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REVIEW ARTICLE

Current Treatment of Dyslipidemia: A New Paradigm for Statin Drug Use and the Need for Additional Therapies

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Abstract Coronary heart disease (CHD) is the leading cause of death in most countries, with the high prevalence currently driven by dual epidemics of obesity and diabetes. Statin drugs, the most effective, evidence-based agents to prevent and treat this disease, have a central role in management and are advised in all published guidelines. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol and assessment guidelines ('new ACC/AHA guidelines') emphasized global cardiovascular (CV) risk reduction as opposed to targeting low-density lipoprotein-cholesterol (LDL-C) levels, stressed the use of statins in two dose intensities, utilized a new risk calculator using pooled cohort equations, and lowered the risk cutoff for initiation of statin therapy. Although there were major strengths of the new ACC/AHA guidelines, substantial controversy followed their release, particulars of which are discussed in this review. They were generally regarded as improvements in an ongoing transition using evidenced-based data for maximum patient benefit. Several guidelines, other than the ACC/AHA guidelines, currently provide practitioners with choices, some depending on practice locations. Cholesterol control with statin drugs is used in all paradigms. However, some patients respond inadequately, approximately 15 % are intolerant, and other factors prevent attaining cholesterol goals in as many as 40 % of patients. Even after treatment, substantial residual risk for ongoing major events remains. Another readily available modality that can rival statin drugs in effectiveness is vast improvement in diet and lifestyle within the general population; however, despite great effort, existing programs to implement such changes have failed. Hence, despite unrivaled success, there is great need for additional drugs to prevent and treat CHD, whether as monotherapy or in combination with statin drugs. New American guidelines do not discuss or recommend any nonstatin drugs for CHD, and the US FDA has moved away from approving drugs based solely on changes in surrogates in the absence of clinical outcomes trials. Both have significantly altered the realities of developing pharmacotherapies and cardiology practice.

Key Points

LDL-C remains the most important target in therapy for dyslipidemia, although non-HDL-C offers advantages.

Statin drugs remain drugs of choice to lower cardiovascular risk, although considerable residual risk remains after goals are attained.

Adverse drug effects, statin intolerance and variability in statin responsiveness have received much recent attention.

Newer lipid-lowering agents now offer a greater spectrum of clinical therapies to complement use of statin drugs.

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Medicine is a science of uncertainty and an art of probability.—Sir William Osler

1 Introduction

Atherosclerosis is a lifelong inflammatory disease of the inner arterial wall in which cholesterol plays a pivotal, causative role. Coronary heart disease (CHD) refers to the process when it involves epicardial coronary arteries, and is the largest contributor to the broader category, cardiovascular disease (CVD). Although present in ancient man, perhaps even in early Homo sapiens after their appearance some 200,000 years ago, vascular calcification and genetic predisposition to CHD has been found in the Tyrolean Iceman, approximately 5300 years old [1], and in mummies from Egypt, Peru, the Aleutian Islands, Europe, and other locations. Less appreciated is the presence of atherosclerosis in buffaloes, cows, hippopotamuses, pigs, and even birds. The disease may occur in vegetarians as well as in carnivores, but is far more frequent in the latter. However, it is only recently that CHD has reached epidemic proportions, a result of complex environmental influences interacting with our Paleolithic genes and modern habits. Contemporary hunter–gatherer societies, as did our distant forebears, have virtually no clinical CVD; their high inflammatory burden is postulated to contribute to the development of CHD, when it does (did) occur.

CHD begins in infancy, if not before birth, and develops during a long incubation period extending throughout childhood into adulthood, during which time subclinical disease may be detected using biochemical markers, imaging, or pathological examination. Often surprisingly, active and advanced disease may be present in the young, an extensive disease burden marked by numerous vulnerable plaques that lead to complications, such as acute coronary syndrome (ACS), myocardial infarction (MI), and stroke. The decades that pass before clinical manifestations emerge represent a missed opportunity for treatment, before the prognosis worsens irreversibly. A robust literature now documents the close relationship between optimum risk factors and prevention of subsequent disease. William Kannel, Director of the Framingham Heart Study, coined the term 'risk factor' in 1961, and today the traditional risk factors are the same: hypertension, cholesterol, smoking, diabetes, physical inactivity, and obesity. In 1998, a global or multivariate risk assessment for CHD, known as the Framingham Risk Score (FRS), was introduced [2]. The epidemiological studies of CHD have been reviewed elsewhere [3], as have the longitudinal studies illustrating the strong links between the number of risk factors present, their duration, and intensity with subsequent major adverse cardiovascular events (MACE) [4]. Although disease progression is influenced by all the above-mentioned risk factors (and others), high levels of apolipoprotein B (apoB)-containing atherogenic low-density lipoprotein-cholesterol (LDL-C), very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), triglyceride (TG)-rich lipoproteins (TRLs), and remnant-like particle cholesterol, are all markers of interest and predictive. Under physiological conditions, high levels of high-density lipoprotein-cholesterol (HDL-C) are protective. A number of landmark observational and randomized trials have established a log-linear relationship between LDL-C levels and event rates and CHD mortality, with no plateauing of the curve at low LDL-C concentrations [5].

