



The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011

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Atherosclerotic cardiovascular disease is the most important public health problem of our time in both Europe and the rest of the world, accounting for the greatest expenditure in most healthcare budgets. Achieving consistency of clinical care, incorporating new evidence and their synthesis into practical recommendations for clinicians is the task of various guideline committees throughout the world. Any change in a set of guidelines therefore can have far reaching consequences, particularly if they appear to be at variance with the existing guidelines. The present article discusses the recent American College of Cardiology (ACC)/American Heart Association (AHA) guidelines 2013 on the control of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults. When compared with the ESC/EAS guidelines on lipid modification in 2011, the ACC/AHA guidelines of 2013 differ markedly. Specifically, (i) the scope is limited to randomized trials only, which excludes a significant body of data and promotes essentially a statin centric approach only; (ii) the abolition of low-density lipoprotein cholesterol (LDL-C) targets in favour of specific statin regimens that produce a 30–50% reduction in LDL-C we believe will confuse many physicians and miss the opportunity for medication adherence and patient engagement in self-management; (iii) the absence of target LDL-C levels in very high-risk patients with high absolute risk or residual risk factors will discourage clinicians to consider the addition of lipid modification treatments and individualize patient care; (iv) a reduction in the threshold for treatment in primary prevention will result in a greater number of patients being prescribed statin therapy, which is potentially good in young patients with high life time risk, but will result in a very large number of older patients offered therapy; and (v) the mixed pool risk calculator used to assess CVD risk in the guidelines for primary prevention has not been fully evaluated. This article discusses the potential implications of adopting the ACC/AHA guidelines on patient care in Europe and beyond and concludes with the opinion that the ESC/EAS guidelines from 2011 seem to be the most wide ranging, pragmatic and appropriate choice for European countries.

In November 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) published a set of guidelines on the control of blood cholesterol to reduce atherosclerotic cardiovascular disease (ASCVD) risk in adults.¹ Long delays in their publication were unexpected, but the gathering of all available evidence and its synthesis must have taken longer than anticipated.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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However, the quantum shift away from the previous set of guidelines published a decade ago² which provided a comprehensive guide to lipid management, has created controversy and confusion about the relative merits of these new ACC/AHA guidelines when compared with existing guidelines such as the ESC/EAS guidelines for 'the management of dyslipidaemias'³ and the more recent European guidelines on cardiovascular prevention in clinical practice which are in full accordance with the ESC/EAS guidelines.⁴ Whereas some have embraced the new ACC/AHA guidelines as 'a step in the right direction' for reasons of simplifying patient care, others disagree; certainly sweeping endorsements are overly optimistic and warrant greater scrutiny.⁵ Both expert panels acknowledge the important contributions arising from decades of genetic and biochemical studies, observational epidemiological and ecological studies, and *in vitro* and animal experiments that associated higher low-density lipoprotein cholesterol (LDL-C) levels with ASCVD risk. These studies provided the rationale for randomized controlled trials (RCTs), which demonstrated that lowering LDL-C levels reduced ASCVD events. The present article sets out to compare and contrast the ACC/AHA guidelines to those of the ESC/EAS and discusses the potential implications of adopting the ACC/AHA guidelines on patient care in Europe and beyond.

Scope

The first and most important factor to consider is the different remit of each set of guidelines. The ACC and AHA originally listed 18 questions they wanted to address but ultimately only addressed 3 of them. Although not stated explicitly, the ACC and AHA aimed to provide guidance around LDL-C lowering for the prevention of atherosclerotic CVD, and for this purpose the guideline committee evaluated only RCT evidence, thus quite distinct from the traditional comprehensive lipid guidelines. The ACC/AHA approach is rigid in limiting the scope of current evidence on CVD prevention to the inclusion criteria of RCTs. Hence, the ACC/AHA guideline may appear inflexible and narrow in its reach, because it ignores a much wider scientific basis of knowledge that is available on CVD prevention. In contrast, the ESC/EAS guideline has a much broader scope, encompassing all available data, to cover the management of all dyslipidaemias and the use of all lipid modification strategies for the prevention of CVD and is based upon the same principles as all the other ESC guidelines.⁶ For instance the ESC/EAS guidelines provide guidance on elevated triglycerides (TG) including the relevance of identifying and treating secondary causes, recommending pharmacological intervention, if fasting TGs are >2.3 mmol/L, using fibrates, nicotinic acid derivatives, or omega-3 fatty acids. Both the 2011 ESC/EAS and the 2013 ACC/AHA guidelines use overall cardiovascular risk to form the decision about starting lipid-modifying drugs. However, the latter focuses explicitly on statins only, because these are the most widely tested lipid-modifying drugs and have the greatest evidence base for benefit in the prevention of CVD, but this may appear a narrow remit for those who cannot tolerate recommended doses of statins or may be intolerant per se. Both highlight the importance of a comprehensive strategy which includes behavioural and lifestyle risk factor management, as well as involving patients as partners in the management of their CVD risk and point out that these guidelines are designed to help clinicians in their

decision-making and do not substitute for clinical judgement in individual cases.

- Both the 2013 ACC/AHA and 2011 ESC/EAS guidelines conclude that LDL-C is unequivocally a causal factor for ASCVD.
- Both the 2013 ACC/AHA and 2011 ESC/EAS guidelines have systematically evaluated scientific evidence.
- Both the 2013 ACC/AHA and 2011 ESC/EAS guidelines encourage lifestyle modification and the engagement of the patient as a partner in disease prevention.
- The 2011 ESC/EAS guidelines considers all available evidence and not just trials as well as the importance of all lipids and provides practical guidance across a broader range of conditions including ASCVD prevention and dyslipidaemias.
- The 2013 ACC/AHA guidelines consider only randomized trial evidence.

