



Low-density lipoprotein cholesterol goals: still not in patients' best interest

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Abstract

In what became a highly-publicised move, the American Heart Association (AHA) and American College of Cardiology (ACC) effectively dropped low-density lipoprotein cholesterol (LDL-C) goals from their most recent guidelines pertaining to the matter. However, due to developments since the AHA and ACC released their current guidelines, some have called for a return to focusing on LDL-C goals. This article puts forth an overview of the salient issues at hand, important evidence-based considerations, and a conclusion that shifting focus away from LDL-C goals is clearly an evidence-based step in the right direction. Indeed, careful scrutiny of the current evidence base shows returning to LDL-C goals would be a mistake, and we should focus instead on overall cardiovascular risk, medications proven to reduce patient-relevant outcomes, and shared decision-making.

Introduction

The American Heart Association (AHA) and American College of Cardiology (ACC) effectively dropping low-density lipoprotein cholesterol (LDL-C) goals from their most recent guidelines on the matter¹ represented a paradigm shift in the prevention and management of cardiovascular disease. Although this was not a universally popular move, in the wake of the IMPROVE-IT trial and the recent approval of two proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, some have now formally called for a return to focusing on LDL-C goals.² Is this really wise, though? Quite the contrary, careful scrutiny of the literature reveals this would be stepping in the wrong direction.

We do not have high-quality evidence from randomised controlled trials clearly demonstrating a benefit from treating to a particular LDL-C level (or any other cholesterol level, but the most fervent attention has been directed toward LDL-C levels). This is not equivocal, and it is for this reason the AHA and ACC appropriately changed their stance on treating to a target LDL-C level.¹ Likewise, no other medication in this general category fares better than statins with respect to reducing patient-relevant outcomes. (Patient-relevant outcomes are, as the name implies, outcomes that truly matter to our patients; in other words, patients ultimately only care about cholesterol, blood pressure, and similar surrogate markers because they want to avoid suffering a myocardial infarction (MI), stroke, and the like.) The AHA and ACC guidelines, though not necessarily flawless, get this right as well.¹ Are the statins or their data perfect? Certainly not. Are the statins a panacea? No. Should they be blindly prescribed? Never. Is the 10-year atherosclerotic cardiovascular disease risk threshold set by the AHA and ACC appropriate? Adopting a strategy

of shared decision-making whenever feasible is more appropriate, and to the guideline authors' credit,¹ they mention patient preferences 18 times in the body of the guidelines (with one additional mention in the appendices); however, one wishes the guidelines would have expounded further on the basic principles of shared decision-making, as this is central to any meaningful consideration or utilisation of patient preferences. Shared decision-making is a fundamental aspect of patient-centered medicine, and it amounts to a partnership between the provider and patient that involves: (1) informing the patient about his/her condition(s) and the evidence surrounding the treatment options available, (2) informing the patient in a manner that is understandable to him/her, and (3) exploring and respecting the patient's values and preferences in order to reach a personalised, informed decision regarding the best approach for his/her particular case. Still, even with all these important considerations about statins, based on the currently-available evidence, statins still clearly perform the best with respect to reducing cardiovascular outcomes, and we should not merely focus on LDL-C levels.

Basic considerations of LDL-C as a surrogate marker

The fact that higher LDL-C levels are associated with increased cardiovascular disease risk does not necessarily mean reducing LDL-C levels by any means will improve cardiovascular outcomes. There is evidence that patients on *statins* with lower LDL-C levels fare better with respect to cardiovascular outcomes; however, it is important to remember this does not mean the lower LDL-C levels were the sole or driving reason for this improvement *per se*, this does not mean reducing LDL-C by any means improves patient-relevant outcomes, and these truths still hold even when considering individual patient data meta-analyses (IPD MAs).³⁻⁵ Interestingly, even the IPD MAs noted the cardiovascular benefit offered by statins was largely unaffected by baseline LDL-C,³⁻⁵ and although proponents of LDL-C targets could try to use this to support the notion that lower LDL-C levels translate to better outcomes irrespective of the baseline LDL-C, the counterview is at least two-pronged: First, it is imperative to remember the data in the IPD MAs came exclusively from statin trials, and statin trials have only studied fixed doses of statins, not statins specifically titrated to various LDL-C levels; second, the beneficial effect being seemingly unaffected by baseline LDL-C could also readily suggest that statins' ability to lower LDL-C is at best just one part of how statins exert beneficial effects on cardiovascular outcomes. It is well-appreciated that statins have effects other than LDL-C reduction (ie, statins have pleiotropic effects).⁶⁻⁸ Thus, effects other than LDL-C reduction

may partly, mostly, or entirely explain the benefits offered by statins even though statins also reduce LDL-C.