The burden of CV risk has increased steadily in both industrialized and developing nations, and despite dramatic reductions in CHD mortality, this disease still occupies top ranking among causes of death in the US and elsewhere. Improvements in the treatment of hypertension, dyslipidemia, and smoking have been substantially offset by a rise in the prevalence in obesity and diabetes. Clustering of risk factors, subclinical and clinical, and multiple comorbidities is increasingly common, with the incidence of 'prediseases' and metabolic syndrome also rising. The average untreated adult LDL-C concentration in the US is approximately 3.4 mmol/L (130 mg/dL). Half of the people with a normal level—2.6 mmol/L (100 mg/dL)—will have atherosclerosis by age 50 years [6]. At an index age of 45 years, overall lifetime risk (the percentage of the cohort who would have an event from the index age to the end of follow-up) for total CVD is 60.3 % for men and 55.6 % for women [7, 8]. However, those who enter middle life free of risk factors—far fewer than 1 % of this age group—enjoy a life 14 years longer, free of CVD. Even so, for individuals at index age 55 years, lifetime risk estimates for total CVD were >40 % for men and >30 % for women, even in those with optimal (not ideal) risk factors, reflecting a very high background CV risk in all adults [9], with a similar pattern evolving in adolescents.

2 Properties of Statin Drugs and Low-Density Lipoprotein (LDL) Levels

Current management of CHD employs screening, assessment of risk and, depending on results, a blend of lifestyle changes, pharmacologic interventions and, when necessary, invasive measures, such as revascularization. In the last Adult Treatment Panel (ATP) III cholesterol guidelines [10], blood LDL-C levels were the main target of lipid-lowering therapy for the prevention of CVD. To lower cholesterol, HMG-CoA reductase inhibitors or statin drugs, one of the best-studied classes of pharmaceuticals and the

most prescribed of all time, are drugs of choice. According to ATP III, high-risk patients (those with CHD or CHD risk equivalents and a 10-year risk of >20 %) should achieve an LDL-C goal of <100 mg/dL; those with moderate risk (more than two risk factors) or moderately-high risk (more than two risk factors and 10-year risk of 10–20 %) should achieve an LDL-C <130 mg/dL, while patients with low risk (zero to one risk factors) should have LDL-C levels <160 mg/dL. An optional goal of LDL-C <70 mg/dL was subsequently recommended for high-risk patients.

The ability of 'statins' to lower LDL-C and reduce the relative risk of CHD by approximately 30 % in a variety of at-risk populations, and indeed even in those with acceptable LDL-C concentrations, and improve outcomes in both primary and secondary prevention, revolutionized the practice of cardiology. LDL-lowering with statins is not only accompanied by improved outcomes, normalization of biomarkers, reduction of plaque volume and regression of lesions, but can also reduce the incidence of unstable angina in ACS [11]. In the past decade, the importance of the percentage reduction in LDL-C produced by statins, rather than the absolute reduction, has also become appreciated. Statin drugs vary in potency but the typical ranges of changes on plasma lipids are (i) a fall in LDL-C of 18–55 % and non-HDL-C of 15–51 %; (ii) a rise in HDL-C by 5–15 %; and (iii) a decrease in TGs of 7–30 %. Doubling of statin doses generally results in lowering LDL-C by approximately 6 %, whereas adverse drug effects (ADEs) of larger doses of statins become limiting.

HMG-CoA reductase inhibition, the rate-limiting enzyme involved in the mevalonate pathway leading to cholesterol synthesis, is believed to be the primary effect of statin drugs but, secondarily, statins lead to upregulation of LDL receptors (LDL-Rs) and enhanced LDL clearance. There are also a wide variety of beneficial 'pleiotropic', cholesterol-independent actions of statins that have received attention (Table 1) [12]. Some of these apply to systems other than CV, such as neuroprotective actions, and modulation of cellular senescence.

Mevalonate depletion due to HMG-CoA reductase inhibition also reduces the availability of downstream isoprenoids, notably farnesyl pyrophosphate and geranylgerany pyrophosphate, and impairs post-translational isoprenylation of proteins. These moieties function as lipid attachments or anchors for molecules, thereby enabling intracellular trafficking. Among the many affected molecules are the small GTPases. Members of this family include rho-kinases I and II ('ROCK I and II') that are crucial to organization and rearrangement of the cytoskeleton, assuming key roles in cell morphology, motility, intracellular translocation, and gene expression. ROCK functions in smooth muscle migration and plaque morphology, and regulates transcription factors involved in atherosclerosis. Rho-kinase promotes inflammation by inducing proinflammatory cytokines such as interleukin (IL)-6, monocyte chemoattractant protein-1, and macrophage migration inhibitory factor, increases endothelial expression of adhesion molecules, and promotes smooth muscle proliferation. Rho-kinase upregulates nicotinamide adenine dinucleotide phosphate-oxidase [NAD(P)H] oxidases, and joins Rac, another small GTPase, to generate reactive oxygen species (ROS). Much evidence points to statin-induced inhibition of Rho isoprenylation and ROCK activity as a principle mechanism of many pleiotropic effects, so much so that rho-kinases are considered therapeutic targets themselves [13]. Non-lipid actions of statins are clinically important, and may help explain why LDL-lowering with other agents does not result in expected outcome improvements [14].

Table 1 Lipid-independent pleiotropic actions of statin drugs

Antiinflammatory
Improved endothelial function
Immunomodulatory
Antioxidant
Plaque-delipidating, modulating, and stabilizing
Antithrombotic
Antiproliferative

An impressive literature supports the general concept that, for LDL-C lowering, 'lower the better' is safe and efficacious down to levels of 50 mg/dL [15, 16]. The Cholesterol Treatment Trialists' (CTT) Collaboration of 2010 [15] reported a 22 % relative risk reduction (RRR) per 1.0 mmol/L fall in LDL-C (a 1 % RRR for every 1.8 mg/dL LDL lowered). Part of the thrust behind the idea that lower LDL-C levels are desirable is the quest to lower residual risk—risk that remains even when patients have attained their LDL-C goals. Residual risk, averaging approximately 65 % in prominent statin studies, helps explain why CV events continue in patients who are considered well-treated [17, 18]. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, aggressive lipid-lowering prevented ≈24 % of cardiac events [19]. In other words, aggressive statin treatment using ATP III guidelines resulted in a 0.5 % reduction of MACE per milligram percent lowering of LDL-C, or a 24 % fall in MACE for each 1 mmol/L (39 mg/dL) fall in LDL-C level. This leaves a yearly ongoing incidence of MACE of ≈9 % in such patients despite aggressive statin therapy [20].