Whom to treat

Both sets of guidelines outline in broad agreement four major patient groups who would benefit from lipid modification therapy (ESC/EAS) or statin therapy (ACC/AHA) as outlined in *Table 1*. These include individuals with established CVD, diabetes mellitus, and familial hypercholesterolaemia. The fourth group contains those individuals not included in the first three, but who after undergoing global risk assessment (based on age, gender, smoking status, systolic blood pressure, total cholesterol and high-density lipoprotein cholesterol; HDL-C) are deemed to be at increased CVD risk. The definition of ASCVD varies between guidelines as the ACC/AHA defines this as acute coronary syndromes, previous myocardial infarction, stable angina, prior coronary or other revascularization, ischaemic stroke or transient ischaemic attack, and atherosclerotic peripheral arterial disease. In contrast, the ESC/EAS include all those mentioned in the ACC/AHA guidelines, but also include any pre-clinical evidence for atherosclerotic disease on the basis of any imaging modality. Importantly, the ACC/AHA guidelines do not include chronic kidney disease (CKD), whereas the ESC/EAS guidelines consider those with CKD (as defined by a GFR <60 mL/min/1.73 m²) as a very high-risk group who require lipid management with a target LDL-C of <1.8 mmol/L or a 50% reduction in LDL-C. The ESC/EAS guidelines also recognize that, while traditional risk factors are the basis of global risk assessment, there may be other factors such as elevated TG, social deprivation, central obesity, elevated lipoprotein (a), subclinical atherosclerosis, or family history of premature CVD which may further modify absolute risk. In contrast, very high HDL-C or family history of longevity may attenuate absolute risk and should form part of the consultation with the patient before deciding on the initiation of lipid-modifying therapy. Furthermore, the two sets of guidelines are also discordant with their level of recommendations for some groups at risk and their interpretation of the level of evidence as well as their recommendations at the extremes of age with the ESC/EAS guidelines generally being less prescriptive (*Table 2*).

The policy change that will have the largest impact on the health-care system is the ACC/AHA statement that statin treatment is recommended for primary prevention in individuals with a 10-year ASCVD risk of 7.5% or higher when compared with previous

Table 1 Comparison of individuals who should be targeted for lipid modification

ACC/AHA (2013) Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults		ESC/EAS (2011) Guidelines for the management of dyslipidaemias	
Clinical risk categories	Treatment	Clinical risk categories	Treatment
Those with clinical ASCVD	High-intensity <i>statin therapy</i> . If 50% reduction is not reached drug combination may be considered	Those with CVD	LDL-C <1.8 mmol/L or 50% reduction in LDL-C
Diabetes mellitus (Type I or Type II) without ASCVD but with LDL-C between 1.8 and 4.9 mmol/L	Diabetes with high risk:High-intensity <i>statin therapy</i> . Diabetes with low risk:Moderate-intensity <i>statin therapy</i>	Diabetes mellitus (Type II) or Type I with target organ damage	LDL-C <1.8 mmol/L or 50% reduction in LDL-C
Those with primary elevation of LDL-cholesterol (LDL-C) >4.9 mmol/L	High-intensity <i>statin therapy</i> , aimed at achieving at least 50% reduction of LDL-C	Familial dyslipidaemia (FH or FCH or chylomicronaemia)	LDL-C <2.5 mmol/L or maximal reduction in LDL-C with any possible drug combination plus LDL apheresis
If none of the above but with estimated 10-year ASCVD risk of 7.5% or more using a pooled populations risk calculator If risk-based assessment treatment decision uncertain assessment of 1 or more of family history, hs-C-reactive protein, CAC Score or ABPI may be considered (Class IIb, Level E), contribution of ApoB, CKD, microalbuminuria or cardio-respiratory fitness is uncertain (Level N) and CIMT is not recommended for routine assessment of individual patients (Level N)	Moderate-to-high-intensity <i>statin therapy</i> if ASCVD risk >7.5%. If risk 5–7.5% risk of CVD event: Reasonable to consider moderate-intensity <i>statin therapy</i>	If none of the above estimate 10 year risk of a first fatal atherosclerotic CV event (SCORE), with a SCORE >10% considered, very high risk, SCORE 5–10% considered high risk and SCORE 1–5% moderate risk Above risk can be modified if additional information is available on: ↑ TGs, social deprivation, central obesity, ↑ Lipoprotein(a), familial hypercholesterolaemia, subclinical atherosclerosis, CKD, family history of pre-mature CVD (× 1.7 – women, × 2 – men), very high HDL-C, family history of longevity	Very high risk LDL-C <1.8 mmol/L or 50% reduction in LDL-C, high-risk LDL-C <2.5 mmol/L, moderate risk LDL-C <3.0 mmol/L

recommendations that considered a substantially higher threshold for 10-year risk of fatal and non-fatal coronary heart disease (CHD).⁷ The ACC/AHA 10-year threshold of 7.5% corresponds to a 2.5% risk for CVD death over 10 years in the SCORE model. In SCORE, those with a 10-year risk of fatal CVD of 2.5% are considered at moderate risk, and the ESC/EAS recommendation is that an LDL-C of <3 mmol/L is achieved. Thus, while the ESC/EAS guidelines allows some scope by virtue of an LDL-C goal for lifestyle before medication are added, patients are more likely to receive medications under the new ACC/AHA guidelines. The consequence will be a greater expenditure to the public health budget.

