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Targeting LDL Cholesterol: Beyond Absolute Goals Toward Personalized Risk

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Abstract

Purpose of Review—The aim of this study was to review and assess the evidence for low-density lipoprotein cholesterol (LDL-C) treatment goals as presented in current guidelines for primary and secondary prevention of cardiovascular disease.

Recent Findings—Different sets of guidelines and clinical studies for secondary prevention have centered on lower absolute LDL-C targets [<70 mg/dL (<1.8 mmol/L)], greater percent reductions of LDL-C (≥50%), or more intense treatment to achieve greater reductions in cardiovascular risk. Population-based risk models serve as the basis for statin initiation in primary prevention. Reviews of current population risk models for primary prevention show moderate ability to discriminate [with c-statistics ranging from 0.67 to 0.77 (95% CIs from 0.62 to 0.83) for men and women] with poor calibration and overestimation of risk.

Summary—Individual clinical trial data are not compelling to support specific LDL-C targets and percent reductions in secondary prevention. Increasing utilization of electronic health records and data analytics will enable the development of individualized treatment goals in both primary and secondary prevention.

Keywords

Cardiovascular disease prevention; Low-density lipoprotein cholesterol; Statins; Major adverse cardiac events

Introduction

Today, more than two decades after initial studies showed the effectiveness of statins in reducing recurrent cardiac events [1–3], controversy persists regarding the appropriate use of

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Compliance with Ethical Standards

Conflict of Interest Morton Leibowitz, Chandra Cohen-Stavi, Sanjay Basu, and Ran D. Balicer declare that they have no conflicts of interest.

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statins and treatment goals for both primary [among individuals without existing cardiovascular disease (CVD)] and secondary (individuals with existing CVD) prevention. Recommendations on the usage of statin medication for the prevention of cardiovascular events and mortality have progressed over the decades reflecting the shift toward evidence-based guidelines and treatment targets derived from clinical trials.

As treatment patterns evolved, the objectives of treatment have progressed as well. Early guidelines upheld lipid treatment targets and percentage reduction in low-density lipoprotein cholesterol (LDL-C) levels to guide treatment practices [4]. Debates stemming from these guidelines have centered on whether lower LDL-C targets [<70 mg/dL (<1.8 mmol/L)] are definitively better and whether greater percent reductions of LDL-C (≥50%) yield progressively greater reductions in cardiovascular risk [5, 6]. More recently, amendments to guidelines have resulted in substantial discrepancies between the various sets of recommendations in different regions. Some recommend statin treatment according to population-based risk stratification and intensity of treatment while others maintain LDL-C treatment targets [6, 7]. One element that is shared across updated guidelines is that there are varying levels of risk among population subgroups. This is exemplified in a multitude of population-based risk models that have been developed to characterize subgroups of high-risk patients for treatment initiation or treatment intensification. These risk stratification models have led to exploratory evaluations of individualized treatment profiling and benefit-based tailored treatment in attempts to identify more relevant treatment strategies for practicing physicians [8, 9••, 10•].

The present review aims to provide an overview of the evolution of these differing treatment objectives, examining the evidence across the spectrum from population-based treat-to-target and percent LDL-C reduction strategies to individualized benefit-based approaches. We further discuss the implications of these strategies for future treatment goals.

