



A review of the clinical evidence related to early treatment of elevated LDL for cardiovascular primary prevention

Kori Sauser,¹ Deborah A Levine,^{2,3} Rodney A Hayward^{2,3}

10.1136/ebmed-2015-110170

¹Department of Emergency Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

²Department of Medicine, University of Michigan, Ann Arbor, Michigan, USA

³Center for Clinical Management Research, Ann Arbor Veterans Affairs Hospital, Ann Arbor, Michigan, USA

Correspondence to:

Kori Sauser,

Department of Emergency Medicine, Massachusetts General Hospital, Zero Emerson Place, Suite 3B, Boston, MA 02114, USA; ksauser@mgh.harvard.edu



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Abstract

Background The American College of Cardiology/American Heart Association updated cholesterol treatment guidelines dropped treatment recommendations based on elevated low-density lipoprotein (LDL) levels. Yet some experts cite the benefit of early statins in patients with elevated LDL for preventing atherosclerosis. We sought clinical evidence for this early LDL treatment hypothesis.

Methods and results A review of the clinical evidence examining the relationship between LDL reduction and outcomes (excluding LDL >190). We found three arguments proposed in the literature citing clinical evidence supporting the early LDL treatment hypothesis: (1), lower risk patients get relatively more primary prevention benefit from statins than higher risk patients, (2), statins demonstrate a legacy effect with prolonged risk reduction even after stopping treatment, and (3), genetic studies illustrate the benefit of lifelong LDL reduction for lowering CV risk. A review of the primary evidence found little clinical evidence supporting the first two arguments, but strong grade B+ evidence for the third. However, we found no evidence for or against whether intervening before 10-year risk exceeds 7.5–12.5% would result in substantial incremental net clinical benefit. If early intervention is practiced, evidence to date suggests that overall CV risk should be the primary indication.

Conclusions We found consistent grade B+ evidence that the effectiveness of LDL reduction on risk reduction will increase over time, however, we found no clinical evidence for or against whether starting before 10-year CV risk is 7.5–12.5% provides substantive additional net patient benefit, and grade A- evidence that elevated age-adjusted CV risk should be the primary indication for early treatment, but found no evidence for or against whether degree of LDL elevation should be a secondary factor. Additional clinical research is needed, especially with regard the long-term safety of statins and how long it takes for LDL reduction to reach full effectiveness.

Introduction

In November 2013, the American College of Cardiology and American Heart Association (ACC/AHA) published updated guidelines for the treatment of blood cholesterol.¹ These guidelines recommend basing statin treatment for primary prevention on overall 10-year cardiovascular (CV) risk and no longer recommend treating based on specific low-density lipoprotein (LDL) levels unless it is *very high* (LDL >190 mg/dL).^{2,3} This decision was grounded in high-quality, randomised, controlled trial (RCT) evidence that one's pre-treatment LDL has no measurable impact on a statin's relative risk reduction (RRR) over a 5–10-year period.^{1–3}

However, not all guidelines have shifted to this approach, and some experts opposed the removal of treatment recommendations for elevated LDL from the new ACC/AHA guidelines. They objected to the guideline committee not considering the implications of the pathophysiological and observational evidence including subgroup analyses of RCTs. While RCTs only consider 5–6-year benefits, these experts argue that evidence demonstrates the advantage of early treatment of elevated LDL for prevention of atherosclerosis and long-term reduction in CV morbidity and mortality that is not achieved if treatment is delayed until 10-year CV risk is increased above a certain threshold (eg, 7.5%). We call this hypothesis the 'early LDL treatment hypothesis.' However, there is no systematic review of the clinical evidence for the early LDL treatment hypothesis.

To address this gap, we reviewed the RCT and longitudinal, observational (ie, cohort, case-control, and quasi-experimental design including Mendelian randomisation) literature to examine the degree to which the early LDL treatment hypothesis is supported by clinical evidence. We were interested in evidence regarding three separable aspects of the hypothesis: (1) evidence for the general early treatment hypothesis (ie, that there is a point at which atherosclerosis has advanced to where statins are substantially less effective than if they had been started earlier), and (2) evidence for the clinical benefit-based early treatment critique (ie, there are specific patients for whom waiting until CV risk is above 7.5% will result in a clinically meaningful reduction in quality or length of life, that could be prevented by lipid lowering being initiated at a specified earlier point in time), and (3) evidence for the LDL-based early treatment critique (ie, that moderate LDL elevation (LDL between 145 mg–190 mg/dL) should be a major determinant of patient selection for early treatment). In this paper, we report the results of our literature review for clinical evidence supporting the early LDL treatment hypothesis. We report our findings by describing the evidence related to the early LDL treatment hypothesis.