Importantly, focusing on LDL-C instead of overall cardiovascular risk could also result in overtreatment of those with isolated LDL-C elevation with low cardiovascular risk or undertreatment of those with elevated cardiovascular risk but low or 'acceptable' levels of LDL-C. Furthermore, medication dose and adherence are important considerations; it would come as no surprise for statin regimens that are more closely adhered to and/or more intense to yield improved outcomes and lower LDL-C levels, even if the LDL-C reduction is merely an epiphenomenon or only partly causal but not fully explanatory of the beneficial mechanism(s) driving the improvement in outcomes. For instance, although it may not provide much insight into varying adherence, the TNT trial provides an example of varying statin intensity.⁹ In the TNT trial, patients with clinically-evident coronary heart disease (CHD) were randomised to either 10 mg or 80 mg of atorvastatin. Compared to the 10 mg group, after a median follow-up of 4.9 years, the 80 mg group experienced a reduction in mean LDL-C levels of 24 mg/dL and a 2.2% absolute risk reduction (ARR) in major cardiovascular events (a composite of CHD death; nonfatal, non-procedure-related MI; resuscitation after cardiac arrest; or fatal or nonfatal stroke), meaning about 46 people with clinically-evident CHD would have to be treated for a median of 4.9 years with 80 mg of atorvastatin instead of 10 mg of atorvastatin for one person to avoid a major cardiovascular event (number needed to treat to benefit one person (NNT, NNTB), 46).

Add-on trial failures

It is also instructive to consider trials of agents added to statin therapy where the agent affected the lipid profile but did not translate into incremental benefit in patient-relevant outcomes. Adding extended-release niacin or a cholesterol ester transfer protein (CETP) inhibitor to statin therapy—as assessed in AIM-HIGH,¹⁰ HPS2-THRIVE,¹¹ dal-OUTCOMES¹² and ILLUMINATE¹³—are examples. These agents may not offer as prominent a reduction in LDL-C as the PCSK9 inhibitors, but niacin and the CETP inhibitors still reduced triglycerides, increased high-density lipoprotein cholesterol (HDL-C), and/or reduced LDL-C; despite these changes, they failed to add incremental benefit to statin therapy with respect to clinical outcomes (see table 1).^{10–13} Additionally, one must remember ILLUMINATE was terminated early after a median follow-up of only 550 days due to a 0.4% absolute risk increase (ARI) in all-cause mortality in the group receiving the CETP inhibitor torcetrapib (number needed to treat to harm one person (NNH, NNTH), 250; hazard ratio (HR), 1.58; 95% CI 1.14 to 2.19; $p=0.006$).¹³ There was also a 1.2% ARI in the primary composite outcome (NNTH, 83; HR, 1.25; 95% CI 1.09 to 1.44; $p=0.001$) of CHD death; nonfatal, non-procedure-related MI; stroke; and hospitalisation for unstable angina (driven to significance primarily by hospitalisation for unstable angina). These outcomes occurred even with the torcetrapib recipients having notable decreases in LDL-C and increases in HDL-C (see table 1). The authors

offered two possibilities for this occurrence: an 'off-target' effect of torcetrapib or a specific effect of the drug in producing aberrant HDL-C. HPS2-THRIVE was concerning for increases in several adverse outcomes (eg, gastrointestinal, musculoskeletal, infectious and serious bleeding) among those receiving extended-release niacin and laropiprant.¹¹ Additionally concerning was the 0.5% ARI in all-cause mortality; this failed to reach conventional statistical significance (rate ratio, 1.09; 95% CI 0.99 to 1.21; $p=0.08$), but it is still noteworthy given HPS2-THRIVE was larger than ILLUMINATE and the all-cause mortality rate in HPS2-THRIVE was slightly greater than that which led to the termination of ILLUMINATE.^{11–13} After HPS2-THRIVE was published, the authors of AIM-HIGH published an exploratory re-examination of their data that found increases in infection and bleeding outcomes consistent with HPS2-THRIVE (increases in gastrointestinal events were also seen, but this was largely expected).^{10–14}