Historical Overview of Statin Therapy Efficacy

In the late 1980s, the National Institutes of Health (NIH) established the National Cholesterol Education Program (NCEP) to increase awareness among both clinicians and patients of the important relationship between cholesterol and CVD. The NCEP released a series of expert panel reports on the treatment of blood cholesterol, entitled Adult Treatment Panel (ATP) I, II, and III in 1988 [11], 1993 [12], and 2001 [4], respectively. The ATP II guidelines discussed treatment of both patients with established ischemic heart disease (IHD) (secondary prevention) and patients without such disease (primary prevention). These guidelines recommended that patients should be treated with medication to lower their LDL-C to below 100 mg/dL (2.6 mmol/L) for secondary prevention and to below 130 mg/dL (3.4 mmol/L) for primary prevention. The parallel European guidelines of the Joint Task Force of the European Society of Cardiology strongly emphasized lifestyle modifications in their early set of guidelines and first focused on achieving targets of total cholesterol of less than 270 mg/dL (<7 mmol/L) with drug therapy [13]. The second Joint European Societies' guidelines provided specific LDL-C target recommendations in addition to total cholesterol targets, which varied minimally from the American guideline targets. Strikingly, both the early American and European guidelines were written based on expert consensus and

epidemiologic associations between LDL-C level and CVD risk, prior to key randomized controlled studies establishing the efficacy of statin treatment [14].

Early statin trials in the mid-1990s were primarily efficacy studies that compared statin treatments to placebo for both secondary and primary prevention of CVD. In 1994, results of the placebo-controlled Scandinavian Simvastatin Survival Study (4S) revealed that statins were not only effective in lowering LDL-C but also significantly reduced cardiac events and mortality in patients with preexisting CVD [1]. With a median follow-up of 5.4 years, the 4S reported a relative risk (RR) of 0.70 (95% CI 0.58–0.85) for total mortality with statin (simvastatin 20–40 mg) versus placebo and a 42% reduction in a risk of coronary death. RR of major coronary events was 0.66 (0.59–0.75).

Similar results were found in another secondary prevention study, the Cholesterol and Recurrent Events (CARE) trial, with a 24% (9–36%; $p = 0.003$) reduction in a risk of fatal coronary event or a nonfatal myocardial infarction and a 31% reduction in a risk of stroke ($p = 0.03$) in those treated with 40 mg of pravastatin versus placebo [15]. The lesser reduction in risk can potentially be attributed to the moderate cholesterol levels of the entry criteria for the study [115 to 174 mg/dL (3.0 to 4.5 mmol/L)]. The results of this study importantly extended cholesterol-lowering benefits of statin treatment to patient populations with coronary disease and lower pretreatment LDL-C levels.

Further expansion of the relevant populations for statin treatment was established through major trials among patients without preexisting IHD in the West of Scotland Coronary Prevention Study (WOSCOPS) [2] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [3]. The WOSCOPS recruited 6595 men, aged 45 to 64 years, and, over an average of 4.9 years of follow-up, reported a 31% reduction in nonfatal cardiac events, a 28% reduction in cardiac deaths, and a 22% reduction in all-cause mortality among those treated with 40 mg of pravastatin versus placebo. AFCAPS/TexCAPS included both men and women with LDL-C levels from 130 to 190 mg/dL (3.4 to 4.9 mmol/L) or an LDL-C/HDL-C ratio greater than 6.0, who received either placebo or lovastatin 20 or 40 mg. They reported a 37% relative reduction in the primary composite endpoint of acute major coronary events (fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death) in the statin-treated group.

Few serious adverse events were recorded in these large trials, therefore establishing statins as safe and effective for lowering the risk of first-time and recurrent cardiac events. The safety of statin therapy, however, has more recently come under increasing scrutiny as larger populations have been recommended therapy.

Potential Risks of Statin Therapy

Per a recently published guideline review, statin therapy discontinuation due to adverse events is low [16••]. While the risks of liver enzyme elevation and myalgias have been classically described in the literature as common, neither risk is significant in the pooled meta-analysis, with an RR of liver enzyme elevation of 1.10 (0.90–1.35; $I^2 = 0\%$) among 11 trials and an RR of myalgias of 0.96 (0.79–1.16; $I^2 = 42\%$) among 7 trials. Less precise

estimates are available for the risk of rhabdomyolysis [RR 1.57 (0.41–5.99) among four trials] or myopathy [RR 1.09 (0.48–2.47) among three trials].