Methods

Literature search and review criteria

We first sought all RCTs examining the association between LDL reduction and patient outcomes. We began by reviewing the references from the 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol¹ and the 2012 Cholesterol Treatment Trialists' (CTT) meta-analysis evaluating the effect of LDL lowering for low risk patients.² In addition to RCTs, we sought clinical evidence from longitudinal observational designs including quasi-experimental, cohort and case-controlled studies. As a strong quasi-experimental design that has been well-applied in the cholesterol literature, we specifically sought Mendelian randomisation studies, which we



► <http://dx.doi.org/10.1136/ebmed-2015-110257>

identified using the PubMed search: (“cholesterol”[MeSH Major Topic] AND “genetic” AND (“low density lipoprotein” OR “ldl cholesterol”[Title/Abstract])). One author screened the 675 returned articles’ titles and abstracts. For each relevant article identified, we screened the references and checked related citations in PubMed, Scopus and Web of Science. Our results and discussion cite all articles that one of the authors found relevant to the early LDL treatment hypothesis.

Expert solicitation

Since the literature on lipids and CV disease is so vast, we also contacted experts in the field (based on guideline authorship and peer-reviewed publications) to solicit help identifying additional arguments and evidence. We especially targeted advocates of treating to LDL targets. We conducted a brief survey of a convenience sample of 19 experts identified by one of the authors (RAH). We informed the experts of the evidence we found, and requested any additional evidence related to early LDL treatment (solicitation email in online supplementary eAppendix 1). We sent a follow-up to non-responders after 1-week. Ten experts responded, identifying two additional articles and no additional arguments based on clinical evidence.^{4 5}

Focused data analysis

From the clinical trials, we extracted cohorts’ baseline risk of vascular events, pretreatment and post-treatment LDL levels in the control and treatment groups, groups’ event rates, and early trial termination. We derived the control and treatment groups’ relative and absolute risk rates for adverse events. For between-study comparisons, we standardised rates to absolute LDL reduction of 40 mg/dL and to 40% LDL reduction (roughly the expected response to 40 mg simvastatin). We used criteria outlined by the Agency for Healthcare Research & Quality to assess the quality of observational and quasi-experimental studies.⁶ We included all arguments with any ‘clinical evidence’ (true or quasi-experiments, cohort, or case-control studies); none were omitted due to the quality of the clinical evidence. Arguments based on pathophysiology or opinion alone were excluded.

Notably, there are small discrepancies in the outcomes used in the ACC/AHA guidelines and other analyses. This does not create major problems for our discussion here, as we are focusing on RRR rather than absolute risk reduction (ARR), but this is an important point to recognise in reviewing this literature and we addressed it to the extent possible.

Results

Our review of the medical literature identified three arguments that cited clinical evidence related to the early LDL treatment hypothesis proposed by advocates of the hypothesis.

Argument #1: Clinical trial evidence suggests that patients with lower CV risk have a higher RRR from statin therapy than those at higher risk. That is, statins are relatively more effective in lower risk patients than in higher risk patients.

Evidence: We found some clinical evidence to support this argument, which is largely based on a

subgroup analysis of the 2012 CTT meta-analysis, but this evidence has several problems.² The CTT investigators reported that there was a statistically significant trend for patients with a lower predicted 10-year CV risk having a greater RRR per absolute LDL reduction than patients with a higher 10-year CV risk ($p=0.003$ for trend). *The CTT group interpreted these results to support a similar RRR per amount of absolute LDL reduction for patients with low and high CV risk,*² but others have referenced this in support of the early LDL treatment hypothesis.⁷

These results do not necessarily apply to primary prevention patients or those with a 10-year risk less than 20%. We discuss methodological issues with this analysis below, but if these results hold up with further analysis (see online supplementary eAppendix 2), this finding would add support to the general hypothesis—in that those with highly advanced disease may get less benefit. However, this analysis does not provide clinical evidence addressing the specific clinical critique (that treatment must begin before CV risk is 7.5–12.5%), in that the relative risks are very similar in this analysis in all those with a 10-year CV risk <21–22%.

The meta-analysis findings may result from observational differences between statin trials rather than true variation in statins’ effect across patient groups: Briefly, the CTT analysis provides observational evidence because there was substantial between-trial differences in the amount of CV RRR demonstrated per LDL reduction.^{8–27} In online supplementary eAppendix 2, we explain this in more detail and propose a statistically robust analytic approach^{28 29} to examine for within-study heterogeneity in RRR by CV risk and provide stronger experimental evidence to clarify whether statins’ benefit for primary prevention differs between lower-CV risk patient and higher-CV risk patient groups.

Early study termination may bias results: Seven of the RCTs (contributing 60% of the low-risk and moderate-risk participants) were terminated early for efficacy at interim analysis.^{9 12 15 18 21 22 26} Early termination systematically over-estimates a treatment’s RRR. The CTT authors included a subanalysis excluding five of these trials,^{9 12 15 21 26} and reported that results were “qualitatively similar... (data not shown).” It is unclear whether these results were statistically significant as the authors concluded *that the results support a similar RRR for patients with low and high CV risk.* The analytic method discussed in online supplementary eAppendix 2 minimises the impact of between-trial differences and allows inclusion of early termination studies without biasing the heterogeneity of treatment effect analysis.