IMPROVE-IT

Amidst this representative sample of negative add-on trials, IMPROVE-IT is the first—and to date, only—major clinical trial to show incremental benefit in clinical outcomes from adding another agent to statin therapy.¹⁵ IMPROVE-IT was an event-driven trial in secondary prevention that had a median follow-up duration of 6 years, and participants were randomised to receive either simvastatin plus placebo or simvastatin plus ezetimibe. IMPROVE-IT investigators ultimately specified a goal of 5250 events and a minimum follow-up duration of 2.5 years, but the initial ClinicalTrials.gov registry entry for this trial (NCT00202878) from 19 September 2005 (https://clinicaltrials.gov/archive/NCT00202878/2005_09_19) is disappointingly vague (though it did at least indicate the overarching elements of the primary composite endpoint and the basic inclusion and exclusion criteria). The event-driven nature was not clearly specified until the ClinicalTrials.gov registry was updated on 3 January 2008 (https://clinicaltrials.gov/archive/NCT00202878/2008_01_03). Later in 2008, the rationale and design were published, and the authors specified an original intent for 2955 events and a minimum follow-up duration of 2.5 years.¹⁶ The goal number of events was subsequently amended to 5250 when trial leadership reviewed new evidence published since IMPROVE-IT's inception (including, but not limited to, pooled and blinded data emerging from IMPROVE-IT).¹⁶ The lack of detailed *a priori* registration of IMPROVE-IT is inexcusable, though this is, unfortunately, not a problem unique to IMPROVE-IT.¹⁷ Setting aside these considerations, at 7 years (when the target number of events had been reached and actually slightly surpassed), there was a 2% ARR (HR, 0.936; 95% CI 0.89 to 0.99; $p=0.016$) in the simvastatin–ezetimibe arm for the primary composite outcome of cardiovascular (CV) death, major coronary event, or nonfatal stroke. This reduction translates to an NNTB of 50 over 7 years, and using the 95% CI for the HR and the control event rate (34.7%), one can calculate a 95% CI for the NNTB of 32 to 359 over 7 years. None of the fatal outcomes (including CV death, CHD death, death from any cause, and fatal MI) were significantly different between the

Table 1 Effects on LDL-C, HDL-C, triglycerides, and the primary composite endpoint for the statin plus add-on agent arms of AIM-HIGH, HPS2-THRIVE, dal-OUTCOMES, and ILLUMINATE¹⁰⁻¹³

Study	Add-on agent studied	At final recording, compared to baseline within-group (statin+add-on agent) measurement			Effect estimate (95% CI) for primary endpoint*
		Δ LDL-C	Δ HDL-C	Δ triglycerides	
AIM-HIGH†	ER niacin	-11 mg/dL	+7 mg/dL	-45.5 mg/dL	NA
HPS2-THRIVE‡	ER niacin-laropiprant	-10 mg/dL	+6 mg/dL	-33 mg/dL	NA
dal-OUTCOMES§	dalcetrapib	+6.4 mg/dL	+16 mg/dL	+5.8 mg/dL	NA
ILLUMINATE¶	torcetrapib	-21.5 mg/dL	+34.2 mg/dL	-10 to 15 mg/dL	NA
At final recording, compared to final recording of statin-only group					
AIM-HIGH†	ER niacin	-6 mg/dL	+4 mg/dL	-31 mg/dL	HR 1.02 (0.87 to 1.21)
HPS2-THRIVE‡	ER niacin-laropiprant	NR	NR	NR	RR 0.96 (0.90 to 1.03)
dal-OUTCOMES§	dalcetrapib	NAD	+12.5 mg/dL	-5.8 mg/dL	HR 1.04 (0.93 to 1.16)
ILLUMINATE¶	torcetrapib	-22.4 mg/dL	+33.7 mg/dL	-11 mg/dL	HR 1.25 (1.09 to 1.44)

*Only the primary composite endpoint effect estimates are provided; thus, the reader is encouraged to consult the text of this article, as well as the corresponding cited publications, to appreciate more completely all the findings (including adverse effects) documented by these trials.

†Data reported are based on median changes at 2 years and come from table 2 of AIM-HIGH.¹⁰ The respective data at 3 years (with fewer participants) were either not materially different from or were identical to the data at 2 years. The primary composite endpoint included death from coronary heart disease, nonfatal myocardial infarction, ischaemic stroke, hospitalisation for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization.