Furthermore, the new ACC/AHA guidelines made specific recommendations about statin intensity, specifically high dose in order to achieve at least a 50% LDL-C reduction and moderate doses to achieve a 30–50% LDL-C reduction, depending upon absolute risk. Also they recommend that those with a predicted risk >7.5% be considered for moderate or high-intensity statin. Similarly, as more people are treated with moderate to high-intensity statins, there will be a greater number of individuals who complain of side-effects and/or who will be referred to specialist clinics for 'statin intolerance'. In some clinics, this 'statin intolerance' already makes up a substantial part of the referral base. While the evidence base for statins across a

range of clinical circumstances is unequivocal, the practical consequences of extending their use to an even wider group of individuals merit consideration.

One important benefit of lowering the threshold for statin initiation in the primary prevention setting is that some of the vagaries among young people with low short-term CVD risk but high-lifetime risk are attenuated. This means, that some younger individuals with a high-lifetime risk will be initiated on statins earlier and are therefore likely to have a greater impact on the disease process. The flip side to this argument is that practically all older individuals (>70 years) who because of the impact of age on 10-year ASCVD risk, will now be offered moderate- to high-intensity statins. As co-morbidities and tolerability of these agents together with poly-pharmacy becomes more of an issue in this age group, the potential for harm is much greater (see Table 4, ACC/AHA guidelines). A logical and sensible alternative is the concept of age-related risk or lifetime risk. However, the guideline committee considered that there was lack of data on lifetime CVD risk, on long-term (i.e. >15 years) follow-up of treatments tested in RCTs, on long-term safety of statins, and on the effects of treatment initiation before the age of 40. Statins are the most widely prescribed class of drugs since the late eighties, so the statement that we lack 'long-term safety' is unrealistic at best. Despite that, however, the committee

Table 2 Gradation of evidence base

ACC/AHA Guidelines	ESC/EAS Guidelines
<p>High-intensity statin for men and women <75 with clinical ASCVD unless contra-indicated (Class I, Level A) If high-intensity statin contra-indicated or risk of statin adverse events then use moderate-intensity statin (Class I, Level A)</p> <p>If clinical ASCVD and aged >75 evaluate benefits and risks of moderate or high-intensity statin treatment. Reasonable to continue statin treatment started before age 75 (Class IIa, Level E)</p> <p>If LDL-C >4.9 mmol/L or TGs >5.68 mmol/L evaluate for secondary causes of dyslipidaemia (Class I, Level B)</p> <p>If aged >21 and LDL-C >4.9 mmol/L treat with high-intensity statin unless contra-indicated when use moderate-intensity statin (Class I, Level B)</p> <p>If aged >21 and untreated primary LDL-C >4.9 mmol/L it is reasonable to intensify statin treatment to achieve \geq 50% \downarrow LDL-C (Class IIa, Level E)</p> <p>If aged >21 and untreated LDL-C >4.9 mmol/L addition of a non-statin cholesterol reducing drug may be considered after maximal intensity statin treatment achieved, to further lower LDL-C. Evaluate risks and benefits (Class IIb, Level E)</p> <p>Moderate-intensity statin treatment is recommended for all with Type I or Type II diabetes mellitus aged between 40 and 75 (Class I, Level A)</p> <p>High-intensity statin treatment is reasonable if aged 40–75, Type I or Type II diabetes mellitus and 10-year ASCVD risk >7.5% (Class IIa, Level E)</p> <p>In adults with Type I or Type II diabetes mellitus aged <40 or >75 it is reasonable to consider the benefits and risks of statin treatment (Class IIa, Level E)</p> <p>Use pooled cohort equations to estimate 10 year ASCVD risk (Class I, Level E)</p> <p>If 10 year ASCVD risk >7.5% and aged 40–75 treat with moderate-to-high-intensity statin (Class I, Level A)</p> <p>If 10 year ASCVD risk between 5–7.5% and aged 40–75 it is reasonable to offer moderate-intensity statin treatment (Class IIa, Level C)</p> <p>Decisions about treatment should be discussed with the patient (Class IIa, Level E)</p> <p>In those who would not otherwise qualify for statin treatment it is reasonable to consider additional risk factors: evidence of genetic dyslipidaemia, family history of pre-mature CVD (<55, first degree males, <65, first degree females), hs-C-reactive protein >2, CAC >300 or >75th percentile, ABPI <0.9, \uparrow lifetime risk. (IIb, E)</p>	<p>Those with known CVD, type 2 diabetes or type 1 diabetes with target organ damage, moderate-to-severe CKD or a score level >10% the LDL goal is <1.8 mmol/L or a 50% reduction (Class I, Level A)</p> <p>In patients at high-CVD risk defined by markedly elevated single risk factors (FH or hypertension), or a SCORE level of 5–10%, an LDL-C target of <2.5 mmol/L (Class IIa, Level A)</p> <p>In patients at moderate CVD risk defined by a SCORE level of 1–5%, an LDL-C target of <3.0 mmol/L (Class IIa, Level C)</p> <p>LDL-C is recommended as a target for treatment (Class I, Level A)</p> <p>Total cholesterol to be considered as target if LDL-C not available (Class IIa, Level A)</p> <p>TGs should be measured during treatment if initially high (Class IIa, Level B)</p> <p>Non-HDL-C to be considered as 2^o target in DM, MetS (Class IIa, Level B)</p> <p>Apo B to be considered as 2^o target (Class IIa, Level B)</p> <p>HDL-C not recommended as a target of treatment (Class III, Level C)</p> <p>ApoB/ApoA1 and non-HDL-C/HDL-C not recommended as targets (Class III, Level C)</p>

recommends that it is reasonable to assess ASCVD risk factors every 4–6 years from ages 20 to 79, and to estimate 10-year ASCVD risk every 4–6 years from ages 40 to 79 (Level B).