Most controversial has been the contention that statins may induce the onset of type II diabetes. The only randomized trial to report an increased risk of type II diabetes was the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, which evaluated high-potency statin therapy and reported a RR 1.25 (1.05–1.49) [17]. The subset of JUPITER trial participants who experienced type II diabetes onset were those who had at least one diabetes risk factor, such as metabolic syndrome, impaired fasting glucose, hemoglobin A1c level >6.0%, or body mass index >30 kg/m^2. Other trials reporting the risk of type II diabetes onset did not detect a similar increased risk [17–21], and one trial reported a decreased risk [hazard ratio (HR) 0.7 (0.50–0.98)] [19], but none of these alternative trials evaluated a high-potency statin.

Apart from the randomized clinical trial literature, secondary analyses have reported mixed results on the association of increased diabetes incidence with statin treatment. Data from the Women's Health Initiative longitudinal cohort showed an increased risk of type II diabetes onset among women using statins [N = 10,834, HR 1.48 (1.38–1.59)] [22], as did a Canadian population-based cohort study (N = 471,250) reporting HRs of 1.22 (1.15–1.29), 1.18 (1.10–1.26), and 1.10 (1.04–1.17) for diabetes incidence with atorvastatin, rosuvastatin, and simvastatin, respectively, compared with pravastatin [23]. In contrast, a case-control study using data from the United Kingdom General Practice Research Database found no such association [588 cases, odds ratio (OR) 1.01 (0.80–1.40)] [24]. While harms of treatment are always a consideration in treatment decisions, the discussion of how critical these risks are is more rigorously debated for primary prevention.

LDL-C Target Levels and Intensity of Treatment

As more potent statin medications were developed, clinical trials focused on comparing outcomes with differing treatment intensities, and many attempts were made to define optimal LDL-C targets for both primary and secondary prevention. The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial compared high-intensity therapy (atorvastatin 80 mg) to standard therapy (pravastatin 40 mg) in 4162 patients within 10 days following hospitalization for acute coronary syndrome [25]. Results from this trial yielded a median achieved LDL-C of 62 mg/dL (1.6 mmol/L) in the atorvastatin-treated group versus 95 mg/dL (2.5 mmol/L) in the pravastatin-treated group. This was associated with a 16% reduction in the HR with high-intensity treatment (5–26%; p = 0.005). Despite a disclaimer that the measured outcome was not the achieved LDL-C level, the authors concluded that these results supported a target LDL-C lower than 70 mg/dL (1.8 mmol/L) for patients following acute cardiac events. The PROVE IT-TIMI 22 study group published a post hoc analysis based on the high-intensity treatment arm of their dataset and observed that there was a nonsignificant trend toward fewer cardiac events in the lowest LDL-C groups (p trend = 0.1) with the lowest rates in the 40 to 60 mg/dL (1.0 to 1.6 mmol/L) and <40 mg/dL (<1.0 mmol/L) LDL-C groups [26].

In the same year, the Treating to New Targets (TNT) study published similar findings [27]. More than 10,000 patients with coronary heart disease (CHD), but no acute events, and LDL-C of less than 130 mg/dL (3.4 mmol/L) were randomized to either an 80 mg atorvastatin-treated group or a 10 mg atorvastatin-treated group after a run-in period during which all patients took 10 mg of atorvastatin. They reported a 22% relative reduction in risk [HR 0.78 (0.69–0.89), $p < 0.001$] with no difference between the two treatment groups in overall mortality. A subsequent substudy of this trial did not show a statistically significant reduction in cardiac events to be associated with 3-month LDL-C levels [28].