‡Data reported are based on study-averaged changes (weighted for participant-years at risk within region) and come from table S2 of HPS2-THRIVE.¹¹ Median follow-up was 3.9 years. The primary composite endpoint included major coronary events (nonfatal myocardial infarction or death from coronary causes), stroke of any type, or coronary or noncoronary revascularization.

§Data reported are based on table 1, figure 1, and figure S2 of dal-OUTCOMES and are reported for the 36-month point (median follow-up in the trial was 31 months, and although the figures provided preclude precise estimation at 31 months, visual inspection suggests the results at 31 months would not be materially different for any of the basic lipid parameters reported in the table).¹² The primary composite endpoint included death from coronary heart disease, nonfatal myocardial infarction, ischaemic stroke, unstable angina, or cardiac arrest with resuscitation.

¶Data reported are based on table 2 and web figures 1a and 1b of ILLUMINATE and are mean change at 12 months, except for triglycerides, which is reported as median change.¹³ Median follow-up at termination was 550 days (approximately 18 months), but data up to this point are not available. Note: There are discrepancies for these parameters between table 2 and the web figures. In most instances, where discrepancies occur for these values, they are on the order of 0.1 mg/dL and conceivably due to issues encountered with rounding. For triglycerides, however, there is a 5 mg/dL difference between table 2 and web figure 1b, which is the reason for the range listed for triglycerides. The primary composite endpoint included death from coronary heart disease, nonfatal myocardial infarction (excluding procedure-related events), stroke, and hospitalisation for unstable angina.

CI, confidence interval; ER, extended-release; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; NAD, no appreciable difference; NR, not reported; RR, rate ratio.

groups. The authors pre-specified a considerable number of subgroup analyses, and although they must always be interpreted with caution,¹⁸⁻²⁰ there was a significant subgroup interaction for age dichotomized at 75 years (p for interaction 0.005, with directionality favoring those 75 years old or older) and diabetes mellitus (p for interaction 0.023, with directionality favoring those with diabetes). Notably, however, the multiplicity of the subgroups analyzed was not addressed, which raises the possibility of false-positive findings.¹⁸⁻²⁰ The effect estimate of a 2% ARR (NNTB of 50) over 7 years seems rather modest, and cost also warrants consideration since ezetimibe is still unavailable in generic form. Still, IMPROVE-IT demonstrated there was another agent that could be added to statin therapy to yield incremental benefit with what appears to be marked safety, and there was also a median time-weighted average difference in LDL-C between the two groups of 15.8 mg/dL. Does this warrant a return to LDL-C goals? Even if one set aside the considerations laid out thus far, the answer is still no. The authors note the magnitude of reduction in LDL-C and cardiovascular outcomes in IMPROVE-IT

is consistent with that seen in the aforementioned statin IPD MAs,³⁻⁵ and this is indeed noteworthy since the additional reduction in LDL-C and cardiovascular outcomes in IMPROVE-IT came from ezetimibe. However, the authors also rightly note: "This trial cannot prove that the effect was mediated by the lowering of LDL cholesterol levels alone, since changes in other lipoproteins and high sensitivity C-reactive protein may have played a role" (ref. 15, p. 2394). In correspondence following the publication of IMPROVE-IT, Egom also rightly reiterated²¹ the fact that pleiotropic effects for ezetimibe have been described elsewhere, and the IMPROVE-IT investigators again acknowledged this in their response: "As we mentioned in the Discussion section of our article, we cannot determine whether, or to what degree, the clinical benefit seen when ezetimibe was added to simvastatin in IMPROVE-IT was mediated solely by the lowering of LDL cholesterol levels or to effects on high-sensitivity C-reactive protein, other lipoproteins such as triglycerides (as noted by Patti and Cavallari), or other potential pleiotropic effects" (ref. 22, p. 1477). One must also remember IMPROVE-IT was not

designed to test various LDL-C targets; rather, it was still ultimately a fixed-dose and fixed-medication study. It is also worth noting that IMPROVE-IT is the only evidence corroborating any kind of patient-important benefit from ezetimibe; despite considerable use of ezetimibe in both primary and secondary prevention prior to the results of IMPROVE-IT being available, there was never any good evidence of benefit with respect to patient-important outcomes prior to IMPROVE-IT. Furthermore, IMPROVE-IT only provides information about secondary prevention, and it would be imprudent to extrapolate these data to primary prevention. Finally, since the statin in IMPROVE-IT was simvastatin 40 mg, IMPROVE-IT only provides information about secondary prevention in patients who cannot tolerate high-intensity statin therapy, and it remains quite possible that the modest additional risk reduction in the simvastatin-ezetimibe arm would have been eclipsed if a high-intensity statin had been used.