The method for LDL standardisation could bias estimates of statins’ treatment effect: As discussed below, the issue of whether short-term statin benefits are a function of absolute or relative LDL reduction remains unresolved. Since the RCTs included in the CTT meta-analysis used statins of different potency, some way of standardisation across studies was necessary. Based on results from observational studies, the CTT group standardised using absolute LDL reduction. However, individual RCTs have not found a consistent association between baseline LDL (a predictor of absolute LDL reduction) and a given statin’s RRR. This

suggests that a statin's short-term RRR may be a function of per cent LDL reduction.^{2 30} LDL's *long-term* impact on atherogenesis could still be based a function of absolute LDL level, which could explain the discrepancy.

If statin's short-term RRR is a function of relative LDL reduction, then standardising RCTs by absolute LDL reduction could potentially lead to lower-risk participants (eg, JUPITER participants) systematically appearing to have greater benefit per amount of LDL reduction than higher-risk participants (eg, 4S participants). However, this apparent difference results from a difference in standardisation methods (see table 1). For example, when LDL reduction is standardised as per cent reduction, JUPITER and 4S participants receive almost identical benefit (RRRs of 35% vs 34% per 40% LDL reduction, respectively). We make this comparison to illustrate how profound this effect *may be* while we acknowledge that a re-examination of the individual-level meta-analysis is needed to know the correct standardisation method (see online supplementary appendix).

Argument #2: Statin trials demonstrate a legacy effect—that is, the CV risk of treated patients continues to be reduced even after the trial ends.

Evidence: Again, we found little evidence for this claim. The only statin follow-up study that documented that LDLs equalised quickly after the trial ended, the HPS, found no evidence of a legacy effect. The HPS investigators found that once the two arms' LDLs converged, the groups' hazard rates also equalised.³¹ This suggests that, although the benefits achieved during the trial were not reversed post-trial, continued treatment is needed to maintain lower CV risk. This contrasts with a true legacy effect, as found in follow-up of the UK Prospective Diabetes Study: the intervention group maintained a greater RRR in the follow-up period after groups' A1c values equalised.³² As a secondary prevention study, it could be argued that HPS is not the optimal study for this question. However, it is a large, rigorous study and all other follow-up studies either reported no statistical testing for a legacy effect or lacked evidence for when and if LDL levels equalised.

Argument #3: Genetic studies illustrate that lifelong LDL reduction is associated with a much greater CV risk reduction than seen in statin trials.

Evidence: This is a strong argument for the general hypothesis with grade B+ evidence supporting it (that there is a point in the pathophysiological disease process at which LDL lowering will be less effective in the long-run). These studies used Mendelian randomisation,

a quasi-experimental design employing instrumental variable analysis.³³ The studies compare individuals with very low LDL related to randomly inherited polymorphisms to individuals without these mutations to then estimate the causal effects of lifetime LDL reduction on long-term CV risk. The CV benefit from lower LDL is then extrapolated to the benefit of having statin-lowered LDL. Meta-analyses of such studies have consistently reported a CV risk reduction per mg/dL LDL reduction that is at least two times *greater* than statin trials and cohort studies such as Framingham.^{34–38} This evidence is frequently cited as demonstrating that life-long LDL lowering results in much greater risk reduction, favouring earlier LDL reduction strategies.³⁹

The genetic observational evidence appears quite strong, but does not address the specific clinical critiques (ie, that there is clinically significant benefit in starting a statin before a patient's 10-year CV risk is 7.5–12.5%, and LDL elevation should be the main factor in targeting patients for early treatment): We must consider the evidence related to: (1), is the estimated magnitude of CV benefit from long-term LDL reduction more accurately captured by the experimental RCT evidence or the genetic studies? And (2), if the degree of benefit is most accurately captured by the genetic studies, how does this support the early treatment hypothesis?

Like all observational study designs, the risk of confounding bias cannot be completely ruled out. The key assumption of genetic randomisation is that the polymorphism has no impact on the outcome (CV events) other than that mediated by the risk factor it affects (LDL). This cannot be proven, but the genetic studies in these meta-analyses are particularly strong in aggregate because the effect sizes per amount of LDL reduction have been consistent over 22 different polymorphisms. Furthermore, many of the strongly positive studies have been very large, making publication bias less likely. The design of these studies and consistency of results are quite robust for observational evidence.

If the genetic evidence represents robust observational evidence, then the alternative explanation is that the RCTs and other observational evidence systematically underestimate the magnitude of the relationship between lower LDL and CV risk reduction. In fact, the observational studies are prone to LDL measurement error where the genetic studies are not, which may lead to systematic underestimation of the true benefit of LDL reduction. Since there is no equivalent to an A1c for lipids, cohort analyses rely on patients' LDL measurements, which have substantial measurement error due to

Table 1 Standardisation of studies by absolute LDL reduction systematically misestimates CV RRR*

	Baseline LDL (mg/dL)	Treated LDL (mg/dL)	Absolute LDL reduction (mg/dL)	Proportional LDL reduction (%)	CV RRR per 40 mg/dL LDL reduction	CV RRR per 40% LDL reduction
JUPITER	108	55	53	49	0.33	0.35
SSSS	188	122	66	35	0.18	0.34