A lower target level of LDL-C is also supported by evidence from LDL-C levels in wild animals (ranging from 1.5–2.0 mmol/L or 58–77 mg/dL through life), the low LDL-C noted at human birth (approximately 1 mmol/L or 39 mg/dL) versus the natural history of LDL-C levels as

man ages, the intersection of the regression line with the abscissa in plots of CV outcomes versus log LDL-C levels [21], LDL-C concentrations in present-day hunter–gatherer societies [also not rising much above 1.81 mmol/L (70 mg/dL)] [22–25], and Mendelian analysis, particularly studies correlating the low number of CV events in patients with loss-of-function mutations in *PCSK9,* which raise the number of LDL-Rs on the surface of hepatocytes. According to this view, the 'physiological' level of LDL-C has been posited to be 50 mg/dL or below, and has generally been supported by PROVE-IT and other major statin studies [26]. However, intravascular ultrasound (IVUS), the technique which showed that most MIs occur not only in severely obstructed arteries (75–80 %) but also typically in those whose lumina were compromised by less than 50 %, demonstrated that regression of atheromata proceeded in concert with LDL lowering and, even at LDL-C $\approx$1.50 mmol/L (58 mg/dL), progression of atherosclerosis still continued [19, 27]. Although current evidence supports 'lower is better', assuming that more intense LDL-lowering to ultra-low levels would eliminate residual risk, without simultaneously addressing inflammation and remnant lipoprotein particles, might be premature.

Individuals with genetic loss-of-function variants in *PCSK9* enjoy a much larger reduction in CHD risk than predicted by their lowered LDL-C alone. This lower risk is considerably greater than observed in statin trials, where a similar reduction in LDL-C would have resulted in only one-third the reduction in risk [28, 29]. Ference et al. [30] performed a series of Mendelian randomization studies to estimate the effect of lifetime exposure to lower LDL-C values mediated by nine polymorphisms in six different genes, chosen to eliminate confounding by pleiotropy. A meta-analysis of the studies was carried out to compare the exposure time, reduction in LDL-C, and clinical benefits. Lifelong exposure to low cholesterol levels was associated with a 54.5 % reduction in the risk of CVD per each mmol/L fall in LDL-C, a threefold greater reduction than treatment with a statin started later in life. These data suggest that time is an added dimension when lowering risk, reinforcing the hypothesis that earlier intervention to lower cholesterol would produce greater results than waiting until symptoms, or a positive coronary artery calcium (CAC) score, were reported. These data also indicate that it is the actual lowering of LDL-C, not the method, that is responsible for the improved outcomes, and not non-lipid factors.

There are some limitations to extrapolating and applying these data without randomized clinical trials (RCTs), particularly the pathway by which LDL-lowering is achieved. However, the data certainly indicate that large falls in LDL-C would be accompanied by plummeting risk for CHD. Recent experience with LDL-C lowering has demonstrated that using LDL-C levels as surrogates instead of hard outcomes is perilous, and it will be necessary to conduct trials for each agent or method used. Other changes would also be necessary. For instance, when LDL-C is very low, use of the Friedewald formula to measure LDL-C might introduce significant error. Caution would be advised because of a lingering concern that LDL-C levels might become too low to maintain some physiological processes. Use of such potent agents would also likely reintroduce some inclusion of LDL-C goals or limits into the guidelines (discussed below).

3 Disenchantment with Statins

Adverse reactions to statin drugs have always been a point of contention since the popular press has emphasized myopathy, new-onset type 2 diabetes mellitus (DM), rhabdomyolysis and autoimmune myopathies, memory and cognitive impairment, depression, fatigue, cancer, hepatotoxicity, sterility, hemorrhagic stroke, renal injury, cataracts, weight gain, etc., whereas RCTs and some reviews reported minimal numbers of ADEs. After the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial documented the increase in new-onset diabetes in patients with prior clinical evidence of glucose intolerance [31], later shown to be 9 % diabetes (odds ratio [OR] 1.09; 95 % CI 1.02–1.17) by Sattar et al. in an analysis of RCTs [32] (and other studies by 12 %), a greater number of papers, blogs, commentaries, and media publications concerning statin 'toxicity' appeared. Much of this had to do with exclusions and run-in phases of RCTs and other studies, incomplete documentation of events, and lack of information in some trials.

In many instances, evidence for anecdotal adverse events fails to materialize [33]. Greater appreciation of the genetic variation in statin metabolism, drug interactions, and higher quality data have shed much light on this subject. While beyond the scope of this review, the seminal paper by Golomb and Evans [34] and the National Lipid Association Task Force on Statin Safety–2014 Update, published as a supplement to the *Journal of Clinical Lipidology* in May 2014 [35], are complete resources. At the time of writing, there were likely over 10,000 papers dealing with the subject matter. A large, recent, retrospective cohort study of 107,835 patients found 17.4 % had documented instances of ADEs, and 59.2 % of patients discontinued statins; 59 % of those were rechallenged with statins, of which 92.2 % were able to tolerate the statins 1 year after rechallenge [36]. Although lipid clinics report rates of ADEs in the order of 10–15 %, vulnerable patients and athletes may have rates of up to 25 %, depending on

the composition of the cohort considered. Because some of the original data have not been released, and under pressure from the *British Medical Journal*, the safety of now widespread statin use, and conclusions of the CTT Collaboration [16], are to be reviewed. Since the results of this trial have been heavily weighed in favor of both the new ACC/AHA and National Institute for Health and Care Excellence (NICE) cholesterol guidelines, any revision could have significant consequences.