After the publication of the PROVE IT-TIMI 22 and TNT results, increasing attention was dedicated to testing the hypothesis that “lower is better” pertaining to treating LDL-C. The concept that more intensive treatment and lower LDL-C levels provided greater benefit was also supported by carefully done studies relating the regression of intravascular lesions to LDL-C levels [29]. In 2010, the Cholesterol Treatment Trialists’ (CTT) Collaboration compiled a meta-analysis of individual participant data ($N = 170,000$) from 26 randomized trials which compared high- to low-intensity statin regimens in patients with and without established CVD [30]. Although few of the included studies individually revealed significant improvements in CVD outcomes with more intensive LDL-C lowering, the meta-analysis suggested that a linear relationship exists between achieved LDL-C level and CVD outcomes. They stated that each 38.7 mg/dL (1.0 mmol/L) reduction in LDL-C, with a standard statin regimen, reduced the incidence of major vascular events (defined as nonfatal myocardial infarction or coronary death, any stroke, or coronary revascularization procedure) by about 20% [30]. While the authors did not mention an absolute lower LDL-C threshold, this meta-analysis became a key reference for both American and European guidelines recommending that clinicians pursue LDL-C levels lower than 70 mg/dL (1.8 mmol/L) [6, 7].

After these landmark treatment intensity trials, the hypothesis was that more intensive statin treatment would lead to more profound reductions in cardiac events. This was followed by more recent trials examining statin treatment with adjunctive therapy, such as the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [31]. The IMPROVE-IT reported lower risk in the simvastatin–ezetimibe-treated group compared to the simvastatin–monotherapy-treated group, with an HR of 0.936 (0.89–0.99; $p = 0.016$) for the risk of death from cardiovascular causes, major coronary event, or nonfatal stroke. It should be noted that 42% of the patients in each study group discontinued the study medication without having died, or the primary endpoint and missing achieved LDL-C values were imputed. Additionally, the study entry criteria for LDL-C levels had an upper limit of 100 mg/dL (2.6 mmol/L) if patients were on a lipid-lowering therapy at the time of recruitment and an upper limit of 125 mg/dL (3.2 mmol/L) if patients were not on lipid-lowering therapy at the time of recruitment.

Percent Reduction in LDL-C

Recent amendments to guidelines have incorporated percent reduction in LDL-C as part of the recommendations for treatment objectives, with a target of ≥50% reduction in LDL-C for high-risk patients with high-intensity statin treatment [6, 32••]. The assumption is that

greater reductions in LDL-C will yield greater benefit in CVD risk reduction. The primary sources of information estimating a linear relationship between the magnitude of LDL-C reduction and risk of CV outcomes are meta-analyses and reviews [5, 30, 33]. While the CTT meta-analysis of 26 trials suggested that there is increasing benefit yielded with greater percent reductions in LDL-C [30], one early post hoc analysis based on the 4S trial data concluded that the relationship was curvilinear, with clinical benefit leveling off at greater percent reductions in LDL-C [34].

Many major primary and secondary prevention trials demonstrated between an average of 20–40% reduction in LDL-C from baseline [1, 2, 19, 27, 35, 36]. More recently, trials examining high-intensity statin treatment have reported the largest percent reductions in LDL-C, both for primary and secondary prevention. The PROVE IT-TIMI 22 study of high-intensity statin treatment reported the greatest average percentage reduction in LDL-C (51%), but this percent reduction was only for treatment-naïve patients within 30 days of follow-up [25]. Additionally, the average percent reduction in LDL-C for patients who were non-statin treatment naïve at baseline was 32%. Further, patients for the study were recruited in the inpatient setting, who had an ACS in the preceding 10 days, which meant that their LDL-C levels were possibly still unstable at baseline even though there was a 24-h stability requirement for inclusion. There was also a fairly high incidence of early revascularization in this trial (79%), which has been highlighted as a potential contributing factor to the observed lower CV risk [37].