*This illustrates the difference between standardising trials based on absolute versus per cent reduction. JUPITER, a study with lower-risk low-LDL participants appears to have much greater benefit per amount of absolute LDL reduction (RRR 33%) than 4S, a study with higher-risk higher-LDL participants (RRR 18%). One might conclude that lower risk participants receive more benefit per LDL reduction than high-risk participants. However, when standardised as per cent reduction, JUPITER and 4S participants receive almost identical relative CV benefit (RRR of 35% vs 34%, respectively). CV, cardiovascular; LDL, low-density lipoprotein; RRR, relative risk reduction.

laboratory error, day-to-day and year-to-year biological variation. This leads to regression dilution bias, which systematically underestimates the 'true' association between the measured risk factor and the outcome. Therefore, we expect traditional cohort analyses to underestimate the true association between LDL level and CV risk.^{40 41} A few analyses have statistically accounted for this,^{4 5} but most have not. In the online supplementary eAppendix, we outline methods to adjust for this systematic underestimation.^{40 41} The genetic studies, in contrast, are protected from such measurement error by using individuals' inherited polymorphisms in aggregate and comparing the average LDLs in those with and without the polymorphism. The group average LDL measure used in genetic studies should more accurately reflect each group's cumulative LDL burden than periodic LDL measures.

Yet if the genetic studies represent a more accurate estimate of LDL's true impact on CV risk, published evidence still does not allow us to determine how long LDL must be reduced to achieve full efficacy. More specifically, the genetic studies do not help us with the two specific critiques: (A) the specific clinical critique, that waiting until CV risk is above 7.5% is too late for some patients to receive the full clinically meaningful benefit of lipid lowering, and (B) the LDL-based early treatment critique, that if earlier treatment *does* produce clinically significant net benefit, then moderate LDL elevation (145–190 mg/dL) should be a primary determinant for early treatment.

First, we lack evidence for determining whether there are specific patients for whom waiting until CV risk is greater than 7.5% to initiate lipid lowering treatment will result in a clinically meaningful reduction in quality or length of life (the specific clinical critique). For example, if many years of LDL reduction are necessary in order to reach full efficacy (the maximum treatment RRR), then the opportunity for much of the potential benefit of LDL reduction could be lost if LDL lowering is delayed past some yet-to-be-determined point in CV pathogenesis. Then it is important to determine how the genetic evidence applies to the two specific questions: whether CV RRR increases over the 4–5-year period of statin trials and whether long-term effects of LDL reduction on CV events are a function of relative or absolute LDL reduction. We could not find an accurate analysis of whether CV RRR increases over the 4–5-year period of statin trials (see online supplementary eAppendices 2 and 4 for further discussion of how these two points may be addressed with the CTT data).

The recent Framingham analysis suggests that the cumulative effect of LDL is in fact an important independent risk factor.⁴² This new evidence is very important as it suggests that we can more accurately estimate CV risk by using cumulative LDL rather than a single given LDL level at a given point in time, and it also provides additional evidence for the general early treatment hypothesis. However, this important evidence does not directly address the two clinical critiques because it provides no evidence that cumulative LDL directly modifies RRR or that long-term CV morbidity and mortality will be substantively improved by initiating treatment before CV risk is around 10%. It does suggest that

tracking cumulative LDL burden could aid predicting CV risk. Another report found that initiation of statins early in life for those with familial hyperlipidaemia led to decreased carotid intima-media thickness at follow-up, yet did not include any clinical end points.⁴³ We could find no evidence to guide how early statin intervention should occur or how safe long-term statin therapy would need to be to justify earlier intervention, assuming that the general early treatment hypothesis is correct.

Discussion

In our literature review for clinical evidence supporting the early LDL treatment hypothesis, we found three arguments that cited clinical evidence to support of the hypothesis: (1), lower risk patients get relatively more primary prevention benefit from statins than higher risk patients, (2), there is a legacy effect illustrated in the statin trials with continued benefit after trial conclusion, and (3) the genetic studies illustrate a greater magnitude of CV benefit with lifelong LDL reduction (**box 1**). We found the clinical evidence in support of the first two arguments to be weak, however, in the online supplementary appendix we propose analyses of existing data that could more rigorously evaluate these questions. The genetic studies provide the strongest support for the general early treatment hypothesis, but we could find almost no direct evaluation of the two important clinical critiques: whether intervention before CV risk is around 10% provide clinically substantive incremental benefit and whether degree of LDL elevation within the commonly observed range should play a major role in early treatment decision-making. Our conclusions are summarised below.

Conclusion #1: There is strong grade B+ evidence for the general early treatment hypothesis.

The genetic studies and the recent evidence on the importance of cumulative LDL provide strong clinical evidence of the general hypothesis.

Conclusion #2: There is no clinical evidence for or against the clinical benefit-based early treatment critique (that there is clinically significant net benefit from treating selected patients before their 10-year CV risk is above 7.5–12.5%).