As far as diabetes is concerned, an important ADE, the incidence was higher when more potent statins were used, in older patients, and when adherence was high. Patients with pre-existing glucose intolerance, such as metabolic syndrome, are more susceptible. Although glucose intolerance is a class effect, not all statins produce the same degree of new-onset DM. Treatment of 255 (95 % CI 150–852) patients with statins for 4 years resulted in one extra case of diabetes. The effect may be front-loaded and nonlinear with respect to time [37]. In absolute terms and relative to the substantial reduction in CV events, benefits of statin therapy greatly outweigh the small risk of diabetes [38]. In patients with diabetes, statin drugs significantly lower MACE (including cerebrovascular events), leaving the overall benefit of statins in this setting overwhelmingly positive. Moreover, if statins are compared with other widely-used drugs that impair glucose intolerance—thiazide diuretics and β-blockers—ORs of the incidence of diabetes are extremely small [39]. One approximation regarding statin use in diabetics for shared decision-making discussions (SDM): in 1000 statin-treated primary prevention patients, there will be five who develop diabetes, five deaths will be averted, ten nonfatal MIs will be prevented and six strokes will be avoided.

The majority of ADEs (and pleiotropic effects) of statins [34, 40, 41] are believed to be the result of (a) inability to prenylate small GTPases (enzymes that can bind and hydrolyze guanosine triphosphate) and other molecules [42]; (b) interference with signaling due to GTPase dysfunction, such as endoplasmic reticulum-to-Golgi trafficking [43] and translocation of glucose transporter type 4 (GLUT4) vesicles into the cell [44, 45]; (c) removal of cholesterol from lipid rafts with disruption of ligand-receptor interactions; (d) diminished insulin secretion by β cells in the pancreas [44]; (e) lowering of mitochondrial energy production due to CoQ10 deficiency and calcium leaks [46, 47]; (f) low levels of selenoproteins, dolichol, and downstream products of the mevalonate pathway [46]; (g) downregulation of PI3k/Akt (phosphoinositide-3-kinase/serine-threonine protein kinase) signaling to raise atrogen-1 expression and promote muscle atrophy) [48]; (h) low peroxisome proliferator-activated receptor (PPAR)-gamma coactivator 1α (PGC-1α) activity, a transcriptional coactivator that promotes mitochondrial biogenesis and protects against the development of muscle damage mediated by the ubiquitination-proteasome pathway [49]; (i) increased apoptosis due to a variety of triggers [50, 51]; (j) delayed muscle power output with differential activation of genes related to mitochondrial dysfunction and apoptosis [45]; (k) upregulated Forkhead box O (FOXO) transcription factors and downstream gene targets to lower carbohydrate metabolism; (l) dysregulation of glucose metabolism and decreased legumain activity [52]; (m) activation of inflammasomes, leading to insulin resistance [53]; (n) loss of regulation of skeletal muscle fiber type [34]; (o) inability to repair muscle with loss in viability of muscle precursor cells; and (p) the integrity of PCSK9 expression and function of LDL-Rs may regulate glucose homeostasis, since familial hypercholesterolaemia (FH) patients enjoy a low incidence of DM.

New medication adherence to statins is only 31 % [54]. Adherence averages below 50 % immediately after treatment is begun and attenuates quickly during the ensuing 2 years. The FDA agrees; with respect to, in particular, multiple cardiac drugs in secondary prevention, approximately 50 % of all patients stop taking prescription drugs within 1 year, followed by an additional 35 % who discontinue their medications by 2 years. Maladherence alone accounts for a treatment failure rate of 30–50 % in chronic conditions. Overall, 62 % of users discontinue the drugs because of side effects. While even patients with high adherence rates fail to reach goals, poor adherence is clearly related to the number of patients who fail to do so, and also distance of LDL-C from goals. In one study, among patients who were at their goal of LDL-C $<$2.59 mmol/L (100 mg/dL), 18 % were not adherent to statins, suggesting the additional problem of teasing non-responders from nonadherers. The relationship between adherence and goal attainment is nonlinear, with goal attainment plateauing when adherence is over 86 % [55].

Another controversy has been the use of statins for primary prevention, where the number needed to treat (NNT) to prevent a nonfatal MI or one death is relatively high [56]. Exclusion of epidemiological evidence, doubt about the RCTs themselves, unavailability of the raw data for one large study, and disagreeing calculations mar the backdrop. One public source offers the following information. Based on data from Ridker et al. [31], Thavendiranathan [57], Baigent et al. [58], and the NNT group estimates for secondary prevention, 5 years of statin therapy results in a reduction in mortality of 1 in 83, reduction in nonfatal MI of 1 in 39, and a reduction in stroke of 1 in 125 [59]. These benefits are counterbalanced by the following numbers needed to harm (NNH): 1 in 50 will develop diabetes, and 1 in 10 will develop muscle pathology [59]. The numbers amount to a 1.2 % lower chance of death, a 2.6 % lower chance of heart attack, and