The PCSK9 inhibitors

The PCSK9 inhibitors are monoclonal antibodies that bind to and inhibit the PCSK9 enzyme. Inhibition of the PCSK9 enzyme ultimately interferes with lysosomal degradation of hepatocyte LDL-C receptors, and the resultant increase in LDL-C receptors on hepatocytes leads to a prominent reduction in LDL-C.²³ The recently-published data from the OSLER²⁴ and ODYSSEY LONG TERM²⁵ trials and the meta-analysis of phase III trials of PCSK9 inhibitors²³ sparked much interest in the potential utility of these agents (particularly the meta-analysis, which reported a preliminary suggestion of reduction in cardiovascular events and total mortality). However, amidst other limitations in these data, it must be emphasised these data can only be considered preliminary, as they: do not come from large, rigorous clinical efficacy trials; provide only a small number of events from which to estimate anything about their potential efficacy; and do not provide satisfactory information about safety. Indeed, although the preliminary data do stimulate interest for the results of properly-designed outcomes trials, as the Food and Drug Administration (FDA)—and even some of those who mistakenly espouse a return to LDL-C goals—have plainly noted,² we currently lack reliable outcomes data for the PCSK9 inhibitors, and we also need further evaluation of potential adverse effects of these novel agents. What we need in the interim are evidence-conscious providers who remain cognizant of these issues. Regressing to LDL-C goals is not the answer, and the fact that multiple other guidelines continue to utilise LDL-C goals² indicates neither the need to return to such a paradigm nor the adequacy of the data surrounding such a choice. Indeed, highlighting the prevalence of LDL-C goals in other guidelines as an implicit measure of the appropriateness or utility of LDL-C goals² ultimately amounts to an admixture of *argumentum ad verecundiam* (argument from authority) and *argumentum ad populum* (argument from popularity). Truth, however, is not measured in mass appeal.

It would be hard to imagine anyone who would want properly-designed outcomes trials of the PCSK9

inhibitors to end up being negative. Having additional agents with proven beneficial effects is certainly desirable; however, capriciously using PCSK9 inhibitors with mistaken excitement and hopeful beneficence is inappropriate. Contrary to what some suggest,² we do not need LDL-C goals to prevent mistaken use of what promises to be an expensive class of medications. The basic responsibility of healthcare providers to judiciously appraise and apply the literature and available treatments will prevent this. A question arises, however, if the PCSK9 outcomes trials are positive: Would this hail a return to LDL-C goals? It would offer further support to the LDL-C hypothesis, but it would not provide incontrovertible evidence that the LDL-C reduction is the reason for the improvement in outcomes, it would not provide guidance for what a reasonable LDL-C goal might be, and importantly, it would not prove that reducing LDL-C by any means is beneficial. Some of the aforementioned trials loom large here, but let us also briefly step away from chronic disease management to consider, for instance, an analogy of fever and leucocytosis in someone with bacterial pneumonia. Acetaminophen and any of the non-steroidal, anti-inflammatory drugs will likely lead to complete or partial defervescence, but would any of these agents help the bacterial pneumonia specifically? Similarly, various immunosuppressive agents could be used to reach a 'goal' of complete or near normalisation of the leucocyte count, and these agents could even potentially continue to decrease the leucocyte count beyond 'goal' levels, but would any provider ever prescribe any of these agents to treat the bacterial pneumonia? Antibiotics, on the other hand, are obviously indicated, and it is worth noting there is often more than one antibiotic choice when treating bacterial pneumonia. Selecting a correct antimicrobial regimen will improve the fever and leucocyte count, but more importantly, the regimen will actually improve the pneumonia. This analogy is admittedly imperfect (eg, elevation in LDL-C is considered a risk factor for cardiovascular disease, whereas fever and leucocytosis are seen as a manifestation of bacterial pneumonia), but the absurdity of the analogy nevertheless helps make the point that we must not focus simply on treating a surrogate marker (LDL-C levels) when we lack proper data supporting such an approach; indeed, it is fallacious to assume that because surrogate X is associated with condition Y, and because one has medication Z (and/or A, B, C, etc) that reduces surrogate X, it must then follow that reducing surrogate X with medication Z (and/or A, B, C, etc) will certainly improve condition Y. The unequivocally disastrous use of class I antidysrhythmics in a prophylactic manner after MI also serves as a chilling example of how treatment of a surrogate marker without proper antecedent study can be harmful, even if the surrogate marker seems reasonably linked to a bad outcome.²⁶ Likewise, with respect to glycaemic control and macrovascular outcomes in type II diabetes mellitus, although elevation in a surrogate marker may be linked to worse patient-relevant outcomes, simply pushing that surrogate marker as close to normal as possible and by any means necessary does not clearly offer benefit and can even cause harm (with the