We found virtually no evidence assessing the potential absolute lifetime incremental benefits of initiating a statin earlier than currently recommended in the ACC/AHA guidelines.⁴⁴ Even though it is unclear how long it might take for statin therapy to reach its maximum RRR, modelling analyses could still be a useful approach of clarifying the circumstances under which earlier statin treatment could improve quality of life or life expectancy sufficiently to be worth increased treatment burdens and risks. These analyses could be similar to those examining the long-term benefits of glucose control or diabetes prevention.^{45 46} In fact, grade B clinical evidence supporting a large ARR is preferable to grade A evidence for a very small ARR. Without some estimation of ARR, it is impossible to weigh potential benefits against the burden and long-term safety of an intervention, particularly when intervening on asymptomatic patients for events most likely to occur greater than 20 years in the future. And as early treatment leads to many more patients taking statins for 15–25 years

Box 1 Summary

Objective: to identify clinical evidence in support of the early use of statins in patients with elevated low-density lipoprotein (LDL) levels (“the early LDL treatment hypothesis”).

Methods: review the evidence examining the relationship between LDL reduction and outcomes. We identified any ‘clinical evidence’ (true or quasi-experiments, cohort studies, or case-control studies), and excluded only those arguments based on pathophysiology or opinion alone.

Conclusions:

- 1 We found strong grade B+ clinical evidence supporting the general early treatment hypothesis—that there is a point at which atherosclerosis has progressed to a point that LDL reduction will have less long-term CV risk reduction than if done earlier.
- 2 We found no clinical evidence for or against the clinical benefit-based early treatment critique—that there is clinically significant net benefit from treating selected patients before their 10-year cardiovascular risk is above 7.5–12.5%.
- 3 We found grade A- clinical evidence supporting that if earlier treatment is indicated, that elevated age-adjusted CV risk should be the primary indication. We found no evidence for or against the use of LDL level in isolation as an important secondary factor in targeting higher benefit patients.
- 4 We identified several specific research priorities that could help elucidate the above clinical issues, including the safety of long-term statin therapy, how long it takes for lipid lowering to reach full effectiveness, and whether the long-term effects of lipid lowering are a function of relative or absolute LDL reduction (see online supplementary eAppendix for details).

before the time when substantial ARR will occur, more rigorous postmarketing surveillance for up to 30 years for potential harms will be important. If 25–30 years of statin therapy results in even a minor change in the aging of muscles or the brain, it would easily overwhelm any potential long-term CV benefits. As demonstrated for glucose control,⁴⁶ even a very small amount of treatment harm can outweigh benefits when those benefits are in the distant future.

Conclusion #3: There is grade A- clinical evidence supporting that if earlier treatment is indicated, that elevated age-adjusted CV risk should be the primary indi-

cation. We found no evidence for or against LDL level in isolation as a secondary factor in targeting higher-benefit patients.

There is currently no clinical evidence for or against whether moderate LDL elevation should be a major secondary factor in patient selection. Even if one's LDL level was a better predictor, it remains an isolated risk factor. Consider a 40-year-old woman with a *high LDL* but no other risk factors. Based on the Reynolds calculator, her 10-year CV risk is less than 1% at age 40 and if her risk factors other than age are unchanged, her CV risk at 60 will be only 2%. In contrast, a man with *low LDL* but several CV risk factors (eg, smoking and hypertension), is at high risk for rapid, premature atherogenesis. While his current CV risk (7%) may be below the recommended treatment threshold, by age 60 his CV risk will increase to over 20% even if BP and LDL levels do not increase. Clearly, a treatment decision based chiefly on LDL level instead of CV risk for these patients would be inconsistent with the clinical evidence currently available, as pointed out in several studies.^{47 48}

It is beyond the scope of this review to consider which CV risk metric is appropriate if a clinician decides to adopt treatment earlier than proposed in the ACC/AHA guidelines. Although the concept of “lifetime risk” has been proposed, such a measure can be heavily influenced by events very late in life, up to 35–50 years in the future. The key is to target those at particular risk for marked atherosclerosis formation over the next 10–15 years. This review is limited to the completeness of our literature review. Given the vastness of the epidemiological lipid literature, it is possible that we overlooked important evidence despite our extensive literature review. To minimise this risk, we contacted 19 experts in the field, oversampling proponents of early treatment of LDL. We informed them of our original review and analysis, and solicited additional evidence and arguments (see online supplementary appendix). Additionally, this paper assumes that LDL reduction is the main mechanism through which statins reduce CV risk, which is not universally accepted.

There are numerous papers discussing the physiological argument, that the known pathophysiology provides prima fascia evidence that atherosclerosis develops many years before CV risk increases. We did not address this common argument, however, as we limited our review to clinical evidence based on common evidence-based medicine principles. Of course, there are some who disagree with the principle that in order to make clinical recommendations, clinical evidence assessing the amount of net treatment benefits of a specific clinical recommendation is needed. Nevertheless, we do find grade B+ clinical evidence to support the general early treatment hypothesis, and this supports the pathophysiological evidence without relying on it.