a 0.8 % lower chance of stroke. For primary prevention, 5 years of statin therapy results in no reductions in mortality, a reduction in MI of 1 in 60, and a reduction in stroke of 1 in 268. These benefits are outweighed by the same NNH as mentioned for primary prevention above [60]. Statin therapy for 5 years confers a 1.6 % chance of avoiding an MI, and a 0.37 % chance of avoiding a stroke. The author of this site adds a note of explanation regarding his conclusion regarding a lack of mortality benefits: "the CTT group consistently does their comparisons of clinical effects of statin and placebo by using a per-cholesterol-reduction metric. In other words, rather than simply comparing statin and placebo groups head-to-head (as…the Ray meta-analysis [61] have done, finding no mortality benefit), the CTT group measures statin effects based on how much cholesterol reduction is achieved. We believe this confounds the analysis and has the potential to advantage statin groups by narrowing the comparison to those whose cholesterol is successfully reduced. It is not clear to us why anyone would choose to promulgate this type of analysis rather than simply presenting comparative results from the two groups, side by side, and we are concerned that it may distort the comparison. In simple comparisons no benefit is found". One interactive risk predictor furnishing visual effects of statin therapy based on baseline characteristics is offered at http://chd.bestsciencemedicine.com/calc2.html. Obviously, these figures vary considerably. For instance, the JUPITER investigators reported significant numbers of deaths avoided in primary care patients [31], as many others have done. The CTT meta-analysis of 2012 [16] reported an NNH of myopathy in non-Asians, excluding use of simvistatin 80 mg, of 0.5 per 1000 statin-treated patients over 5 years and, for diabetes, a 5-year NNH of 200 [32]. However, a National Health and Nutrition Examinations Survey (NHANES) in the US suggests muscle symptoms occur in 53 per 1000 patients, 100-fold greater than found by the CTT. Another view is that there is a minor reduction in future MI and stroke over a 5- to 10-year period in primary prevention, with an absolute risk reduction of approximately 7 in 1000, for a 5-year NNT of 1 in 140, meaning 99.3 % of statin-treated patients receive no benefit.

4 American Heart Association/American College of Cardiology (AHA/ACC) Guidelines and the Removal of LDL Goals as Targets

The new AHA/ACC Assessment and Cholesterol Guidelines [62, 63] (Box 1 in Appendix) relied solely on evidence-based trials, included a risk score that included stroke, was applicable to Black patients, and would conform with new Institute of Medicine criteria for guidelines. Four major statin benefit groups were identified, for whom the evidence was extremely high (Box 1 in Appendix). These guidelines expanded statin use from 43 million (38 % of Americans) to approximately 56 million (or approximately 50 %). Of the 13 million-person difference, 10.5 million do not have clinical heart disease, therefore the major increase in newly statin-eligible individuals is in primary prevention. Using ATP III criteria, 66.9 million adults aged 40 years through 75 years are statin-ineligible, whereas using the new ACC/AHA guidelines, 58.7 million adults are ineligible. ATP III criteria said 18 million more people should take statins, whereas the new guidelines say 31.0 million more should be taking statins, along with the approximately 25 million who already take stains. This is because the new guidelines call for statin use in individuals without CVD or DM, but do have an LDL-C of 70–189 mg/dL and a calculated 10-year CV risk, according to new pooled risk equations, of $\geq$7.5 %. In the older age group (60–75 years), ATP III called for 46 % to take statins but the new guidelines recommend 75 %. The major increase is in men, older individuals (even without other risk factors), and those with hypertension.

Major strengths of the new guidelines include the addition of stroke to the outcomes, applicability to African Americans, and the identification of well-characterized groups, except for the 7.5 % risk cutoff, in whom statin therapy is strong, of the highest quality, and practical. Following the release of the new cholesterol guidelines, concerns were voiced concerning the perils and inappropriateness of the wider use of statins. Two surveys of physicians have been conducted, one in the *New England Journal of Medicine*, which presented a case of a 52-year-old male Caucasian jogger with an HDL-C of 0.90 mmol/L (35 mg/dL) and LDL-C of 115 mg/dL (3.00 mmol/L), who was a smoker; the ATP III 10-year risk was 13 %, and with his LDL-C of <130 mg/dL (3.40 mmol/L) he was ineligible for a statin. According to the new risk calculator, the patient's 10-year risk is 10.9 %, for which the new guidelines recommend statin therapy since it is >7.5 %. Three choices were given to physician respondents: not begin a statin, begin a statin with monitoring of LDL-C, and begin a statin without monitoring, with only the third choice consistent with the new guidelines [67]. Half chose not to begin a statin, 29 % chose starting a statin with LDL-C monitoring, and 17 % voted to begin a statin without LDL-C monitoring—79 % of physicians did not follow the new guidelines. In the UK, the medical publication *Pulse* revealed two-thirds of general practitioners are disregarding NICE guidelines to expand statin use to individuals with a 10 %, rather than 20 %, 10-year risk of a CV event. Overall, the dissension also involves cardiologists and researchers who are split, uncertain, and/or confused about aspects of the new guidelines [68–75].

There is also a substantial difference between the results of RCTs, when the results may not even apply to every participant within the RCT, and an individual patient seeking advice in a clinical setting dissimilar to the entry criteria of those RCTs. The allocation of statins according to the use of scoring systems itself has not been subjected to RCT analysis using hard outcomes, and in a sense may not be evidence-based. One observation is that the pooled cohort equations in the 2013 ACC/AHA Assessment Guidelines are insufficiently calibrated and validated, and overestimate risk [69, 70, 76]. The data on which the calculator was based were decades old. Although debated at the time, a recent analysis with data from a more contemporary study revealed that among patients with an AHA/ACC atherosclerotic cardiovascular disease (ASCVD) risk score (predicted event rate) of 7.5–10 %, the actual event rates were only 3 % in men and 5.1 % in women, well below the threshold for initiating statin therapy [77]. The new ACC/AHA ASCVD risk score was found to overestimate risk by 86 % in men and 67 % in women, for an overall net overestimation of 78 %. The Reynolds Risk Score, which includes family history, CRP levels, and HbA1c in diabetic patients, and is based on more recent populations, overestimated risk by just 9 % in men, underestimated risk by 21 % in women, and was the best calibrated model, having the lowest discordance between actual and predicted events [77]. Valid risk scores are crucial in stratifying patients not only statin therapy but also for other treatments. Overestimation risks overtreatment and exposure to adverse drug reactions, and has public health implications [78]. For statins alone, this view is tempered by a potential benefit, even at low levels of absolute risk [31].