- Both the 2013 ACC/AHA and 2011 ESC/EAS guidelines clearly identify four patient groups at the greatest risk of ASCVD. Specifically those with established ASCVD, diabetes mellitus, FH and a high predicted CVD risk based on global risk assessment.
- The 2011 ESC/EAS guidelines extend the scope of the definition of ASCVD to include findings from imaging and not simply a clinical presentation thereby including patients at an earlier stage of disease.
- The 2011 ESC/EAS guidelines are less prescriptive and allow incorporation of a wider body of evidence which might help reclassify intermediate risk patients to high risk including blood-based measurements and imaging, social deprivation in contrast to a much more narrow and prescriptive set of factors considered in the 2013 ACC/AHA guidelines.
- The 2011 ESC/EAS guidelines include CKD as a very high-risk group, whereas the 2013 ACC/AHA guidelines do not provide guidance for CKD.
- The 2013 ACC/AHA primary prevention threshold for treatment is 7.5% over 10 years with advice on offering moderate-to-high-intensity statin treatment to achieve a 30–50% lowering of LDL-C. This corresponds to a SCORE risk of 2.5% for fatal CVD over 10 years and an LDL-C target of 3 mmol/L.
- The 2013 ACC/AHA primary prevention threshold if applied will result in many more patients receiving statins and in many cases higher doses than currently used in Europe.

What to treat

The ESC/EAS guidelines place considerable weight to the measurement of LDL-C to determine future CVD risk. For instance, when assessing if treatment is warranted in primary prevention the ESC/EAS provide an algorithm which combines SCORE risk with measured LDL-C levels. This is of advantage as for non-specialists it highlights the importance of screening for genetically elevated LDL-C levels.⁸ This would identify an individual for pharmacological intervention who has SCORE risk < 1% (as LDL-C is not included in SCORE) but in whom LDL-C is > 4.9 mmol/L. Additionally, LDL-C measurement is recommended for CVD risk assessment among those with established CVD, hypertension, smoking, type 2 diabetes, obesity, family history of pre-mature CVD or familial hypercholesterolaemia, CKD, or chronic inflammatory disease (all class I, level of evidence C), as well as men > 40 years and women > 50 years (class IIb, level of evidence C). This is at variance with the new ACC/AHA guidelines where LDL-C measurement should not necessarily be sought, if absolute risk is high enough to warrant statin therapy, but if found in individuals with an LDL-C > 4.9 mmol/L, then it identifies a high-risk group for statin therapy. Implicitly, the effect of adoption of the ESC/EAS guidelines will allow many more cases of undiagnosed familial hypercholesterolaemia to be identified which are much more common than the 1:500 than is generally perceived.⁸

With respect to treatment, the aim of both guidelines is to use statins to lower LDL-C. It is here that the first quantum shift occurs because the new ACC/AHA guidelines discard the use of lipid

targets to guide physicians and patients, citing an absence of RCT data that have used such a strategy. Therefore, the ACC/AHA guidelines recommend only high- or moderate-intensity statin therapy for patients at high risk of ASCVD. The available evidence on potential goals or targets is clearly interpreted differently as highlighted in *Table 2*. While the ACC/AHA guidelines treat risk alone, the ESC/EAS guidelines treat risk, create a greater understanding of the role of LDL-C in CVD risk assessment, and use LDL-C monitoring for measuring therapeutic efficacy and patient compliance. Furthermore, the ESC/EAS guidelines have recognized the wealth of emerging evidence on the role of other lipid fractions such as TG-rich lipoproteins, remnants, and conditions associated with low HDL-C where LDL-C may not be as informative as non-HDL-C or apolipoprotein B (apoB), but for which there are clear data (Class IIa, Level B).^{3,9,10} This subtle difference between the two guidelines where the ACC/AHA has a 'fire and forget' approach has large-scale implications for our patients.

The ESC/EAS guidelines allow us to individualize patient care by potentially assessing other more appropriate factors driving lipid-mediated so-called 'residual risk' (*Table 2*). For instance among patients with diabetes and low HDL-C, it is not uncommon to see an LDL-C level < 1.8 mmol/L, but their non-HDL-C can be as high as 3.0 mmol/L thus above the 2.6 mmol/L target. In such situations which become more common with the growing population of patients with diabetes or the metabolic syndrome, the ESC/EAS guideline allows greater flexibility to tailor individual care by using additional therapies to lower the non-HDL-C or apoB. In the ACC/AHA guidelines, those patients would not be considered for treatment optimization, but left to a trial-based regimen of high-intensity statin with no additional consideration to residual risk.