The JUPITER trial, which evaluated high-intensity statin treatment for primary prevention also reported a fairly high average percentage reduction in LDL-C of 41.2–42.8% from a baseline mean LDL-C of 104 mg/dL (2.7 mmol/L) among patients taking rosuvastatin 20 mg versus placebo [38]. The entry criteria for patients in the study had an upper LDL-C limit of 130 mg/dL (3.4 mmol/L) for LDL-C, meaning that the study population had lower starting LDL-C levels than average for primary prevention. Further, the trial was discontinued early, and therefore, this reporting should be interpreted with caution as the median follow-up period was only 1.9 years. Consequently, guidelines that advise treatment goals of ≥50% reduction in LDL-C for high-risk patients with high-intensity statin treatment are not well supported by the individual trial evidence.

These above-reported results are population averages and, as has been shown in meta-analyses of trial data, there is a wide range of individual variation in the percent LDL-C reductions [38, 39]. One recent analysis concluded that baseline LDL-C plays a distinct role in determining individual statin treatment effect, independent of individual risk, and, therefore, warrants particular focus in treatment decisions [9••]. Additionally, the individual variation in LDL-C is just one component of a patient’s total risk of first-time or recurrent CV events. As some have argued, focusing on just one factor of a patient’s risk is not sufficient for preventing major events, given that the numbers needed to treat (NNT) are relatively high for preventing one major event [40, 41]. These varied risk factors become even more prominent in the discussion on the use of statins for primary prevention, where the trade-offs in benefit and harms may not be as straightforward or as easily justified.

Use of Risk Modeling for CV Risk Stratification

In ATP II and III, the NCEP expert panel emphasized that assessing CVD risk among persons without a history of CVD was paramount to identify those patients in whom, after the failure of diet and exercise, one might justify the administration of medication for primary prevention [4, 12]. The ATP reports initiated a shift in the focus of treatment decision-making from specific biomarker targets to a patient's multidimensional set of risk factors and highlighted the need for refinement and further validation of CV risk models. The European Joint Task Force also emphasized the use of risk estimation to help physicians in making treatment decisions [13]. The Framingham Risk Score was the first major population-based risk model developed in the late 1990s, with an increasing number of risk models developed since then. Early European guidelines used adaptations of the Framingham Risk Score but were subsequently replaced by the Systematic Coronary Risk Evaluation (SCORE) project in 2003 [42] because it was thought that the US population used for the Framingham Risk Score was not representative of European populations. Since the initial SCORE project, there have been attempts to define unique scores for individual countries of the European region [43, 44].

Wading through the plethora of risk models to identify their utility in diverse contexts requires sifting through the various technical aspects of these models to understand the implications for practical application: aspects such as the endpoints, covariates, time horizons, predictive performance (discrimination and calibration), and risk thresholds [45]. In a recent systematic review of CV risk models, more than 70 different definitions were identified for the two most common endpoints of fatal or nonfatal CHD or the combined outcome of CVD [46•]. As the authors highlight, different definitions of CVD endpoints lead to different estimated predictor effects and predicted probabilities, which, in turn, would indicate different treatment strategies. This review concludes that most existing prediction models have not been directly compared or externally validated and many do not provide sufficient information to even allow for external validation by others. While population-based risk models enable the consideration of multiple factors that contribute to an individual's risk of heart disease, a substantial issue remains unresolved about how they might best be used in clinical practice for determining individualized treatment decisions.

In November 2013, a joint committee of the American College of Cardiology/American Heart Association (ACC/AHA) published new guidelines for the treatment of cholesterol to reduce cardiovascular risk in the USA, which continued the ATP III's focus on population-based risk stratification for statin treatment decisions [32••]. A set of risk equations called the pooled cohort equations (PCEs) was prominent in these guidelines. These risk equations based on pooled cohort data included risk scores for both white and black men and women [47]. Without compelling evidence in the literature for setting specific LDL-C targets for primary prevention, the ACC/AHA committee's recommendations were centered on the intensity of treatment, recommending higher-intensity treatment regimens for individuals at greater estimated CVD risk of ≥7.5%, based on the PCE risk calculation. In a tacit concession to the limited specificity of population-based risk scores when applied to individuals, the committee also suggested that serious discussion takes place between the physician and patient when deciding on statin treatment for primary prevention.

