The case for more intensive use of statins

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The notion that you cannot have too much of a good thing, coined first by Shakespeare, seems inherently primordial, and has been shared with us from Mae West to Casanova's memoirs. However true this might appear, things in medicine are rarely black and white, and cardiovascular disease (CVD) management is no exception.

Meta-analyses of blood pressure treatment trials have demonstrated the progressive cardiovascular benefits of larger blood pressure reductions. However, the issue of a possible 'J-point', whereby lower achieved diastolic blood pressures might be associated with increased mortality, and whether, if true, it is causally related to the blood pressure therapy, is contentious [D'Agostino *et al.* 1991; Hansson *et al.* 1998; Boutitie *et al.* 2002; Wang *et al.* 2005]. In the case of diabetes, the UK Prospective Diabetes Study (UKPDS) found patients with type 2 diabetes receiving intensive glucose therapy compared with conventional therapy achieved significant reductions in microvascular complications over 10 years [UKPDS Group, 1998]. In a legacy follow up of UKPDS participants, significant long-term microvascular, macrovascular and mortality event reductions were borne out despite relative equalization of glycated haemoglobin levels between the two original treatment arms [Holman *et al.* 2008]. However, in the Action to Control Cardiovascular Risk in Type 2 Diabetes (ACCORD) trial, intensive compared with usual glycaemic management was associated with an increase in mortality [Gerstein *et al.* 2008], an observation that still remains largely unexplained [Boyko, 2010]. In contrast, combination antiplatelet therapy (such as aspirin and clopidogrel together) has proven to be unequivocally better than aspirin alone in preventing recurrent ischaemic events, [Mehta *et al.* 2001; Steinhubl *et al.* 2002], even though higher aspirin doses alone have not been proven better than current standard doses of between 75 and 150 mg daily [Antithrombotic Trialists Collaboration, 2002]. Moreover, there is emerging

evidence that higher doses of clopidogrel loading and earlier therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI) can reduce major adverse cardiac events [Dangas *et al.* 2009; Mehta *et al.* 2010]. Thus, higher dose or more intensive therapy for CVD has clear benefits in some settings, but in others has no proven benefit and even in some cases the possibility of harm.

Statin therapy for lipid level control is now widely accepted as a core component of occlusive coronary disease treatment and prevention. Patients with established CVD (secondary prevention) or who have a high (>20%) 10-year risk of CVD (primary prevention) are empirically recommended statin therapy according to US National Cholesterol Education Program (NCEP) guidelines and UK National Institute for Health and Clinical Excellence (NICE) guidelines [NCEP Expert Panel, 2002; Cooper *et al.* 2008]. ATPIII guidelines suggest consideration of statin therapy in lower risk groups according to baseline low-density lipoprotein (LDL)-cholesterol levels and also offer different targets. For example, they suggest lifestyle modifications and consideration of statin therapy in individuals with moderate (10–20%) 10-year CVD risk with a LDL-cholesterol level greater than 3.36 mmol/liter. In individuals with a low (<10%) 10-year CVD event risk but with two or more risk factors, the recommended LDL-cholesterol level at which to consider intervention is greater than 4.1 mmol/liter [NCEP Expert Panel, 2002].

Prior to the emergence of statins, LDL-cholesterol lowering was far more difficult to achieve due to the lesser efficacy and poor side-effect profiles of earlier available therapies such as bile acid sequestrants [Hou and Goldberg, 2009]. Significant improvements in lipid profiles and CVD prevention have been achieved since. In 2005 the Cholesterol Treatment Trialists' Collaboration published a prospective meta-analysis of individual

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patient data from 90,000 people in 14 trials comparing statin therapy with control [Baigent *et al.* 2005]. In that report, the authors were able to quantify the efficacy of statin therapy according to LDL-cholesterol reduction, and showed that a highly significant proportional relationship exists between the average amount of LDL-cholesterol lowering achieved from statin therapy in each trial and its major vascular event reduction: For each 1 mmol/liter reduction in LDL cholesterol achieved, major vascular events are reduced by about 20%. This applied over 5 years of follow up (dose response trend, $p = 0.0002$).