- Both guidelines seek to lower LDL-C with statin therapy as their principal aim.
- The 2013 ACC/AHA guidelines offer guidance only on treating those at risk of ASCVD.
- The 2013 ACC/AHA guidelines do not consider emerging data on the use of lipid fractions other than LDL-C as being informative.
- The 2011 ESC/EAS guidelines treat CVD risk, create a greater understanding of the role of LDL-C in CVD risk assessment, and use LDL-C monitoring for measuring therapeutic efficacy and patient compliance.
- The 2011 ESC/EAS guidelines provide much broader pragmatic clinical advice on the utility of other lipid fractions such as TG-rich lipoproteins, remnants, and conditions associated with low HDL-C where non-HDL-C or apolipoprotein B is more informative

How to treat

The ACC/AHA guidelines essentially recommend either high-intensity or moderate-intensity statin treatment. High-intensity statin treatment is defined as those regimens which reduce LDL-C by ~50%. Of note, while atorvastatin 40, 80mg and rosuvastatin 20mg are endorsed as RCT outcomes tested high intensity statins, rosuvastatin 40mg is not, even though it is Food and Drug Administration (FDA) approved.

Moderate-intensity statin treatment (assessed in outcomes studies) is defined as regimens which reduce LDL-C by 30–50% (atorvastatin 10 mg, simvastatin 20 or 40 mg, pravastatin 40 mg, fluvastatin 40 mg bd, rosuvastatin 10 mg), again note that atorvastatin 20 mg and rosuvastatin 5 are not included as those doses were not used in outcomes studies but are FDA approved doses. They suggest that physicians consider CVD risk reduction with either high (to achieve at least a 50% LDL-C reduction) or moderate-intensity statin regimens (to achieve a 30–50% reduction in LDL-C) against the risk of adverse events such as new-onset diabetes (0.1/100 patient years with moderate-intensity and 0.3/100 patient years with high-intensity statin), myopathy, and haemorrhagic stroke.

In these ACC/AHA recommendations, there is no mandated requirement to measure LDL-C levels or to attain a specific LDL-C goal as the recommendations draw on dosage of statin rather than specific LDL-C level attainment. However, they suggest that in high-risk patients, therapy could be intensified, if 50% reduction in LDL-C is not achieved (50% being the proxy for response to high-intensity statins among adherent patients) at the doctor's discretion. The 50% reduction does not seem to have a hard RCT evidence base which was claimed to be the sole criterion of the ACC/AHA guidelines. This is a marked divergence from existing ATP-III guidelines and other international guidelines which all recommend specific LDL-C goals. The remaining role of LDL-C measurements seems to be for monitoring adherence to lifestyle and medication, suggesting a fasting lipid panel at 4–12 weeks and every 3–12 months thereafter. This seems a futile exercise, if the physician is not advised to consider residual risk or a specific target. The maximum tolerated intensity of statin therapy should be used where high- or moderate-intensity statin therapy is recommended but not tolerated. Furthermore, a potentially significant 'real-world' problem of the recommendations regarding % reductions as treatment objectives instead of an on treatment LDL-C target is that the baseline LDL-C may not be known when the patient is already taking a low-dose statin. Hence % reductions may be quite complicated in settings such as primary care and quite simply be unfeasible.

Another surprise in the ACC/AHA guidelines is the notion that physicians should consider decreasing the statin dose if LDL-C <1.03 mmol/L on two occasions. This contradicts the genetic lifetime data on safety and the observational data from RCTs^{11,12} and does not seem to have an RCT evidence base, which is the scope of the new guidelines.

The ACC/AHA guidelines abandon the use of lipid targets on the grounds of lack of RCT evidence particularly if not titrated. While the ACC/AHA guidelines clearly acknowledge LDL-C as a causal factor for CHD and ASCVD, it is surprising not to consider it a treatment target. Furthermore, building guidelines around just RCT evidence runs the risk of ignoring a much broader evidence base which was used in the EAS/ESC dyslipidaemia management guidelines and the European guidelines on cardiovascular prevention in clinical practice.^{13,14} It can be argued that treatment targets are arbitrary and often based on extrapolations from the available data, but they are also based on an evaluation of a larger pool of knowledge. They are widely used in different other guidelines and clinical settings, such as for blood pressure or blood glucose, which are also not always based only upon RCT.

Targets are important in physicians' everyday practice, particularly considering doctor–patient communication, but also to help

optimizing the patients' compliance. Arguably, the greatest opportunity to improve LDL-C lowering is to support medication adherence, which has been shown to be significantly reduced using a 'fire and forget' approach. In the 'real-world', the issue of adherence is by far the most important issue as approximately up to one-third of statin medications are discontinued. The problem of the 'fire and forget' strategy is not the 'fire' but the 'forget'. Guidelines are not produced only for specialists but for a much broader audience, primarily for general practitioners who are overwhelmed by a plethora of guidelines for different diseases so they demand clear, simple messages, and user-friendly recommendations, and they definitely favour target values. Few will deny that LDL-C is the main driver of ASCVD risk, and that reaching lower LDL-C levels will result in lower risk of ASCVD. However, the efficacy of a targeting strategy has not been tested because it requires a long-term RCT that is too expensive to be funded by independent organizations.

Lack of RCT evidence for efficacy is not the same as RCT evidence for lack of efficacy. The major impact of the use of an LDL-C goal is that it gives non-specialists a broad outline of absolute risk and in whom treatment should be optimized. This has led to policy changes in countries like the UK where general practitioners are paid to reach specific LDL-C targets in >80% of their target population. LDL-C goals not only allow the physician freedom to consider additional therapies like bile acid absorption inhibitors and ezetimibe, and target those additional therapies with a specific aim in mind, but also are important to convey to the patient what is acceptable and what is not.

