High Blood Pressure & Cardiovascular Prevention
https://doi.org/10.1007/s40292-019-00330-8

REVIEW ARTICLE

Impact of Lipid-Lowering Therapy on Mortality According to the Baseline Non-HDL Cholesterol Level: A Meta-Analysis

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Received: 21 May 2019 / Accepted: 11 July 2019

Abstract

Introduction Previous report showed that more intensive lipid-lowering therapy was associated with less mortality when baseline LDL-C levels were > 100 mg/dL. Non-HDL-C is a better predictor of cardiovascular risk than simpler LDL-C.

Aim The objective of this meta-analysis was to define the impact of lipid-lowering therapy on the reduction of total and cardiovascular mortality by different baseline levels of non-HDL-C.

Methods We performed a meta-analysis including randomized, controlled clinical trials of lipid-lowering therapy, reporting mortality with a minimum of 6 months of follow-up, searching in PubMed/Medline, EMBASE and Cochrane Clinical Trials databases. The random-effects model and meta-regression were performed.

Results Twenty nine trials of lipid-lowering drugs, including 233,027 patients, were considered eligible for the analyses. According to the baseline non-HDL-C level, the results on cardiovascular mortality were: (1) ≥ 190 mg/dL: OR 0.63 (95% CI 0.53–0.76); (2) 160–189 mg/dL: OR 0.82 (95% CI 0.75–0.89); (3) 130–159 mg/dL: OR 0.71 (95% CI 0.52–0.98); (4) < 130 mg/dL: OR 0.95 (95% CI 0.87–1.05). When evaluating mortality from any cause, the results were the following: (1) ≥ 190 mg/dL: OR 0.70 (95% CI 0.61–0.82); (2) 160–189 mg/dL: OR 0.91 (95% CI 0.83–0.98); (3) 130–159 mg/dL; OR 0.88 (95% CI 0.77–1.00); (4) < 130 mg/dL: OR 0.98 (95% CI 0.91–1.06). The meta-regression analysis showed a significant association between baseline non-HDL-C and mortality.

Conclusions In these meta-analyses, lipid-lowering therapy was associated with reduction in the risk of all-cause and cardiovascular mortality when baseline non-HDL-C levels were above than 130 mg/dL.

Keywords Lipid-lowering therapy · Non-HDL-cholesterol · Mortality · Meta-analysis

1 Introduction

Cardiovascular disease is the principle cause of morbidity and mortality. Lipoproteins, particularly low density lipoprotein (LDL) and other apolipoprotein B-containing lipoproteins including very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and lipoprotein (a) play a fundamental role in the initiation and evolution of atherosclerosis [1, 2].

Clinical trials using lipid-lowering drugs have unequivocally shown that lowering LDL-cholesterol (LDL-C) results in significant reductions in both morbidity and mortality in patients with or without established coronary heart disease [3–6]. Recently, studies using aggressive plasma LDL-C reduction as secondary prevention have demonstrated increased survival rates [7, 8]. Consequently, LDL-C is a well-established risk factor for cardiovascular disease, being

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40292-019-00330-8) contains supplementary material, which is available to authorized users.

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Published online: 16 July 2019

the primary therapeutic target in both primary and secondary prevention according to dyslipidaemia guidelines [9–11].

However, despite reductions in LDL-C with maximally tolerated statins and newer lipid-lowering agents, many people still experience cardiovascular events, which may, in part, relate to triglyceride or the cholesterol content within triglyceride-rich lipoproteins (cardiovascular residual risk) [12, 13].

The non-high density lipoprotein-cholesterol (non-HDL-C) comprises cholesterol carried by all potentially atherogenic particles [14]. Non-HDL-C is simpler, more convenient and more predictive than LDL-C, but this is less widely recognized and hence less frequently used. In some guidelines, non-HDL-C has been designated as secondary treatment targets, which if increased, might lead to intensification of lipid-lowering therapy. In this context, the non-HDL-C targets were 30 mg/dL higher than the recommended LDL-C goals.

A recent meta-analyses showed that more intensive compared with less intensive LDL-C lowering was associated with a greater reduction in risk of total and cardiovascular mortality in trials of patients with higher baseline LDL-C levels [15]. This association was not present when baseline LDL-C level was less than 100 mg/dL, suggesting that the greatest benefit from LDL-C–lowering therapy may occur for patients with higher baseline LDL-C levels.

Understanding differences in treatment effects across different basal lipid levels could have an important effect on guideline recommendations, cost-effectiveness analyses and health policy decisions.

Therefore, the objective of this meta-analysis was to define if the baseline level of non-HDL-C determines a different impact on the reduction of total and cardiovascular mortality by indicating a more aggressive lipid-lowering therapy.