This led to the next hypothesis to evaluate directly – that more aggressive lowering of LDL cholesterol, either with higher doses of the same statin or the use of newer more potent statins, compared with others should result in even greater reductions in cardiovascular events. More recently a number of trials have been completed comparing the use of more intensive statin therapy with less intensive regimens in patients with established coronary disease, attempting to ascertain if additional cardiovascular benefits can be achieved by aggressively lowering LDL cholesterol to even below ‘normal’ population levels [Armitage *et al.* 2010; Cannon *et al.* 2004; De Lemos *et al.* 2004; Waters *et al.* 2004; Pedersen *et al.* 2005]. Only two of the five major trials individually demonstrated a significant reduction in major vascular events with high-dose statin therapy [Larosa *et al.* 2005; Pedersen *et al.* 2005], leaving some uncertainty about the additional value of higher dose therapy.

However, in late 2010 the Cholesterol Treatment Trialists’ Collaboration incorporated the results of the five major ‘more *versus* less’ trials in an updated meta-analysis, as well as the data from seven more ‘statin *versus* control’ trials published since the first analysis with their existing data [Baigent *et al.* 2010]. This provided information on nearly 130,000 individuals in statin *versus* control trials and nearly 40,000 individuals in ‘more *versus* less’ trials. Compared with usual dose statin therapy, high-dose treatment was associated with a highly significant reduction in major vascular events of 28% per mmol/liter LDL-cholesterol reduction achieved. After analysing trial results according to baseline LDL-cholesterol values, it was shown that a significant cardiovascular event reduction of about 20% continues to be achieved per mmol/liter reduction in LDL cholesterol even down to starting levels at less than 2.0 mmol/liter (Figures 1–3).

Figure 1. Relation between proportional reduction in incidence of major coronary events and major vascular events and mean absolute low-density lipoprotein (LDL) cholesterol reduction at 1 year. Squares represent a single trial plotted against mean absolute LDL cholesterol reduction at 1 year, with vertical lines above and below corresponding to one standard error (SE) of unweighted event rate reduction. Trials are plotted in order of magnitude of difference in LDL cholesterol difference at 1 year. For each outcome, regression line (which is forced to pass through the origin) represents weighted event rate reduction per mmol/liter LDL cholesterol reduction. [Reproduced from Baigent *et al.* [2005] with permission]. Reprinted from The Lancet, Vol. 366, Cholesterol Treatment Trialists’ (CTT) Collaborators, Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins, Page No. 1271, Copyright 2005, with permission from Elsevier.

On average, the high-dose trials actually lowered LDL cholesterol by an additional 0.5 mmol/liter, effectively offering around 15% greater reduction in CVD risk.

Figure 2. Effects on any major vascular event in each study. In the left panel, unweighted rate ratios (RRs) for each trial of the comparison of first event rates between randomly allocated treatment groups are plotted along with 99% confidence intervals (CIs). Trials are ordered according to the absolute reduction in low-density lipoprotein (LDL) cholesterol (LDL-C) at 1 year within each type of trial comparison (more *versus* less statin and statin *versus* control). In the right panel, RRs are weighted per 1.0 mmol/liter LDL-C difference at 1 year. Subtotals and totals with 95% CIs are shown by open diamonds. (Reproduced from Baigent *et al.* [2010] with permission). Reprinted from The Lancet, Vol. 376, Cholesterol Treatment Trialists' (CTT) Collaboration, Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials, Page No. 1673, Copyright 2010, with permission from Elsevier.

With the efficacy of intensive statin therapy apparent even at levels of LDL cholesterol traditionally considered low, issues of safety would appear to be the only major potential obstacle to an empiric recommendation to routine high-dose statin use. Whilst this will be of major importance to the balance of benefit and harm in individuals at low risk (e.g. <10% 10-year risk of CVD) [Cholesterol Treatment Trialists' (CTT) Collaborators, 2012] it will be of less concern in those at high risk or with clinically established CVD. To date, the major safety concerns that have emerged relate to an increased risk of myalgias, myositis, symptomatic myopathy, rhabdomyolysis, and very rarely

significant liver dysfunction. More recently, evidence of a small absolute increase in risk of new diabetes has been reported and concerns have been raised about an increased risk of intracranial haemorrhage, cognitive impairment and even cancer. Broadly speaking the conclusions of the latest CTT Collaborators analyses were that no particular major adverse effects had been identified with significantly higher frequency using high *versus* conventional dose statin therapy in spite of the additional lowering of LDL cholesterol [Baigent *et al.* 2005, 2010]. However, it is helpful to review the data relating to each of these stated individual safety concerns in turn.