Criticism of the PCEs and their accompanying guidelines quickly emerged, claiming that the new guidelines and equations could result in overtreatment or unnecessary treatment with "more than 45 million middle-aged Americans who do not have CVD being recommended for consideration of statin therapy (33, 090, 000 at ≥7.5% 10-year risk)" [48]. A study published shortly after the release of the new guidelines showed that the PCEs substantially overestimated risk among three contemporary observational cohorts [49], which was likely because the pooled cohort risks were based on relatively old datasets [50•].

In efforts to test the clinical applicability of pooled risk model recommendations in different populations, Kavousi and colleagues compared the PCEs using CVD and stroke to the ATP III 10-year risk of CHD-only guidelines and to the European Society of Cardiology (ESC) guidelines among a European cohort aged 55–75 years and older from the Rotterdam study [49]. The proportion of men for whom treatment would be *recommended* (versus *considered* and *no treatment*) was 96.4% based on the ACC/AHA guidelines, whereas based on the ESC and ATP III guidelines, treatment would be recommended for 66.1 and 52.0% of men, respectively. These proportions for women were 65.8, 39.1, and 35.5% in the ACC/AHA, ESC, and ATP III guidelines, respectively. Some of this discrepancy comes from the different endpoints used in the different models, which underscores how treatment decisions are directly tied to the type of events considered in the outcomes. It is important to note that all three risk models provided only moderate to good discrimination [with c-statistics ranging from 0.67 to 0.77 (95% CIs ranged between 0.62 and 0.83) for men and women among the three models] and poor calibration with all overestimating the risk. The authors called for a search for better population-wide predictive models.

These population-based risk models do not account for the harms or side effects of initiating statin treatment in patients without known CVD, which would require harm-benefit assessment for individual patients. Additionally, the use of population-based risk models and corresponding risk thresholds inherently assumes that treatment benefits are constant for all eligible individuals; however, treatment response is not uniform and may vary considerably among individuals [10•].

Individualized Treatment Effect and Clinical Relevance

A recent a review by van der Leeuw and colleagues has highlighted the importance of moving from population-based risk models to methodologies yielding individual *treatment scores* that would summarize the benefits and harms of starting statin therapy to the individual patient and ideally minimize unnecessary treatment [51••]. Determining individualized treatment effect can be achieved by modeling available group-level data from clinical trials. In order to make clinical trial results more relevant for individual patient treatment decisions, NNT has been noted as an easier and more clinically meaningful measure than absolute or relative risk reductions [51••]. NNT is the number of patients in that particular population who would have to receive therapy in order to prevent one event, which can be calculated by applying individuals' absolute risk reduction to the risk ratio for the population from clinical trial data.

One study employed such clinical trial data from the TNT and Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trials to assess individualized predicted treatment effect for patients with stable coronary artery disease (CAD) [52]. The authors developed and validated a model using 13 clinical covariates to predict the effect of high-dose statins for individual patients in reducing a 5-year absolute risk of major adverse cardiac events, and demonstrated an improvement in NNT from ≥50 to ≤25. They qualify, however, that the development and validation of this model were based on selective clinical trial patient populations.

In an examination of optimal treatment strategies for primary prevention, another group of researchers conducted simulations comparing an estimated net benefit “tailored treatment” strategy to a “treat-to-target” strategy [53]. They found that a tailored treatment strategy prevented more CAD morbidity and mortality and resulted in higher treatment efficiency. It has also been proposed that NNTcan be reported as individual numbers needed to treat (iNNT), which would be based on the specific characteristics of the patient [51••]. The use of such an iNNT could help identify the particular intervention that would have the greatest impact on prevention, i.e., stopping smoking versus losing weight versus starting a statin.