Conclusion

We found grade B+ evidence supporting the general early treatment hypothesis—that there is some point at which atherosclerosis has progressed to the point that initiation of statin therapy will be significantly less effective over the long-term than if it had been started

earlier in life. However, we found no evidence informing the specific clinical critique, or how early this intervention would need to start, or quantifying the potential benefits, risks, and treatment burden of initiating statins earlier than that proposed by the new AHA/ACC guidelines. Current evidence suggests that overall CV risk should still be the primary metric for targeting patients if early statin treatment, but we found no evidence for or against whether degree of LDL elevation should be an important secondary factor in those with LDL < 190 mg/dL. Finally, we conclude that three questions should be a high priority for future clinical research: (1) If the relative benefit of statins increases over time, how much more would starting a statin before an individual's 10-year CV risk is 7.5–12.5% reduce absolute risk of CV morbidity and mortality when compared with the current AHA/ACC guidelines?, (2) Is the short-term association between CV risk and cumulative LDL reduction a function of relative or absolute change in LDL?, and (3) Is there evidence of substantive harms from being on a statin for 25–35 years?

Glossary

General early treatment hypothesis: This hypothesis posits that there is some point at which atherosclerosis has advanced to a level that statins and other lipid lowering therapies are substantially less effective than if they had been started earlier.

Specific clinical critique: This hypothesis posits that there are specific patients for whom delay in lipid lowering therapy until CV risk is above 7.5% will result in a clinically meaningful reduction in quality or length of life, which could have been prevented by earlier initiation of treatment.

LDL-based early treatment critique: This hypothesis posits that for patients with moderate LDL elevation (145–190 mg/dL), LDL level in isolation should be a major determinant for initiation of early treatment.

Clinical evidence: True experiments, quasi-experiments, cohort or case-control studies in which meaningful clinical end points are examined.

Relative Risk Reduction (RRR): This is the proportion by which an exposure, such as a treatment, reduces a risk. In a clinical trial, the RRR is the difference in the event rates in the control and intervention arms divided by the rate in the control arm.

Mendelian randomisation: A type of quasi-experiment in which genetic polymorphisms are used to isolate effect of specific biological changes. For example, studies of gene mutations that result in low LDL levels have been used to try to estimate the impact of LDL reduction independent of the means by which it is reduced. The key assumption is that the polymorphism has no impact on the outcome (CV events) other than that mediated by the risk factor it affects, such as LDL in the above example.

Grade A evidence: Based on high-quality, well-designed studies in representative populations, there is high certainty that the net benefit is substantial.⁴⁹

Grade B evidence: Based on available evidence that may be limited by study quality, inconsistent findings, or generalisability, the available evidence indicates that there is net benefit, however, as more information

becomes available the magnitude or direction of the effect could change and potentially alter the conclusion.⁴⁹

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Acknowledgements The authors thank Elyse N Reamer, BS, University of Michigan, assisted with reference collection.

Contributors RAH conceived the study. KS and RAH conducted the review; and KS, DAL, and RAH all contributed to interpreting the data, reporting the findings, and drafting the manuscript.

Funding Financial support from The Department of Veterans Affairs Quality Enhancement Research Initiative (QUERI DIB 98-001), the Robert Wood Johnson Foundation, and the Michigan Center for Diabetes Translational Research supported by NIDDK of The National Institutes of Health (P60 DK-20572). DAL is funded by National Institutes of Health (NIH) grant K23 AG040278 and received support from NIH grant P30DK092926.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/ebmed-2015-110170>).

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SUPPLEMENTAL MATERIAL

eAppendix 1: Letter Soliciting Expert Input

Dear ___:

We have conducted an extensive literature review on an area of major controversy that surrounds the 2013 ACC/AHA Cholesterol Guidelines – whether early treatment of elevated LDL results in greater relative risk reductions than waiting until CV is already moderately elevated. We have conducted an extensive literature review, but we ask your help, as an expert in the field of cholesterol treatment, in identifying clinical evidence that we might have missed in our literature. This is particularly important given how extensive the cholesterol evidence is, and how little clinical evidence we have found addressing this issue.

We have limited our literature review to 1) randomized controlled trials, 2) high quality quasi-experiments, and 3) high-quality observational longitudinal studies (cohort studies and case-controlled studies). Below we briefly list three key arguments we have found on the early LDL treatment hypothesis, along with the supporting evidence referenced:

- ***Those at lower CV risk get more benefit per amount of LDL reduction.***
 - o Evidence found: Only evidence found: 2012 Cholesterol Treatment Trialists meta-analysis, however, we cannot find even a hint of this finding within any clinical trial, even though many should have moderate statistical power to do so if cardiac risk was evaluated as a continuous risk factor. Whenever this has been addressed within a trial, however, no evidence of this finding can be found.
 - o Problem: 1) The meta- analysis ignored strong heterogeneity between trials and failed to distinguish between within trial effects (strong evidence) vs. between trial effects (weak evidence), and 2. The approach taken in the meta-analysis was not able to deal with early termination studies appropriately (exclusion of such studies resulted in the results no longer being statistically significant).
 - o Question: Are you aware of any individual randomized controlled trials that have found that lower CV risk subjects have a greater relative treatment effect than higher risk subjects (even if not statistically significant)? Are you aware of any reports of the CTT group addressing these concerns in subsequent re-analyses?