Figure 3. Effects on major vascular events per 1.0 mmol/liter reduction in low-density lipoprotein (LDL) cholesterol (LDL-C), by baseline LDL-C concentration on the less intensive or control regimen. Rate ratios (RRs) are plotted for each comparison of first event rates between treatment groups, and are weighted per 1.0 mmol/liter LDL-C difference at 1 year. Analyses were done with trial-specific and subgroup-specific LDL weights for each baseline LDL-C category. Missing data are not plotted. RRs are shown with horizontal lines denoting 99% confidence intervals (CIs) or with open diamonds showing 95% CIs. (Reproduced from Baigent *et al.* [2010] with permission). Reprinted from The Lancet, Vol. 376, Cholesterol Treatment Trialists' (CTT) Collaboration, Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials, Page No. 1676, Copyright 2010, with permission from Elsevier.

Myalgia

Statin-induced myalgia (typically presenting as proximal, symmetric muscle weakness and soreness) is a well documented adverse effect of statin therapy. A recently published review identified ongoing inconsistencies in the reported frequency of myopathy in various trials. Some observational studies have reported symptoms in up to 10% of patients, whilst many randomized controlled trials have reported virtually none [Whayne, 2011]. It is thought that the prevalence is likely to be in the range of 1–5% for most patients in clinical

practice [Thompson *et al.* 2003]. A clinically significant statin-induced myopathy, which by traditional definition should have an elevated serum creatine kinase (CK) more than 10 times the upper limit of normal, is reported to occur far less frequently, with estimates from 0.1% to 0.5% [Bocuzzi *et al.* 1991; Pedersen *et al.* 1996; Thompson *et al.* 2003]. Complicating its diagnosis, the value of an elevated CK has been questioned because biopsy-proven myopathy can occur without an elevated CK. It therefore can be unclear, without an invasive biopsy, as to whether

the patient's symptoms are truly related to their statin therapy. The greatest risk for a serious statin-caused myopathy is currently thought to relate to either higher doses of statin therapy or concomitant use of other medications that alter statin metabolism, such as some fibrates (most notably gemfibrozil), macrolide antibiotics, antifungal agents, cyclosporin, antiretroviral agents and consuming greater than a litre (or quart) of grapefruit juice a day [Wortmann, 2005]. In addition there is emerging evidence that a genome association with statin myopathy exists: individuals with the CC genotype in the SLC01B1 gene have a substantially higher risk of myopathy with simvastatin by impairing statin metabolism and producing higher statin concentrations, which may explain a greater risk with higher dose therapy [Link *et al.* 2008]. Although not yet known, it is postulated that the same risk may apply to other statins, because this genotype is known to alter circulating concentrations of other statins too [Whayne, 2011]. Widespread observational experience reports success in trialling an alternative statin after a statin-free period in cases of myopathy, based on individual differences in chemical structure. It is recognized that some, albeit few patients, will tolerate only one or even no statins [Whayne, 2011].

Rhabdomyolysis

The risk of rhabdomyolysis (defined as muscle necrosis and the release of intracellular muscle constituents into the circulation) with statin therapy is rare. In the original CTT meta-analysis, statin therapy was associated with a 5-year excess risk of rhabdomyolysis of 0.01% [Baigent *et al.* 2005]. In the most recent cycle, among the more *versus* less trials there was an excess of four cases per 10,000 participants (14 *versus* 6 cases in total) compared with an excess of one case per 10,000 (14 *versus* 9 cases in total) among the 21 statin *versus* control trials [Baigent *et al.* 2010]. All of the excess cases with more intensive therapy occurred in the two trials with simvastatin 80 mg *versus* simvastatin 20 mg. One of these trials, the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) [Armitage *et al.* 2010] identified 53 definite cases (0.9%) of symptomatic myopathy with 80 mg simvastatin compared with two cases in the lower dose 20 mg simvastatin group (0.02%) amongst the total 12,067 trial participants. There were seven (0.1%) cases of rhabdomyolysis in the 80 mg simvastatin group compared with no cases

in the 20 mg simvastatin group, although there were another seven cases in the 80 mg simvastatin arm with CK rises more than 40 times the upper limit of normal without available data on end organ damage to confirm the diagnosis of rhabdomyolysis.