In this regard the ESC/EAS guidelines offer clear goals such as a 50% reduction from baseline LDL-C level is suggested as a goal in those at very high total risk if the LDL-C target of <1.8 mmol/L could not be achieved. There are differential LDL-C targets such as a level <2.5 mmol/L for high risk and <3.0 mmol/L for those at moderate risk. This allows greater flexibility, targets the most powerful treatments for those at greatest risk and allows the option to occasionally use cheaper lower potency statin regimens for those in whom absolute risk is lower. The later may be especially important in countries where higher-intensity regimens may not be financially viable. Moreover, reality dictates that across the European continent, only a few per cent atorvastatin prescriptions are filled out for the atorvastatin 80 mg dose, clearly demonstrating the lack of enthusiasm for the higher dose of this potent statin, even in the face of its wide evidence base.

- The 2013 ACC/AHA guidelines have a fire and forget approach without the need for lipid monitoring to assess compliance or efficacy of treatment.
- The 2013 ACC/AHA guidelines principally use statin doses used in trials and push for the achievement of a 50% reduction in LDL-C using high-intensity statins (atorvastatin 40/80 mg or rosuvastatin 20 mg).
- The 2013 ACC/AHA guidelines are ambiguous about the role of additional lipid-lowering therapies among those with high residual absolute risk despite achievement of a 50% reduction in LDL-C.
- The 2011 ESC/EAS guidelines categorize people in moderate, and very high CVD risk with guidance on specific LDL-C targets for each level of absolute risk.
- The 2011 ESC/EAS guidelines recommend LDL-C and other lipid measures for monitoring efficacy, compliance, assessing residual

risk and allow a greater scope for modifying individual patient care by considering additional therapies if clinically warranted.

Risk assessment tools in primary prevention

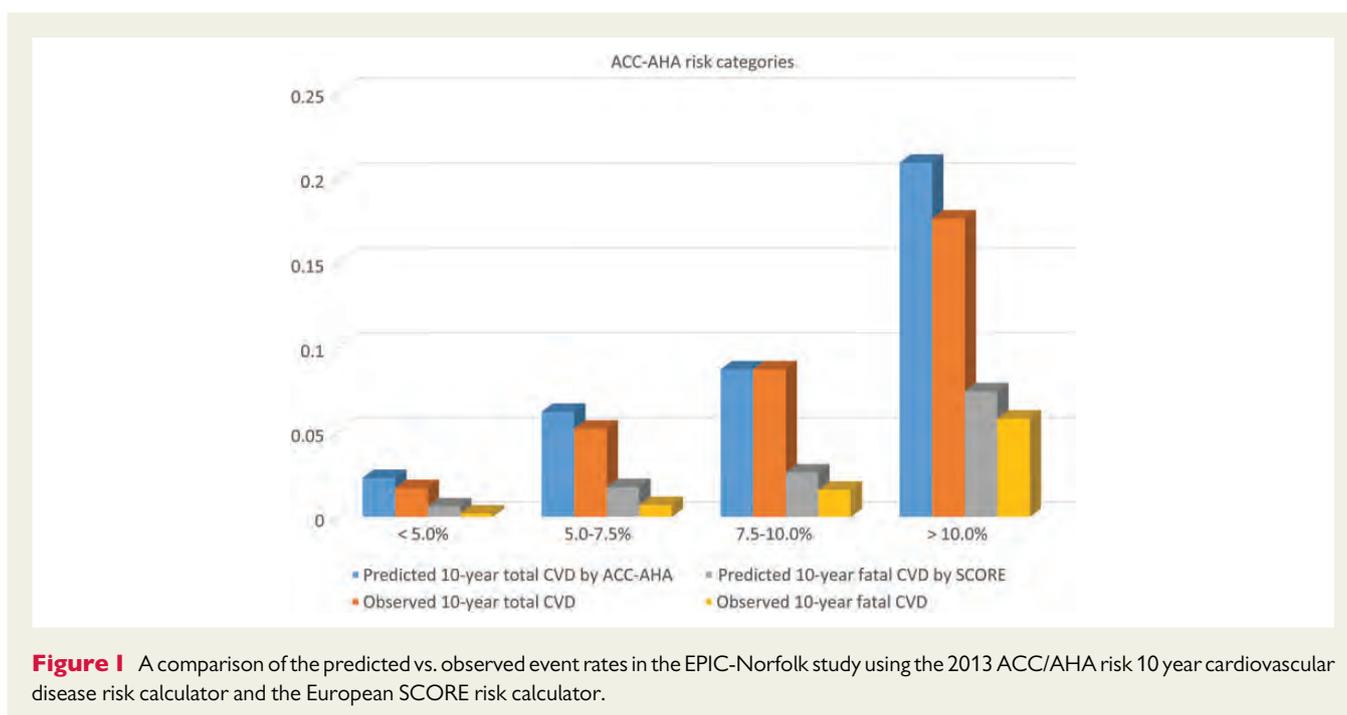
One of greatest challenges that we face in primary prevention is risk prediction, i.e. to correctly identify those individuals at risk of incident CVD. Inaccurate risk prediction will result in denying potentially beneficial treatment to high-risk individuals, as well as over-treatment of low-risk individuals thus exposing them to the unnecessary risk of side-effects and higher healthcare costs. Risk prediction tools are unlikely to be completely generalizable throughout the world as populations vary in their genetic background and more importantly their lifestyle and hence environmental exposure. Cardiovascular disease as a complex disease involving the interplay of multiple genes and multiple risk factors therefore probably requires region-specific tools.