• Genetic studies have suggested that long-term LDL reduction is needed to achieve full benefit:

o Evidence found: Genetic studies have found that those with mutations that reduced LDL levels over selected controls, suggesting that a lifetime of lower LDL may result in a greater relative risk reduction than if one waited to start a statin later in life than found in statin trials.

- Jonathan Cohen, et al. Sequence Variations in PCSK9, Low LDL, and Protection against Coronary Heart Disease. NEJM 2006
- Brian Ference, et al. Effect of Long-Term Exposure to Lower Low-Density Lipoprotein Cholesterol Beginning Early in Life on the Risk of Coronary Heart Disease. JACC 2012
- Sekar Kathiresan, et al. Polymorphisms Associated with Cholesterol and Risk of Cardiovascular Events. NEJM 2008

o *Problems:* 1. Garber AM, et al (Circulation 1997) reported that in the first 2 years after statin therapy that statins' treatment effect was lower than expected, but that subsequently, statins achieved the level of risk reduction that was very close to that expected by having had that LDL all one's life (suggesting that maybe only treating 2-3 years early is all that is needed to achieve the full effect of LDL lowering), 2) presence of the genetic mutation was not an independent predictor of CV risk, over traditional risk factors, in the one study that evaluated this, 3) these results would suggest that there should be an age*LDL interaction (i.e., the longer you've had your naturally elevated LDL the higher the relative risk, which is not the case).

o *Questions:* 1. Are you aware of other evidence supporting or countering the finding reported by Garber et al (that after 2-3 years statins give as much benefit as a naturally lower LDL)?, 2. Are you aware of any clinical study finding that an LDL lowering mutation is an independent CV risk factor?, 3. We did not find any true Mendelian randomization studies (a natural true experimental design that compares those receiving the mutation with those having a parent with the mutation but not receiving the mutation). Are you aware of any such studies?

• Clinical trials have a "legacy effect", in that those treated more intensively during the 4-5 years of a clinical trial have a lower than expected hazard rate when they stop a statin, and for those continuing a statin, they have a lower hazards than controls who started a statin after trial cessation:

o Evidence found: Long-term follow-up of the West of Scotland Coronary Prevention Study, and of the Heart Protection Study.

- Ford et al. Long-term follow-up of the West of Scotland Coronary Prevention Study. NEJM 2007

- Heart Protection Study Collaborative Group. Effects of 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomized controlled trial. Lancet 2011

o *Problem:* This appears to be a misunderstanding of these trial results. As correctly pointed out by the HPS investigators, these studies found a statistically significant cumulative risk reduction, but this cumulative risk reduction was in steady decline since there was no legacy effect (i.e., event rates almost immediately reverted to the expected hazards, without any residual effect from earlier treatment, once statin therapy equalized between groups after the trial period ended).

o Question: Are you aware of any long-term follow-up studies that have illustrated a true legacy effect?

Thank you so much for your time and attention. Given the controversy over the 2013 AHA/ACC Guidelines, a complete and thorough review of the clinical evidence for or against the early LDL hypothesis will be a valuable service to the practicing community.

Sincerely,

Kori Sauser, MD, MSc
Rodney Hayward, MD

Robert Wood Johnson Foundation Clinical Scholars Program
University of Michigan

eAppendix 2: Proposed Analyses using CTT data

1. To assess CV risk-associated heterogeneity in treatment effect (HTE):

Consideration of cardiovascular (CV) risk as a continuous variable: Although not a source of true bias, dividing the CV risk groups into categories reduces subgroup comparison power substantially[1] and is not consistent with the stated hypothesis – that as CV risk increases the proportion of patients who already have extensive atherosclerosis increases. By this hypothesis, the decline in statin RRR should be monotonic. Therefore, an analysis of the CTT database limited to studies with substantial heterogeneity in CV risk and treating CV risk as a continuous factor could test for an interaction between estimated CV risk and a statin’s RRR (predicted CV risk * % LDL reduction, with examination of a quadratic function to test for a gradually diminishing of the interaction effect).[2] This approach is both consistent with the underlying hypothesis and yields much greater statistical power.

2. To assess whether a given statin’s RRR varies as a function of baseline LDL:

Consideration of LDL risk reduction as a multiplicative effect: Re-analysis with standardization of studies by percent LDL reduction rather than absolute LDL reduction would better capture the multiplicative nature of the change in risk with LDL reduction. Use a multilevel model allowing for random slopes of baseline LDL to assess within versus between trial evidence of variation in RRR by baseline LDL. Alternatively, this could be examined qualitatively by examining the interaction of baseline LDL (optimally as a linear variable with a quadratic function) and the RRR of the statin used for each study individually.

