARE, LIPID), and in people at risk of developing cardiovascular disease using pravastatin and lovastatin (AFCAPS/TEXCAPS, WOSCOPS), demonstrated reduction in coronary morbidity and mortality and in all-cause mortality where statistical power was sufficient. The use of rosuvastatin in primary prevention (Ridker et al, 2009) demonstrated that low density lipoprotein cholesterol reduction to levels <1.8 mmol/litre with statin therapy alone may reduce cardiovascular disease risk by over 50%. Furthermore, meta-analysis of statin studies has demonstrated a 9% and 13% reduction in all cause mortality per mmol/litre reduction in low density lipoprotein cholesterol level achieved with statin therapy in subjects with and without diabetes (Cholesterol Treatment Trialists' Collaborators, 2008), which translates into up to 50% reduction in cardiovascular disease per 1.95–2.00 mmol/litre reduction in low density lipoprotein cholesterol level.

However, in all cholesterol-lowering studies, there remains a substantial risk in the treated groups. This may relate to a low baseline level of high density lipoprotein cholesterol, which remains predictive of cardiovascular events even during treatment with statins (Nissen et al, 2003). In a pooled analysis of four statin trials, the modest elevation in levels of high density lipoprotein cholesterol produced by these drugs correlated with regression of coronary atherosclerosis (Gordon et al, 1989). Similarly the angiographic progression of coronary stenosis is reduced significantly and independently by comparable percentages of low density lipoprotein cholesterol reduction and high density lipoprotein cholesterol increase (Gordon et al, 1989), with the influence of high density lipoprotein cholesterol being some 1.3 times greater. Furthermore epidemiological analysis suggests that a 2–3% (0.03 mmol/litre) greater high density lipoprotein cholesterol is associated with an low density lipoprotein cholesterol-independent reduced risk of cardiovascular events over a 7–10-year follow-up period (Tyroler, 1990). It is also noteworthy that there is a log-linear relationship between low density lipoprotein cholesterol reduction and the reduction in cardiovascular disease risk; hence there is incrementally less cardiovascular disease risk reduction achieved with further low density lipoprotein cholesterol reduction at lower levels of low density lipoprotein cholesterol.

A post-hoc analysis of the TNT data demonstrated that the relationship between high density lipoprotein cholesterol and cardiovascular risk was maintained, even at very low concentrations of low density lipoprotein cholesterol (Barter et al, 2007). Data for some of the major statin intervention trials have also been stratified for high density lipoprotein cholesterol at baseline (Sacks et al, 2000), with the incidence of cardiovascular events being inversely proportional to baseline high density lipoprotein cholesterol levels, while statin therapy produced similar reductions in absolute cardiovascular risk at all levels of high density lipoprotein cholesterol. Thus, while statins are clearly of benefit in patients with low high density lipoprotein cholesterol, they do not eliminate the excess risk associated with low high density lipoprotein cholesterol and additional therapy to rectify this issue may be required. Indeed in a meta-analysis of lipid-lowering studies maximal event rate reduction results from alterations in both low density lipoprotein and high density lipoprotein cholesterol concentrations; in other words, increasing high density lipoprotein cholesterol augments the effects of low density lipoprotein cholesterol reduction on cardiovascular disease (*Figure 4*).

Addressing factors other than low density lipoprotein cholesterol levels, such as plasma triglyceride levels, low high density lipoprotein cholesterol levels, elevated concentrations of Apo B-containing lipoproteins and small dense low density lipoprotein cholesterol, may contribute to attenuating the marked residual cardiovascular risk which persists despite statin therapy.

Figure 4. Additive effects of low density lipoprotein and/or high density lipoprotein changes on cardiovascular outcomes.