potential harm ranging from increased medication burden and cost to increased hypoglycaemia and weight gain to possibly increased cardiovascular and total mortality).^{27–31} Although one might be inclined to contend these different surrogate marker examples cannot necessarily be treated the same way, that would miss the reason for including these examples; rather, these examples simply help to further establish the point that instead of unduly focusing on LDL-C levels, we must carefully consider the totality of the evidence we currently have and the potential mechanisms of cardiovascular risk reduction within that overall body of evidence. Additionally, even if quality evidence that truly justifies LDL-C goals were to one day accumulate, it would still be imperative for us to thoroughly understand and appreciate the importance of *how* we go about reducing LDL-C and how *far* we go.

Conclusion

Based on the currently-available evidence, we should focus on overall cardiovascular risk and risk reduction, not LDL-C goals. We should use estimates of overall cardiovascular risk as part of shared decision-making, which should also include: (1) providing an evidence-based estimate of the benefit a given patient might experience by taking a proven medication (based on the currently-available evidence, this amounts to a statin, or possibly a statin plus ezetimibe if judiciously applying the results of IMPROVE-IT); (2) considering cost, side effects, and the often-overlooked notion of general medication burden; and (3) exploring and respecting the patient's values and preferences after s/he has been duly informed. This is pivotal if we truly want to practice excellent, patient-centered medicine. As aforementioned, statins are still the agents of choice within this broad category of medications, and IMPROVE-IT showed us that ezetimibe can be considered as an add-on therapy in secondary prevention for patients who cannot tolerate high-intensity statin therapy. We should be mindful of the limitations in the current PCSK9 data and await results of properly-designed outcomes trials. Other add-on therapies have not yielded an improvement in clinical outcomes, and this is noteworthy beyond the notion of doing something for nothing. In addition to conferring no additional clinical benefit, patients will also experience increased medication burden in terms of quantity and cost, and there is also the potential for increased risk of adverse events. Perhaps we will one day have evidence supporting specific LDL-C goals, but it would be an embarrassing mistake to return to LDL-C goals based on the currently-available evidence. This controversial issue is unlikely to be resolved completely anytime soon, but at the very least, a unifying feature is our desire to serve our patients. Still, objective and critical appraisal and application of the evidence as a part of shared decision-making are the real needs in this arena, not LDL-C goals.

Key messages

- ▶ LDL-C goals are still advocated by some, but evidence and rationale truly supporting this approach are lacking.
- ▶ Patients and providers should instead use overall cardiovascular risk as a part of shared decision making when considering a medication proven to lower cardiovascular risk.
- ▶ Statins are still unequivocally the medication of choice within the broad category of medications including statins, fibric acid derivatives, bile acid sequestrants, niacin, ezetimibe, and the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.
- ▶ IMPROVE-IT shows ezetimibe can be considered as an add-on therapy in secondary prevention for patients who cannot tolerate high-intensity statin therapy. Compared to taking simvastatin 40 mg alone, ezetimibe 10 mg plus simvastatin 40 mg offers a 2% absolute risk reduction (number needed to treat to benefit one person, 50) over 7 years for the composite outcome of cardiovascular (CV) death, major coronary event, or nonfatal stroke, with benefits apparently limited to nonfatal outcomes.
- ▶ Currently-available evidence for the PCSK9 inhibitors is ultimately inadequate to support clinical use. Properly-designed outcomes trials will elucidate what role these agents might have in reducing cardiovascular risk.

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