3. To assess CV risk-associated heterogeneity in treatment effect (HTE): *Only include clinical trials with substantial heterogeneity in baseline risk to facilitate within-study*

(i.e., experimental) comparisons of heterogeneity of treatment effect (HTE) by CV risk: HTE refers to different patient groups experiencing varying treatment effects –in this case, a better RRR in lower-risk patients.[3] HTE based on between-trial differences is an observational finding (weaker), but experimental (stronger) when HTE is based on within-trial differences.[4,5] The CTT analysis provides observational evidence because there were substantial between-trial differences in the amount of CV RRR demonstrated per LDL reduction.[1,6–24]

Many statin trials had predominantly low-moderate CV risk or predominately high CV risk study subjects. An analysis of the CTT data that is restricted to the 8 studies with good dispersion of subjects across risk groups[8–11,13,16,17,22] may better evaluate for HTE by CV risk, that is, whether the RRR per amount of LDL reduction differs between lower and higher CV risk patients. Also, when examining for HTE, studies with relative homogeneity in the examined patient attribute (in our case, CV risk) lack sufficient variance and should be excluded,[3] which was not done.

This approach is analogous to the method of propensity score matching. Propensity score matching is used in the analysis of observational data to eliminate the effect of poor balance between comparison groups. For example, if some of those receiving

treatment A in an observational study are too dissimilar than any of those receiving treatment B, or vis versa, it is essential to remove those observations to achieve balance between comparison groups. Although within group trial HTE analyses are represent true experimental analyses, between trial comparisons are observational. Therefore, analogous to propensity score matching, only using trials that had both lower and higher CV risk subjects provides balance between trials by eliminate comparisons of populations that are too different to allow a fair comparison. especially important given the large between-study HTE in CV risk reduction by amount of LDL reduction observed in statin clinical trials.

Limiting the analysis to those trials with a broad range of CV risk would provide this balance between trials. And although the number of trials examined is reduced, the power of the analysis should be strong both given the excellent heterogeneity in CV risk across the trials, and by examining CV risk a continuous variable.[3,8] This analysis should use a random effects model that accounts for clustering by trial to account for between-trial heterogeneity. And reported results should include the coefficients for treatment arm, baseline CV risk, and the interaction term between the two for each of the 8 statin trials in order to provide further transparency regarding the consistency of the HTE by CV risk effect.

eAppendix 3: Potential analyses that could provide evidence for or against the main two competing hypotheses regarding the genetic studies

As we discussed in the main paper, we concluded that the genetic studies provide strong grade B+ evidence that a lower LDL provides a greater relative risk reduction (RRR) than that found in the observational studies and statin trials. Unfortunately, the published genetic studies do not answer the question, “How long does LDL need to be reduced in order to obtain most or all of the hypothesized RRR?” In other words, if the genetic evidence is correct, does it take 5-10 years or 30 years to obtain the greater predicted RRR? We propose potential analyses of currently available data that may provide additional evidence on this important question.

1. See eAppendix 2 for a potential approach to examining heterogeneity of treatment effect (HTE) by cardiovascular risk in the CTT database.
2. The CTT database could examine LDL changes as a time-varying covariate. Many statin trials had substantial treatment contamination (cross-over and statin non-adherence) and this contamination often increased substantially over the course of the trial. An analysis that updates LDL separation between group annually (i.e., time-varying covariate) will reduce potential bias that may result in under-estimating the CV RRR per change in LDL on average and also could provide a more reliable assessment of whether a statin’s RRR increases with number of years of treatment. For the functional form of the time-varying covariate, see #3 below.
3. Cohort studies with long-term follow up and annual lipid values could examine cumulative elevation of non-HDL cholesterol using a time-varying covariate (similar to the analyses examining LDL in this way recently been published by the Framingham group).[25]
4. Older cohort studies that have good CV risk factor information for young adults or adolescents could potentially link these data to national registry death files. For example, a study that measured CV risk factors, including non-HDL cholesterol, in the 1970s or 1980s could use registry data to examine long-term CV mortality to better examine how LDL earlier in life predicts long-term CV death. The currently available data suggests that this association is quite small, but this evidence is quite limited and does not adjust for regression dilution. An old cohort study with repeat measures of blood pressure and non-HDL cholesterol would be ideal in order to account for measurement error in these two risk factors, but errors in variable regression could also be used by employing external evidence on test-retest reliability in risk factor assessment.[26]
5. Examination of the genetic studies should evaluate whether the polymorphisms improve CV risk prediction. We could only find one genetic study that reported this examination (finding that it did not improve risk prediction),[27] but this could be examined in the other genetic literature. A single study may lack sufficient power because most patients do not have the genetic deficit. But lack of a substantive

improvement in risk prediction of an individual-level meta-analysis would raise question as to the validity of these studies' finding. Inclusion of these polymorphisms should improve predictiveness, given that no observed or unobserved factor other than LDL should be correlated with the genetic polymorphism (which is the key assumption in a valid instrumental variable analysis).

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