High density lipoprotein, triglyceride and other lipid subfractions: impact on cardiovascular risk

The role of triglyceride and high density lipoprotein cholesterol levels in determining vascular risk has been demonstrated by large population-based studies such as the PROCAM study (Assman et al, 1998). Within each low density lipoprotein cholesterol sub-group the risk of myocardial infarction increased with increasing triglyceride levels and reduced high density lipoprotein cholesterol levels, an effect which was most pronounced in

subjects with lower low density lipoprotein cholesterol levels. The Air Force / Texas Coronary Atherosclerosis Prevention Study further illustrated the importance of high density lipoprotein cholesterol levels in predicting coronary heart disease risk in subjects with average low density lipoprotein cholesterol levels. In this study subjects with low levels of high density lipoprotein cholesterol and average low density lipoprotein cholesterol levels benefited disproportionately from statin therapy (Gotto et al, 2000).

The results of the Strong Heart Study (Frost et al, 1996) indicate that non-high density lipoprotein cholesterol may be a superior predictor of cardiovascular events than low density lipoprotein cholesterol, high density lipoprotein cholesterol or plasma triglyceride levels alone in both men and women with type 2 diabetes. The utility of non-high density lipoprotein cholesterol in predicting cardiovascular events in non-diabetic subjects is supported by data from the SHEP (Systolic Hypertension in the Elderly Program) and Lipid Research Clinics (LRC) studies (Tyroler, 1990), in which non-high density lipoprotein cholesterol was found to be a better predictor of cardiovascular events than low density lipoprotein cholesterol in patients followed over 4.5 years and 19 years respectively.

Although evidence accumulates to support plasma triglyceride as a coronary heart disease risk factor, the effects of triglyceride reduction on coronary heart disease risk are unclear. In the 4S population triglyceride reduction did not contribute to risk reduction (Scandinavian Simvastatin Survival Study, 1994). In the CARE trial only a minor risk reduction was seen with triglyceride reduction in patients with baseline triglyceride levels above the median of 1.6 mmol/litre. Indeed treatment guidelines suggest that the correction of hypertriglyceridaemia (>1.6 mmol/litre) should only be considered following the optimal management of both low density and high density lipoprotein cholesterol.

Therefore, optimal risk reduction and lipid-regulating therapy may require either monotherapy or combination therapy resulting in the development of a targeted strategy using a variety of agents. The precedent for such an approach has been set in the evolution of pharmacotherapy in hypertension.

Conclusions

Although there is evidence that more intensive low density lipoprotein cholesterol reduction may result in greater protection from atherosclerosis and cardiovascular disease, it is unlikely that further low density lipoprotein cholesterol reductions alone will make additional inroads into the residual cardiovascular risk that exists despite low density lipoprotein cholesterol lowering therapy. A low level of high density lipoprotein cholesterol is an independent cardiovascular risk factor and is not sufficiently increased by statins which are the current mainstay of low density lipoprotein cholesterol lowering therapy. The addition of drugs effective in raising high density lipoprotein cholesterol levels to statins may provide a rational approach to reducing cardiovascular risk beyond that achieved by statin monotherapy.

Although a low level of high density lipoprotein cholesterol is not currently considered a therapeutic target, there is convincing evidence of the importance of low levels of high density lipoprotein cholesterol in the aetiology of cardiovascular disease. **BJHM**

Conflict of interest: Dr M Evans has received research awards from Sanofi Aventis, GSK and Novo Nordisk and has acted in an advisory capacity for MSD, Novartis, Sanofi Aventis, GSK, Novo Nordisk, Eli Lilly and Boehringer Ingelheim.

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KEY POINTS

- Despite reductions in levels of low density lipoprotein cholesterol and total cholesterol decreasing cardiovascular morbidity and mortality with statin therapy, there still remains a considerable burden of residual cardiovascular risk.
- Low levels of high density lipoprotein cholesterol appear to be an important determinant of the residual cardiovascular risk beyond statin therapy.
- Low levels of high density lipoprotein cholesterol remain an important determinant of cardiovascular risk even very low levels of low density lipoprotein cholesterol.
- Plasma triglyceride is an important cardiovascular risk factor, but should only be considered as a therapeutic target following optimal treatment of both low density and high density lipoprotein cholesterol.
- Optimal cardiovascular risk reduction with lipid-regulating therapy may require either monotherapy or combination therapy resulting in the development of a targeted strategy using a variety of agents.

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