2 Methods

Data extraction and quality assessment: Our meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews [16]. A literature search was performed that identified clinical trials of lipid-lowering drugs that are recommended by the current cholesterol guidelines based on the results of clinical trials that showed efficacy in the reduction of cardiovascular events, and published between January 1980 and December 2018 in English. Two independent reviewers searched the electronic PubMed/MEDLINE, Embase and Cochrane Controlled Trials databases using the following terms: ‘statins’; ‘lipid-lowering drugs’; ‘simvastatin’; ‘atorvastatin’; ‘rosuvastatin’; ‘pravastatin’; ‘pitavastatin’; ‘fluvastatin’; ‘lovastatin’; ‘ezetimibe’; ‘PCSK9 inhibitors’. Eligible studies were randomized controlled trials including at least 1000 patients and reporting data from all-cause mortality and cardiovascular mortality with a minimum follow-up of 6 months. Trials performed in populations with heart failure or end-stage renal disease requiring hemodialysis were excluded. The following variables were also collected from the retrieved articles: description of treatment and control arms; baseline and on-treatment plasma levels of non-HDL-C; and total and cardiovascular mortality. More intensive therapy was defined as the more potent pharmacologic strategy, while less intensive therapy corresponded to the control group of the original trial.

The Jadad scale was used to assess the quality of the trial designs. Studies were scored (ranging from 0 to 5 points) according to the presence of three key methodological features: randomization; blinding; and withdrawal/dropout rates. Studies with a Jadad score >2 points were considered high quality, while those scoring <2 points were deemed poor quality.

Meta-analysis and meta-regression analyses: The summary effect of lipid-lowering drugs on the endpoint of total and cardiovascular mortality was estimated. Exploratory meta-regression analyses were performed to examine the potential associations between baseline non-HDL-C levels and the effect sizes of lipid-lowering drugs on mortality.

Statistical analysis: Measures of effect size were expressed as odds ratios (ORs), and the I2 statistic was calculated to quantify between-trial heterogeneity and inconsistency. Because studies differ in their lipid-modifying regimens and effect sizes, a random-effects model was chosen. However, to assess the relationship between differences in basal non-HDL-C levels and variations in natural log-transformed ORs of mortality, a random-effects meta-regression model was performed. Stratified analyses were prespecified for commonly used clinical cut-points of mean baseline non-HDL-C (<130 mg/dL, 130–159 mg/dL, 160–189 mg/dL, and ≥ 190 mg/dL). To compare mean effects between subgroups, a Z test was used. Statistical analyses were performed using the R software for statistical computing version 3.5.1 with additional specific packages [17, 18]. The level of statistical significance was set at a two-tailed alpha of 0.05.

Sensitivity analyses: The sensitivity analysis consists of replicating the results of the meta-analysis, excluding in each step one of the studies included in the review. If the results obtained are similar, both in direction and magnitude of the effect and statistical significance, it indicates that the analysis is robust.

Analysis of publication bias: A funnel plot using the standard error (SE) for log OR was created, and Begg and Mazumdar rank correlation were also performed.

3 Results

Twenty nine eligible trials of lipid-lowering drugs, including 233,027 patients, were identified and considered eligible for the analyses. There was a total of 117,678 subjects allocated to receive more intensive therapy and 115,349 subjects allocated to the respective control arms for the analysis of cardiovascular mortality. In the analysis of total mortality, there was a total of 114,740 subjects allocated to receive more intensive therapy and 113,939 patients allocated to the respective control arms.

A flow diagram of the study's screening process is shown in Fig. 1. All studies were randomized and showed good quality (≥ 2 points of Jadad's score for each eligible trial).

The studies selected in this meta-analysis included patients with and without cardiovascular history (primary and secondary prevention), of both sexes, and of a wide age range. Follow-up ranged from 7 to 73 months. Description of trials selected for this analysis is summarized in Table 1.

Overall, this meta-analysis showed that more intensive therapy was associated with a significant reduction in cardiovascular mortality (OR 0.79; 95% CI 0.72–0.88; $p < 0.0001$; $I^2 = 70\%$) and total mortality (OR 0.90; 95% CI 0.85–0.96; $p < 0.0005$; $I^2 = 54\%$).