Abandoning LDL-C targets has also caused considerable attention, and other organizations such as the National Lipid Association (NLA), American Association of Clinical Endocrinologists, European Cardiology Society, and International Atherosclerosis Society have retained LDL goals. The NLA and NICE guidelines also endorse non-HDL-C as a target. Defined LDL-C targets provide signposts for patients, a navigation tool for physicians, help correlate intensity of statins with actual effects and identify poor adherence, and enable adjustments for individual variation in statin responsiveness and disease progression. Another argument made against LDL targets was that, since the new ACC/AHA Cholesterol Guidelines found no benefit from adding any agent to statins while treating dyslipidemia, there was no point in pursuing targets [79]. Since the results of IMPROVE-IT demonstrated efficacy of ezetimibe in improving outcomes, and the approval of PCSK9 inhibitors capable of lowering LDL-C to levels below 1.2 mmol/L (50 m/dL) is imminent, on-treatment LDL-C levels now assume new importance [80].

One observer suggested that an RCT be conducted to compare the new model against other paradigms of statin and treatment allotment, not only to predict risk accurately but also to optimize patient outcomes at different treatment thresholds and in subgroups [68]. The response to the inclusion of an SDM has been uniformly favorable. The rules, steps, and treatment options in managing patients according to these new assessment and cholesterol guidelines are summarized in Box 1 in Appendix and Tables 2 and 3.

The interindividual LDL-C response to statin drugs is highly variable and the proportion of patients reaching therapeutic levels of LDL-C is unpredictable. In a meta-analysis of statin trials of 38,133 patients, over 40 % of participants receiving high-dose statin therapy failed to achieve an LDL-C <70 mg/dL. There was a clear relation between LDL-C achieved and events at 1 year, from an event rate of 4.4 % in patients with LDL-C <50 mg/dL, rising to 10.9 % for LDL-C levels from 50 to <70, and to 34.4 % in those with LDL-C ≥190 mg/dL [81]. While an observation study, these data suggest that LDL-C levels attained, rather than intensity of satins prescribed, matter. Even though high-intensity statin therapy produces greater LDL-C and event lowering than moderate statin therapy within groups, individual outcomes remain uncertain. Recently, 647 patients with angiographic CHD who were prescribed statin therapy underwent serial IVUS imaging [82]. Approximately 20 % of the cohort failed to lower their LDL-C by at least 15 % and, in some, LDL-C levels actually rose. Such statin hyporesponders (defined as percentage reduction of LDL-C <15), after adjusting for baseline clinical characteristics and measures of plaque burden, suffered greater atheroma progression ($+0.83 \pm 0.58$ % vs. -0.21 ± 0.52 %; $p = 0.006$) over a follow-up period ranging from 18 to 24 months. The authors noted that adopting the latest ACC/AHA cholesterol guidelines may lead to insufficient monitoring of LDL-C, and under-identification of hyporesponders who require additional treatment.

The content of the new ACC/AHA guidelines most certainly changes the milieu of dyslipidemia therapy in several ways. At the time of writing, since there were no acceptable, compelling RCTs, no non-statin drugs were considered. The IMPROVE-IT results change this view [80]. An update is planned to address some issues of importance, based on data published since 2013. It has also been suggested that one of these might provide for greater cholesterol screening in young adults since such individuals may have dyslipidemia for decades and need greater protection against cumulative effects of exposure to those 'lipid years' later in life.

On the other hand, imaging studies inform that the new guidelines may identify more candidates with verifiable

Table 2 Sequential steps in ASCVD risk assessment

A. Identify patients with either very high-risk or high-risk conditions. Further risk assessment is not required after identifying the highest applicable risk level
Very high risk
(i) ASCVD
(ii) DM with two or more other major ASCVD risk factors or end organ damage[a]
High risk
(i) DM with zero to one other major ASCVD risk factors
(ii) Chronic kidney disease stage 3B or 4[b]
(iii) LDL-C ≥190 mg/dL
B. Count major ASCVD risk factors
(i) If zero to one and no other major indicators of higher risk, assign to the low-risk category. Consider assigning to a higher risk category based on other known risk indicators, if present
(ii) If three or more major ASCVD risk factors are present, assign to the high-risk category
C. If two major ASCVD risk factors are present, risk scoring should be considered and additional testing may be useful for some patients
(i) If quantitative risk scoring reaches the high-risk threshold[c], assign to the high-risk category
(ii) Consider assigning to the high-risk category if other risk indicators are present, based on additional testing
(iii) If, based on the above steps, no indication is present to assign to the high-risk category, assign to the moderate-risk category

ASCVD atherosclerotic cardiovascular disease, *CHD* coronary heart disease, *CKD* chronic kidney disease, *CV* cardiovascular, *DM* diabetes mellitus, *GFR* glomerular filtration rate, *LDL-C* low-density lipoprotein-cholesterol

[a] End organ damage indicated by increased albumin/creatinine ratio (≥30 mg/g), CKD, or retinopathy