Thanassoulis and colleagues evaluated the iNNT approach to risk management in a proof-of-concept study using data on 2134 individuals from the NANHES study group [10•]. They compared an individualized benefit approach with a more standard population-based risk approach and extrapolated the results to the US population and found that a benefit-based strategy would prevent an additional 266,508 cardiovascular events over 10 years. Nine and a half million patients were identified with the benefit-based approach who were expected to benefit from statins, but who, with the population risk-based approach, had lower risk (<7.5% risk). The population they identified with this approach was also younger than the population identified by traditional risk assessment (mean age of 55.2 versus 62.5 years; $p < 0.001$) with higher LDL-C [140 versus 133 mg/dL (3.6 versus 3.4 mmol/L); $p = 0.01$]. This benefit-based approach could also, therefore, deviate from the strong influence of age found in population-based risk stratification and lead to younger patients with substantial risk to be eligible for preventive measures much earlier in the course of their disease. They also make the observation that computing individual numbers needed to harm (iNNH) on this same population suggests that high potency statins may not be ideal for primary prevention. A challenge in assessing individual treatment benefit is incorporating the trade-offs of potential side effects and evaluating absolute risks of harm. This difficulty derives from the relative scarcity of serious side effects and the difficulty in calculating harm scores when occurrences in clinical trials are rare [51••].

An issue that has been raised in examining the risks and benefits of statin treatment is the question of these trade-offs in elderly patients (older than 65 years of age) who have often been absent from much of the clinical trial data and for whom the question of primary prevention is particularly complex [54]. Employing an individualized benefit approach to elderly populations over 70 years of age, Stam-Slob et al. [55•] analyzed individual absolute risk reduction (i-ARR) among individuals with and without vascular disease from several clinical trials. They assessed individual benefit and harms by accounting for physicians’ willingness to treat and compared three treatment strategies for primary and secondary

prevention separately: treat none, treat all, and treat based on risk model prediction. Their findings underscore the advantages of using individualized risk and benefit modeling for primary prevention treatment decisions to discern who will benefit most from statin therapy, even in elderly populations.

Summary

Differences between guideline recommendations exist, with some focused on specific LDL-C treatment targets, others on percent reduction of LDL-C, and yet others on intensity of treatment and patient risk. With such variance in expert recommendations, it is clear that the available evidence is inconclusive. There is general agreement that a single population-based average marker such as LDL-C level is a crude target for individual patient treatment decisions; however, target LDL-C levels can be an important element for practical use in engaging and motivating patients. This review found that there is a lack of robust evidence from major clinical trials to support specific achieved LDL-C or LDL-C percent reduction targets [i.e., <70 mg/dL (1.8 mmol/L) or ≥50% reduction], despite that these measures of cholesterol are important guides for physicians in treatment decisions. This review, however, is limited because it was not a systematic review and, rather, focuses on a historical overview and broad assessment of debated treatment target strategies found in the various sets of guidelines.

Conclusions

There is consensus that future treatment guidance for CVD prevention should move from specific population-based single marker targets toward treatment objectives based on individual benefit and harm trade-off assessments [56••]. Yet, the tools that currently exist to affect this paradigm shift are not ripe for practical application, given the underperformance, lack of accuracy, and scarce external validation for most of the population-based risk models. Furthermore, deficiencies in standardized definitions of endpoints and inputs can be prohibitive to the translation of tools' utility across contexts. This points to the challenges in clinical practice application of such models; therefore, it is likely premature to focus on specific recommended risk threshold targets for treatment initiation. The growth of electronic medical record databases comprising increasingly diverse populations will facilitate and advance the importance of utilizing individualized treatment goals through data analytics that assess individual treatment benefit and harms. This will provide interactive tools to determine the individual patient's net benefit for the practicing physician. Until then, the practicing physician will utilize individual risk factors, achieved LDL-C target levels, and discussions with patients regarding personal benefits and risks.

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