In the analysis stratified according to the baseline non-HDL-C level, the results were the following when cardiovascular mortality was evaluated: (1) ≥ 190 mg/dL: OR 0.63 (95% CI 0.53–0.76); (2) 160–189 mg/dL: OR 0.82 (95% CI 0.75–0.89); (3) 130–159 mg/dL: OR 0.71 (95% CI 0.52–0.98); (4) < 130 mg/dL: OR 0.95 (95% CI 0.87–1.05). In the same analysis, but when mortality from any cause was evaluated, the results were the following: (1) ≥ 190 mg/dL: OR 0.70 (95% CI 0.61–0.82); (2) 160–189 mg/dL: OR 0.91 (95% CI 0.83–0.98); (3) 130–159 mg/dL; OR 0.88 (95% CI 0.77–1.00); (4) < 130 mg/dL: OR 0.98 (95% CI 0.91–1.06). These data show that in analysis by subgroups of baseline non-HDL-C level, all-cause mortality risk and cardiovascular mortality risk were associated with a reduction only in the trials with baseline non-HDL-C levels of 130 mg/dL or greater. The subgroup with baseline non-HDL-C levels of 190 mg/dL or greater yielded the highest reductions. The graphic representation of the analysis according to the baseline non-HDL-C level is shown in Figs. 2 and 3.

In a meta-regression, more intensive vs. less intensive therapy was associated with a change in ORs for all-cause mortality of 0.91 (95% CI 0.85–0.98; $P = 0.009$), and with change in ORs for cardiovascular mortality of 0.87 (95% CI 0.76–0.98; $P = 0.027$) for each 40 mg/dl higher baseline non-HDL-C level. Figures 4 and 5 shows meta-regression analysis of cardiovascular and all-cause mortality by baseline non-HDL-C level.

The funnel plot of standard error by Log OR of endpoints does not suggest publication bias (Fig. 6). In the same way, Begg and Mazumdar's test for rank correlation gave a p value of 0.15, not indicating possible publication bias.

The sensitivity analysis showed that the results were robust (Figures 7–10, supplementary material).

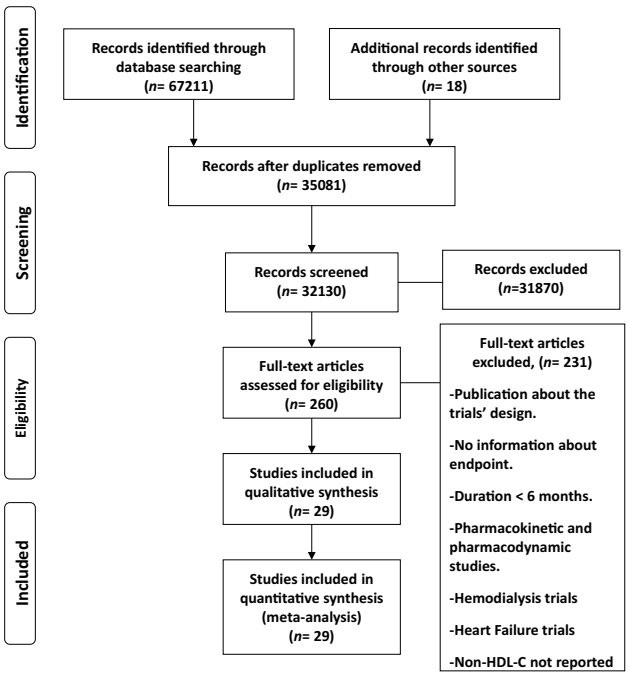


Fig. 1 Flow diagram of the study screening process

4 Discussion

In these meta-analyses and meta-regression, more intensive compared with less intensive non-HDL-C lowering was associated with greater reduction in the risk of all-cause and cardiovascular mortality in patients with higher baseline non-HDL-C levels. These associations were not present when baseline non-HDL-C levels were less than 130 mg/dL.

An elevated serum cholesterol level is an independent risk factor for coronary heart disease [19]. The subjects who reduce serum cholesterol levels by 1 mmol/l (38.7 mg/dL) reduce cardiovascular risk by 22% [8]. The absolute risk reduction depends on the levels of serum cholesterol prior to treatment, the global cardiovascular risk and the extent of achieved serum cholesterol lowering. However, the evidence from statin trials suggests that there is a considerable "residual cardiovascular risk" in statin treated patients [20]. Such situation is thought to be a direct consequence of the persistent high concentrations of other atherogenic particles involved in the atherosclerotic process [21].