[b] For patients with CKD stage 3 (GFR 30–59 mL/min/1.73 m^2) or stage 4 (GFR 15–29 mL/min/1.73 m^2) risk calculators should not be used because they may underestimate risk. Stage 5 CKD (or on hemodialysis) is a very high-risk condition, but results from randomized controlled trials of lipid-altering therapies have not provided convincing evidence of reduced ASCVD events in such patients. Therefore, no treatment goals for lipid therapy have been defined for stage 5 CKD

[c] The calculation for 10-year hard CHD event risk of ≥10 % is based on the National Cholesterol Education Program Adult Treatment Panel III Framingham Risk Score. Clinicians may prefer to use other risk calculators but should be aware that these vary in the clinical outcomes predicted (e.g. CHD events, ASCVD events, CV mortality), the risk factors included in their calculation and the timeframe for their prediction (e.g. 5 years, 10 years, long-term or lifetime). Such calculators provide only an approximate risk estimate and require clinical judgment for interpretation

Table 3 Treatment based on total risk, according to the new AHA/ACC 2013 assessment and cholesterol guidelines. Using the general rules in Box 1 in Appendix, patients should be assessed as per Table 2 and treated as below

Intensity of statin therapy-two dose categories	
High-intensity daily dosage to ↓ LDL-C ≥50 %	Moderate-intensity daily dosage to ↓ LDL-C 30 % to <50 %
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Fluvastatin 40 mg bid
	Fluvastatin XL 80 mg
	Lovastatin 40 mg
	Pitavastatin 2–4 mg
	Pravastatin 40–80 mg
	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg

Individual responses to statin therapy should be expected to vary in clinical practice. The intensity of statin therapy to be used is detailed in Box 1 in Appendix. Moderate- or high-intensity statin therapy is preferred unless not tolerated

AHA/ACC American Heart Association/American College of Cardiology, *bid* twice daily, *LDL-C* low-density lipoprotein-cholesterol, ↓ indicates decrease

CHD. In a recent retrospective study of adults, the initiation of statin therapy was either recommended or not recommended using both the ATP III guidelines and the new ACC/AHA guidelines. Ninety-two percent of patients who had heavy plaque burdens on CT angiography would have been advised to take statins according to the 2013 guidelines but only 53 % would have been advised to do so using the ATP III guidelines [83]. In the Rule Out Myocardial Infarction with Computer-Assisted Tomography (ROMICAT) study of patients at low–intermediate risk of

CVD seen for ACS, the new 2013 cholesterol guidelines identified more candidates for statin therapy than ATP III (106/252 patients vs. 51/252). Patients with obstructive CHD (stenosis ≥50 %) were 3.42-fold more likely to be eligible for statins using the new guidelines compared with the old; those with non-obstructive CHD were 2.10 more likely to be eligible for statins, and those without any CHD were 1.65-fold more likely to be statin-eligible using the new guidelines [84]. Most surprising was the author's observation that despite the greater use of statins with the 2013 cholesterol guidelines, perhaps 40 % of individuals with non-obstructive CHD and 20 % of those with obstructive CHD remain unidentified as needing statin therapy. These data are consistent with a view that the extremely high CV risk burden in the population is accompanied by subclinical and clinical disease which needs to be addressed even further. Lowering the threshold for statin eligibility will certainly include more patients with disease, simply because the disease is inordinately prevalent. Part of the appeal to precede with a model that drastically raised statin use was the expiration of the patent on atorvastatin (Lipitor®), for without generic atorvastatin the economics of the new guidelines would have been different. In the UK, this consideration has been more evident in their guideline deliberations.

An additional point is also pertinent. While waiting for ATP IV, it was clear that statins were being underused. The need for these drugs is directly related to the remarkable deterioration in CV health in the US (and globally), also reflected in the striking low prevalence of ideal CV health. Healthy lifestyles lower CV risk much more rapidly and completely than is appreciated. Public response to such initiatives as Healthy Heart 2010 and 2020, the Million Hearts Program and, indeed, even to the Strategic Goals for 2020 by the AHA, known as 'My Life Check—Life's Simple 7' (http://mylifecheck.heart.org/Multitab.aspx?NavID=3) has been disappointing, despite the inordinate time, effort, and other resources invested. One reason for expanded use of statins was the desire to stem the tide of rising CV risk. As a result, the urgency of treating more patients, whether it be through a high-risk individual approach or population-based method, is understandable and is in fact the purpose of medicine—to prevent disease, reduce suffering, and lower mortality. Therefore, to a certain extent, the background noise in the population to the prospect of taking statins is unrealistic, as the alternative—improving diet, physical activity, and maintaining a healthy weight—has been repeatedly proposed and overwhelmingly rejected.

Patient adherence to statin therapy, in the absence of realizing individual improvements by measuring LDL-C, may wane. When taking statins, patients may feel their protection is great enough to compensate for an unhealthy diet, sedentary life, and excess weight. Between 1999 and 2000, patients receiving statins had significantly lower caloric intakes than non-statin users, but between 2005 and 2006 this was no longer the case. There appeared to be an increase in daily fat, caloric intake, and body mass index (BMI) between statin users during 1999–2000 and during 2001–2009 compared with individuals not using statins [85]. In a cohort of older men being followed for osteoporosis, those beginning statins experienced a faster deterioration in physical activity than non-users [86]. While these are associations, and in the second instance may have been due to ADEs on muscle, the data are suggestive.