In Europe, the SCORE charts have been validated in numerous populations in high-risk and low-risk European countries and found to perform well. The ACC/AHA guidelines rightfully seek to improve risk prediction models based on more contemporary data than the previously recommended Framingham risk score. The current recommendation (Table 2) is to use race and sex-specific pooled cohort equations for non-Hispanic African Americans and non-Hispanic Whites aged between 40 and 79. Use of the sex-specific Pooled Cohort Equations for non-Hispanic Whites may be considered when estimating risk in patients from populations other than African Americans and non-Hispanic Whites.¹⁵ The guidelines go on to state that, if after such an assessment the treatment decision remains uncertain (and here one assumes close to but just below the threshold for treatment) then assessment of one or more additional factors may be considered. These include a

family history, hs-C-reactive protein, coronary artery calcium score or ankle brachial pressure index. However, the guidelines state that, the contribution of apoB, CKD, microalbuminuria, or cardio-respiratory fitness is uncertain and CIMT is not recommended for routine assessment of individual patients.

Given the increasing ethnic diversity and the lack of data in general in younger individuals and especially women, it is unclear how this risk equation will perform in traditionally under-represented populations. Another problem might be that since RCTs have not randomized individuals based on risk levels and no RCTs exists providing evidence on a possible threshold at which one has to be prepared to intervene with lifestyle and/or drug therapy. Also the vast majority of individuals over age 60 have much more than 10 years of life expectancy and using the ACC/AHA guidelines risk calculator one cannot get the lifetime risk once you reach age 60.

To assess the potential impact of the new mixed pooled cohort equations, we explored the EPIC-Norfolk prospective population study. In a population of 21 772 individuals, 4917 had an established indications for statin therapy based on prevalent CVD, LDL-C >4.91 mmol/L, or diabetes mellitus. In addition, 7841 (44.2%) would be offered statin therapy based on an estimated ASCVD risk >7.5%. This number would increase to 9877 (55.6%), if the 5–7.5% 'reasonable category' is included. Thus, the new ACC/AHA guidelines could result in a staggering 65% of the general adult population becoming eligible for statin therapy. Furthermore, it has been suggested that the new mixed pooled cohort equations would result in considerable overestimation of ASCVD risk, as shown in validation cohorts.⁵ In contrast, in EPIC-Norfolk, these new risk equations performed reasonably well, with only mild overestimation of total ASCVD risk in most categories. However, the magnitude of overestimation was similar for instance to that observed for the SCORE algorithm predicting CVD mortality, therefore there would seem to be no major advantage of this new ACC/AHA algorithm over and above SCORE. (Figure 1).



- The SCORE risk algorithm works well in Europe.
- The ACC/AHA mixed pooled cohorts equation when assessed in the EPIC-Norfolk European cohort offered no meaningful advantage over SCORE hence there appears to be no need to move away from SCORE in Europe.
- The ACC/AHA mixed pooled cohorts equation did not work well in three North American populations overestimating risk and requires much greater scrutiny before use.

Applicability of the ACC/AHA guidelines in the rest of the world

Beyond simple comparisons between American and European guidelines for the management of dyslipidaemia, it should also be recognized that this controversy has potential implications for the clinical management of patients worldwide. Atherosclerotic cardiovascular disease is the leading global cause of mortality and as a result, approaches to reducing vascular risk have become a public health challenge worldwide. This is reflected in observations that measures of atherogenic lipid states strongly associate with vascular risk in global studies.¹⁶

In recent years, a number of countries have updated their own national guidelines for management of dyslipidaemia for cardiovascular risk reduction. In Australia, these guidelines adopt a more traditional target-based approach highlighting the need to achieve aggressive lipid control for the management of high-risk patients, defined as established cardiovascular disease, diabetes, familial hypercholesterolaemia or CKD. These guidelines include targets of LDL-C <1.8 mmol/L, HDL-C >1.0 mmol/L, TGs <2.0 mmol/L, and non-HDL-C <2.5 mmol/L.¹⁷ Of interest, the inclusion of targets for HDL-C and TG further illustrates evidence beyond that derived from the RCT setting. In the primary prevention setting, in individuals without diabetes, moderate-to-severe CKD, familial hypercholesterolaemia or severe uncontrolled hypertension, the Framingham risk score continues to be used to stratify patients for the use of aggressive risk reduction strategies. The presence of a 5-year Framingham risk >15% or 10–15% in the setting of persistent hypertension (BP >160/100 mmHg), family history of pre-mature CVD or specific populations where Framingham scores typically underestimate risk (Aboriginal and Torres Strait Islander people, South Asian, Maori and Pacific Islander, Middle Eastern), warrants use of lipid-lowering therapy to achieve a LDL-C <2.0 mmol/L.¹⁸ Accordingly, these guidelines reflect ongoing treatment targets, inclusion of information beyond RCTs and permit flexibility of the use of the Framingham score, according to additional risk factors and specific populations. Furthermore, the ACC/AHA recommendations on high-intensity statins may not be feasible in some ethnic groups. For instance, among the Chinese a higher incidence of myopathy has been noted already at much lower statin doses in studies such as HPS THRIVE. Furthermore, among countries such as Japan where the starting dose of atorvastatin is 5 mg and rosuvastatin 1 mg there is already a reluctance to use much more than moderate doses of statins as a top dose.