In 2011, in response to data from the SEARCH trial along with other trials and observational data, the US Food and Drug Administration (FDA) issued a warning on the prescription of 80 mg simvastatin in association with modified product labelling, recommending only those people on 80 mg simvastatin for greater than 12 months without any identified problems should continue on this medication, otherwise an alternative statin should be prescribed [US FDA, 2011]. It is currently thought, including by the authors of the SEARCH trial [Armitage *et al.* 2010], that high-dose simvastatin may confer a greater risk of muscle-derived complications than other statins, although the explanation for this is not readily apparent. Following on from their recommendations for simvastatin, the FDA conducted a review of drug–drug interactions with lovastatin, due to its comparable physicochemical and pharmacokinetic properties. As lovastatin is a sensitive *in vivo* cytochrome P450 3A4 substrate, a series of recommendations on drug–drug interactions, contraindications and dose limitations have been made with altered labelling information in early 2012 [US FDA, 2012]. Previous FDA case reports between 1999 and 2005 of the frequency of rhabdomyolysis according to statin, unadjusted for dosage, listed atorvastatin at 2.1 cases per million prescriptions, simvastatin at 7.8 and pravastatin at 2.1 [Alsheikh-Ali *et al.* 2007]. Postmarketing analyses from the FDA database between 2003 and 2004 for rosuvastatin reported rhabdomyolysis at a frequency of about 15 per million prescriptions [Alsheikh-Ali *et al.* 2005]. Such analyses are limited by the fact they reflect only reported events and do not factor in dosages used or the magnitude of LDL-cholesterol reduction achieved.

Diabetes development with statins

Statin therapy in people with diabetes without a history of CVD has been shown to produce equivalent proportional reductions in major vascular events to patients with established CVD, affirming their utility in this growing patient population [Kearney *et al.* 2008]. However, there has been recent data emerging suggesting there may be a small increase in risk for developing diabetes

on statin therapy. This was calculated at a 9% relative risk increase over 4 years in a meta-analysis performed of 13 randomized controlled trials of statin *versus* placebo among 91,140 participants [Sattar *et al.* 2010], representing four new cases of diabetes per 1000 patients treated with statin therapy. This represented a number needed to harm of 255 over 4 years to cause one new case of diabetes compared with a number needed to treat of 47 over the same time period to avoid one major coronary event. A more recently published meta-analysis examined these effects among trials of intensive-dose *versus* low-dose statin therapy over a combined trial population of 32,752 people [Preiss *et al.* 2011]. A 12% increase in incident diabetes was identified over a mean follow up of 4.9 years, representing an absolute increase of two cases per 1000 patient years among those treated with intensive-dose therapy compared with standard-dose statin treatment (18.9 *versus* 16.9). The corresponding number needed to harm was 498 per year, compared with a number needed to treat of 155 to prevent a cardiovascular event. The authors noted that the latter number needed to treat is likely underestimated due to the fact that intensive-dose statin therapy has been shown to reduce recurrent cardiovascular events over time, whilst these calculations were based on the first incident cardiovascular event alone. However, in many cases the recording of newly diagnosed diabetes in the participating trials was based on physician adverse event reporting and differing or nonstandard diagnostic criteria, which might suggest the true rate of developing diabetes might also have been underestimated [Sattar *et al.* 2010; Preiss *et al.* 2011]. These two factors – underestimating the full efficacy of statin therapy in preventing cardiovascular events, and potentially underestimating the rate of incident diabetes, must both be taken into consideration when examining these numbers needed to treat and harm respectively.