5 Conclusions

Since their introduction, statin drugs have consistently produced a vast improvement in CV morbidity and mortality; experience with these agents is immense, and their role in treatment remains unequalled. New CV assessment and cholesterol guidelines in the US and UK now focus on the treatment of populations as well as individuals. Commitment of guideline authors to rigorous evidence-based standards and new concepts is evident, and interval updates promise to address some differences that have arisen. What has emerged is a welcome and thorough review of treatment, and a new, fresh focus on current issues that matter to our patients. At the same time, the new guidelines directly impact the use of non-statin lipid-lowering drugs; their content and import raise the bar on evidence required for both old and new drugs before they can be incorporated into current practice, and this paradigm change is shared by the FDA.

The reality is that a sizeable proportion of patients do not reach LDL-C goals, many have high residual risk even if at goals, management of patients with atherogenic dyslipidemia remains a challenge and, with an ever-increasing number of statin-treated patients, intolerance to these drugs has become an issue. While statins will certainly remain a mainstay of therapy, patients need additional and more potent agents, and their physicians need greater choice in order to individualize treatment and optimize patient outcomes. Ongoing collaboration between industry, researchers, and clinicians now present a number of promising agents, many with great appeal, as discussed in a sister paper published in this issue [80].

Compliance with Ethical Standards

Conflict of interest Richard Kones and Umme Rumana have no conflicts of interest to declare.

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Appendix

Box 1 Features of the 2013 ACC/AHA Assessment and Cholesterol Guidelines [62–64]

1. All adults in the general population over 21 years of age should have LDL-C measured and other CV risk factors screened. Lifestyle measures to reduce CV risk should be used first; however, the remainder of the guidelines do not address or actually incorporate this advice
2. Statin therapy is divided into high-intensity therapy or moderate-intensity. High-intensity statin treatment means a reduction in baseline LDL-C by ≥50 % below the baseline with the use of atorvastatin 40–80 mg or rosuvastatin 20–40 mg daily. Moderate-intensity statin treatment means reaching a 30 % to <50 % reduction from baseline using atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40–80 mg, fluvastatin 40–80 mg, or pitavastatin 2–4 mg
3. Patients with established CVD should receive high-intensity statin therapy
4. Patients with LDL-C ≥190 mg/dL (4.9 mmol/L) should receive high-intensity statin therapy
5. Other patients should be assessed using the new pooled risk equations, developed for African Americans and Caucasians, facilitated with the use of a calculator available at http://tools.cardiosource.org/ASCVD-Risk-Estimator/ or http://www.cvriskcalculator.com/
6. Patients with DM (type I or II) between the ages of 40 and 75 years and with LDL-C values of 70–189 mg/dL (1.8–4.9 mmol/L) should receive a moderate-intensity statin if their 10-year risk for CVD is <7.5 %, or a high-intensity statin for a 10-year risk ≥7.5 %
7. Patients 40–75 years of age without diabetes but with LDL-C values between 70 and 189 g/dL (1.8–4.9 mmol/L) should receive a moderate- to high-intensity statin if their 10-year ASCVD risk is ≥7.5 %. For an intermediate 10-year risk of 5.0–7.5 %, moderate-intensity statins are acceptable. In this intermediate-risk category, and for individualized risk assessment, CRP levels, ankle/brachial ratio, or CAC may be considered, but are not required, and criteria for use are not discussed
8. For patients with intolerance to high-intensity statin treatment, or due to concomitant drug interactions, an age over 75 years, unexplained elevations in ALT levels, or other reasons, a moderate-dose statin should be used before other lipid-lowering drugs are considered
9. Drugs other than statins are not advised due to the absence of RCT data. LDL-C goals are eliminated, and no monitoring of LDL-C is advised, other than a 1-month repeat to determine adherence, although epidemiological studies do support the use of LDL-C goals. No titration of agents is recommended since the model predicts that the benefits using the two levels of statins will be sufficient. No additional means of measuring or addressing residual risk is mentioned, and non-HDL-C measurement is eliminated, either for assessing residual risk or as a secondary target
10. In the absence of LDL-C monitoring, methods of measuring success of the new guidelines in terms of outcomes, within the context of other factors changing the landscape of cardiovascular risk, remain unclear
11. The 2013 guidelines are 'tailored', not in the sense of a tailor taking all measurements and making a suit to order but rather statistically conforming to a predictive model based on data from RCTs of similarly situated patients. They are 'individualized' with respect to the variables entered, similarity to characteristics of patients who are enrolled in the RCTs used for modeling, and the content of the SDM discussion. The risk calculator has not been prospectively tested for its accuracy in predicting CV risk [65]. The predictive model does not include younger adults, certain ethnic groups, and other data, such as LDL-P. Results from the pooled risk equations also lower the number of patients in the intermediate-risk group compared with ATP III, therein curtailing the use of testing to refine risk, such as CAC score, CRP, and LDL-P
12. There is no randomized trial comparing the value of one particular method of statin allocation, using the new ASCVD calculators in these new guidelines, for instance, versus other global risk prediction models, which would identify individual patients in whom statins would be of maximum benefit [65]. The RCTs that form the backbone of the new guidelines did not use a global risk prediction score as an entry criterion, or allocate statins on the basis of a risk score
13. One of the features of the new guidelines is the SDM discussion with patients, during which benefits and risks are explained, and patients may ask questions and indicate choices and preferences [66]

ACC/AHA American College of Cardiology/American Heart Association, *ALT* alanine transaminase, *ASCVD* atherosclerotic cardiovascular disease, *ATP* Adult Treatment Panel, *CAC* coronary artery calcium, *CRP* C-reactive protein, *CV* cardiovascular, *CVD* cardiovascular disease, *DM* diabetes mellitus, *LDL-C* low-density lipoprotein-cholesterol, *LDL-P* lipoprotein particle number, *RCT* randomized clinical trial, *SDM* shared decision making

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