In a similar fashion, the updated Canadian guidelines continue to be based on a Framingham risk score approach to triage of patients to use of intensive risk factor modification strategies.¹⁹ Patients

determined to be of intermediate risk by Framingham are encouraged to undergo additional testing to enhance risk stratification. Particular emphasis is based on the underestimation of risk by the Framingham score in specific populations. Patients determined to be at high risk are also treated according to a traditional cholesterol based target (LDL-C <2.0 mmol/L) or the demonstration of at least a 50% reduction in LDL-C with therapy.

However, with increasing recognition of the global prevalence of cardiovascular disease, the greatest uncertainty with recent guideline changes may be observed in many regions who do not have their own treatment guidelines. Rather, physicians in many of these countries traditionally follow guidelines in the USA. Therefore, the uncertainty that has been raised following the release of the recent ACC/AHA guidelines may promote particular confusion in these regions. This suggests that the time has come to produce globally relevant treatment guidelines for the reduction in cardiovascular risk that incorporates elements specific to different populations in determining their risk.

- Most world guidelines including those in Asia, Australia, and Canada provide some form of lipid targets for monitoring the response to lipid modification therapy and patient compliance.
- Most world guidelines (similar to ESC/EAS 2011) consider evidence beyond clinical trials to provide a practical and more comprehensive clinical management base for a wider group of patients.
- The ACC/AHA mixed pooled cohorts equation is unsuitable for most parts of the world as these populations were not included. These include south east Asia, the Indian subcontinent, Pacific islanders including Maori and Australian aboriginals.
- The reduction in the primary prevention threshold from 20 to 7.5% will result in a significantly greater number of patients offered statin therapy and in many cases higher doses. In some regions of the world, this will be simply unaffordable and among some ethnic groups will lead to a greater number of side-effects being observed.
- The 2013 ACC/AHA guidelines are impractical in the Asia-Pacific region.

In summary, the new ACC/AHA guidelines differ quite considerably from their predecessor and the ESC/EAS guidelines as well as those in other geographical regions by discarding targets. This approach appears unhelpful for family physicians. Furthermore, considering only RCT data seems too narrow an approach as it provides no clear guidance in many grey areas of prevention. Fortunately, the lowering of the primary prevention threshold will usefully offer those who are younger with high absolute lifetime risk earlier treatment, but may lead to over-treatment of older patients, because of the overemphasis on age. The ACC/AHA will if generally adopted, result in an increase in the number of patients treated, potentially at considerable cost. The new pooled mixed cohorts equation used to assess ASCVD risk requires more careful evaluation as already suggested by independent evaluation in three population based cohorts as well as in our own EPIC-Norfolk assessment.⁵ Currently therefore, the ESC/EAS guidelines from 2011 seem to be the most wide ranging, pragmatic, and appropriate option for European countries and beyond.

- The 2011 ESC/EAS guidelines for lipid modification appear to be the most appropriate for European countries.
- The 2013 ACC/AHA guidelines will result in a much larger proportion of patients being treated with statins and especially at higher doses.
- The new pooled mixed cohorts equation used for risk prediction in primary prevention requires further evaluation.

Conflict of interest: K.K.R. reports to having received honoraria for advisory boards or lectures from Agerion, Abbott, Pfizer, AZ, Sanofi, Regeneron, Amgen, MSD, Roche, Kowa, Novartis, Novo Nordisk, Daiichi, Bayer, Lilly. J.J.P.K. is a consultant to and has received honoraria from Dezima Pharmaceuticals, Eli Lilly, Sanofi, MSD, Omthera, The Medicines Company, Amgen, CSL Behring AstraZeneca, Aegerion, Genzyme, Vascular Biogenics Ltd, Isis Pharmaceuticals, Boehringer Ingelheim, Catabasis, Atheronova, Servier, UniQure, Cerenis, Esperion, Novartis, Kowa, Vivus. S.M.B. reports to having received honoraria from Pfizer for consultancy/ advisory meetings. S.J.N. declares having received research support from AstraZeneca, Eli Lilly, Roche, Novartis, LipoScience, Resverlogix, Anthera, and InfraReDx and has served as a consultant for AstraZeneca, Pfizer, Merck, Takeda, Roche, CSL Behring, Boehringer Ingelheim, Omthera, Atheronova and Eli Lilly. K.T.K. reports no conflict of interest. C.M.B. declares having received grant/research support (paid to institution, not individual) from Abbott, Amarin, Amgen, Eli Lilly, GlaxoSmithKline, Genentech, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi-Synthelabo, NIH, AHA, and has served as consultant-Abbott, Aegerion, Amarin, Amgen, Arena, Cerenis, Esperion, Genentech, Genzyme, Kowa, Merck, Novartis, Pfizer, Resverlogix, Regeneron, Roche, Sanofi-Synthelabo. Speakers Bureau-Abbott. A.L.C. reports to having received honoraria for advisory boards or lectures from Agerion, Pfizer, AstraZeneca, Sanofi, Regeneron, Amgen, MSD, Roche, Kowa, Novartis, Lilly. Ž.R. reports to having received honoraria for advisory boards or lectures from Abbott, AZ, Sanofi. T.F.L. reports that he has received honoraria and research grants from AstraZeneca, Roche, MERCK and Pfizer. The authors state the views expressed are their own based upon their knowledge and clinical experience. A.L.C. is president of the EAS and states that the views expressed are his own.

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