There is currently no well understood mechanism explaining the slight increased diabetes risk with statin therapy. The meta-analysis of statin therapy *versus* placebo trials suggested that the lowest risk of developing diabetes was seen in the primary prevention trials with low diabetes risk cohorts (Air Force/Texas Coronary Atherosclerosis Prevention Study and West of Scotland Coronary Prevention Study [Downs *et al.* 1998; Shepherd *et al.* 1995] and a higher risk was seen in trials with older patients [Sattar *et al.* 2010]. An analysis

of three separate high-dose atorvastatin trials [Treating to New Targets (TNT), Incremental Decrease in Endpoints through Aggressive Lipid-lowering (IDEAL) and Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)] [Larosa *et al.* 2005; Pedersen *et al.* 2005; Amarenco *et al.* 2006] concluded that the risk of development of diabetes was greater with higher baseline fasting glucose levels, higher triglycerides, higher body mass index, and hypertension, predictors that were consistent across all three trials examined [Waters *et al.* 2011]. This would imply that patients with a greater overall cardiovascular risk also appear to have a higher, albeit small risk of developing diabetes on statin therapy. The type of statin may possibly be a factor, but there is insufficient evidence to evaluate this currently. The meta-analysis of statin therapy *versus* placebo trials identified an independently increased risk of incident diabetes in trials with rosuvastatin compared with the other statins, noting that the overall combined statin trial population result was also significant, and nonsignificant trends towards an increased risk of diabetes were seen across simvastatin trials and the one included atorvastatin trial, although not for pravastatin trials or the single included lovastatin trial [Sattar *et al.* 2010]. The significantly increased risk in the rosuvastatin trials was largely driven by the results of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), which compared rosuvastatin with placebo in patients without established CVD but with an elevated high-sensitivity C-reactive protein [Ridker *et al.* 2008]. In this trial, diabetes was diagnosed solely by physician-based reporting and the authors regarded the finding of an increased diabetes risk largely as hypothesis generating. Statin potency would appear to be a factor, based on the slightly higher rates of diabetes in the ‘more *versus* less’ trial analyses. In addition, a *post hoc* analysis of the SPARCL trial [Amarenco *et al.* 2006] identified increased rates of incident diabetes in patients treated with 80 mg atorvastatin compared with placebo, with a similar absolute event rate to the more *versus* less trial meta-analyses [Waters *et al.* 2011]. Whether the risk of developing diabetes relates more directly to the magnitude of LDL-cholesterol reduction achieved with statin therapy (than the statin dose given) is not yet clear, although baseline total cholesterol and LDL-cholesterol levels do not appear to be related to the risk [Preiss *et al.* 2011; Waters *et al.* 2011].

This suggests a need for future or ongoing statin trials to incorporate the incidence of type 2 diabetes as a defined safety endpoint to help clarify this issue further.

Overall, the net cardiovascular benefit of intensive statin therapy remains clearly demonstrated, whilst acknowledging a call for some vigilance in people without diabetes on statin therapy in awareness of a small excess risk of developing diabetes. The case for statin use among people with diabetes (arguably even among those whose diabetes has been induced by statins) remains compelling [Kearney *et al.* 2008].

Haemorrhagic stroke

The most recent CTT Collaboration meta-analysis noted a comparatively small nonsignificant absolute increase in haemorrhagic stroke with high-dose/statin therapy compared with low-dose/control. It was noted that if these data were combined with the published data from two other statin trials, SPARCL [Amarenco *et al.* 2007] and Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA) [Abraham *et al.* 2006], the increase in haemorrhagic stroke achieved a conventional level of significance (perhaps a few extra haemorrhagic strokes annually per 10,000 patients treated) [Baigent *et al.* 2010]. If true, this would represent a 50 times smaller hazard than the benefits of statin therapy in cardiovascular event and mortality reduction in high-risk patients. A recently published retrospective propensity matched cohort study among 17,872 patients with recent ischaemic stroke initiated on statin therapy found no association between statins and intracranial haemorrhage over a median of 4.2 years (hazard ratio 0.87; 95% confidence interval 0.65–1.17), albeit noting the obvious limitations of this type of analysis [Hackam *et al.* 2012].

Cognitive impairment

There have been some reported associations between statins and cognitive impairment. An FDA review of its adverse events database as well as published literature (predominantly case reports and observational studies) noted post-marketing reports of ill-defined memory loss or impairment which was reversible upon discontinuation of statin therapy. The time course appeared to range from 1 day to years after exposure to statins. There was no association with

fixed or progressive dementia or the statin used. They concluded that there is no suggestion that cognitive changes associated with statin use are common or lead to clinically significant cognitive decline [US FDA, 2012]. The only large body of randomized evidence comes from the Heart Protection Study, in which all surviving subjects underwent a cognitive status questionnaire at closeout Modified Telephone Interview for Cognitive Status (TICS-M). No differences between those allocated simvastatin or placebo were seen in rates of cognitive impairment, dementia or other psychiatric disorders [Heart Protection Study Collaborative Group, 2002].

Cancer risk

The potential relationship between statin use and cancer risk has previously been an issue of contention. The Prospective Study of Statins in the Elderly at Risk (PROSPER) assessing statin use in older people found a 25% increase in new cancer diagnoses [Shepherd *et al.* 2002]. However when incorporated into a broader meta-analysis at the time they found this result lost significance [Shepherd *et al.* 2002]. Moreover, the data from PROSPER constituted one of the sources for the CTT Collaborative meta-analysis in 2005, which found no evidence for an increase in cancer diagnoses or cancer mortality with statin use [Baigent *et al.* 2005]. A 2007 meta-analysis of 23 statin treatment arms including 75,317 statin-allocated patients was performed to identify any relationships between LDL-cholesterol lowering and adverse outcomes [Alsheikh-Ali and Karas, 2007]. Although the authors did not identify an increase in cancer risk relating to the proportional or absolute LDL-cholesterol reduction, they did find a significant inverse relationship between cancer incidence and achieved LDL-cholesterol levels ($R^2 = 0.43$, $p = 0.009$). This study was criticized for not incorporating age into their analysis which may have confounded the association argued [Degoma *et al.* 2008; Rembold and Rembold, 2008]. The same authors subsequently published a regression meta-analysis including control arms of statin treatment trials which found that although there was an inverse association in their data between on-treatment LDL cholesterol and incident cancer, the LDL-cholesterol lowering by statins is not independently associated with an increased risk of cancer [Alsheikh-Ali *et al.* 2008]. The most recent CTC meta-analysis identified no adverse effects on cancer incidence in the more *versus* less intensive

therapy trials, nor in statin *versus* control trials. A strong weight of evidence thus supports the notion that the LDL-lowering effects of statin therapy are not associated with increased cancer incidence or mortality, at least over the same time period as sizable cardiovascular benefits (5–6 years) are reported, and any suggested associations between cancer and low LDL levels probably relates to other mechanisms.

Conclusion

Overall, current evidence supports a directly proportional relationship between the reduction in absolute LDL-cholesterol concentration and the reduction in major vascular events with statin therapy. For each 1 mmol/liter LDL-cholesterol reduction, the risk of occlusive major vascular events is reduced by about 20%, even if LDL-cholesterol concentrations are less than 2 mmol/liter. Whilst US NCEP guidelines suggest an LDL-cholesterol target in high-risk patients of below 2.6 mmol/liter, or optionally of below 1.8 mmol/liter for very high-risk patients [Grundy *et al.* 2004], there is no current convincing evidence to support relaxing therapy if these goals are met. Conversely, there is good evidence to support greater LDL-cholesterol reduction regardless of the achieved level, with expected additional cardiovascular benefits. Clinicians should be mindful of the small risk of myopathy, with comparatively small absolute risks of new diabetes, rhabdomyolysis and possibly of intracranial haemorrhage. However the weight of evidence is strongly in favour of the highest tolerated statin prescription to maximally prevent cardiovascular events, noting that the greatest cardiovascular benefits and relative safety of statin therapy will be seen in those at greatest risk of future cardiovascular events. Aggressive and continued LDL-cholesterol lowering with high-dose statin therapy provides a greater cardiovascular benefit than less intensive dosing regimens, and in most cases should be considered for integration into the routine management of patients with established or very high risk of ischaemic vascular disease.

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Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

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