Table 1 Study baseline characteristics

Study, year	N	Follow-up (years)	Less intensive therapy (mg)	Baseline non-HDL-C	More intensive therapy (mg)	Baseline non- HDL-C
4S, 1994 [3]	4444	5.4	Placebo	217.0	Simvastatin 10–40	217.0
WOSCOPS, 1995 [31]	6604	4.9	Placebo	225.0	Pravastatin 40	225.0
CARE, 1996 [32]	4159	5.0	Placebo	170.0	Pravastatin 40	170.0
The Post CABG trial, 1997 [33]	1351	4.3	Lovastatin 2.5–5 + colesty-ramine 8	187.0	Lovastatin 40–80 + colesty-ramine 8	186.9
AFCAPS-TexCAPS, 1998 [34]	6605	5.2	Placebo	185.0	Lovastatin 20–40	185.0
LIPID, 1998 [35]	9014	6.1	Placebo	182.0	Pravastatin 40 mg	182.0
GISSI-P, 2000 [36]	4271	2.0	Control	183.3	Pravastatin 20	183.9
ALLHAT–LLT, 2002 [37]	10,355	4.8	Control	176.3	Pravastatin 40	176.1
GREACE, 2002 [38]	1600	3.0	Usual care	218.0	Atorvastatin 10–20–80	218.0
LIPS, 2002 [39]	1677	3.9	Placebo	162.0	Fluvstatin 80	162,.0
ASCOT-LLA, 2003 [40]	10,305	3.1	Placebo	162.4	Atorvastatin 10	162.4
A to Z, 2004 [41]	4497	3.1	Simvastatin 20	145.0	Simvastatin 20–80	146.0
ALLIANCE, 2004 [42]	2442	4.3	Usual care	184.0	Atorvastatin 80 mg	186.0
CARDS, 2004 [43]	4248	3.9	Placebo	152.0	Atorvastatin 10 mg	153.5
PROVE IT-TIMI 22, 2004 [44]	4162	2.0	Pravastatin 40	141.0	Atorvastatin 80	143.0
TNT, 2005 [45]	10,001	4.9	Atorvastatin 10	128.0	Atorvastatin 80	128.0
IDEAL, 2005 [46]	8863	4.8	Simvastatin 20	149.8	Atorvastatin 80	150.8
ASPEN, 2006 [47]	2410	4.0	Placebo	147.0	Atorvastatin 10	147.0
MEGA, 2006 [48]	7832	5.3	Diet	184.8	Diet + pravastatin 10–20	184.8
SPARCL, 2006 [49]	4731	4.9	Placebo	162.3	Atorvastatin 80	161.4
JUPITER, 2008 [6]	17,802	1.9	Placebo	136.0	Rosuvastatin 20 mg	137.0
SEAS, 2008 [50]	1873	4.4	Placebo	164.0	Simvastatin 40 + ezetimibe 10	165.0
SHARP, 2011 [51]	9270	4.9	Placebo	147.0	Simvastatin 20 + ezetimibe 10	147.0
IMPROVE-IT, 2015 [52]	18,144	6.0	Simvastatin 40	120.5	Simvastatin 40 + ezetimibe 10	120.5
ODYSSEY LONG TERM, 2015 [53]	2341	1.5	Placebo	152.0	Alirocumab 150	152.6
FOURIER, 201 [54]	27,564	2.2	Placebo	124.0	Evolocumab 140/420	124.0
SPIRE-1, 2017 [55]	16,817	0.6	Placebo	114.0	Bococizumab 150	114.3
SPIRE-2, 2017 [55]	10,621	1.0	Placebo	160.3	Bococizumab 150	160.5
ODYSSEY OUTCOMES, 2018 [27]	18,924	2–8	Placebo	123.0	Alirocumab 150	122.0

With the emergence of the concept of "residual cardiovascular risk", non-HDL-C has been proven to perform better in terms of risk prediction for cardiovascular disease [22–24].

Another concept that emerged for the management of lipid-lowering treatments is the "threshold" concept. We understand by "threshold" as that lipid value above which we must indicate a specific lipid-lowering therapy [25]. A recent European Task Force suggest use LDL-C threshold values for considering new lowering-lipid drugs, for instance PCSK9 monoclonal antibody therapy, based on consideration of absolute cardiovascular risk and the absolute LDL-C reduction required [26].

A recent meta-analyses showed that more intensive compared with less intensive LDL-C lowering was associated with a greater reduction in risk of total and cardiovascular mortality in patients with higher baseline LDL-C levels, but not when baseline LDL-C level was < 100 mg/dL [15]. Similarly, in the ODYSSEY OUTCOMES study, which evaluated the use of alirocumab in patients with a recent acute coronary syndrome treated with high-potency statins, the maximum benefit was obtained in the subgroup of patients with a LDL-C greater than 100 mg/dL [27]. These findings are aligned with the European recommendations previously mentioned for the use of the new lipid-lowering drugs, suggesting that the greatest benefit from lipid–lowering therapy may occur for patients with higher baseline LDL-C levels.

The present analysis evaluated non-HDL-C, a lipid marker that more accurately represents the total of atherogenic particles and, unlike LDL, can be used in the context of elevated triglycerides [28].

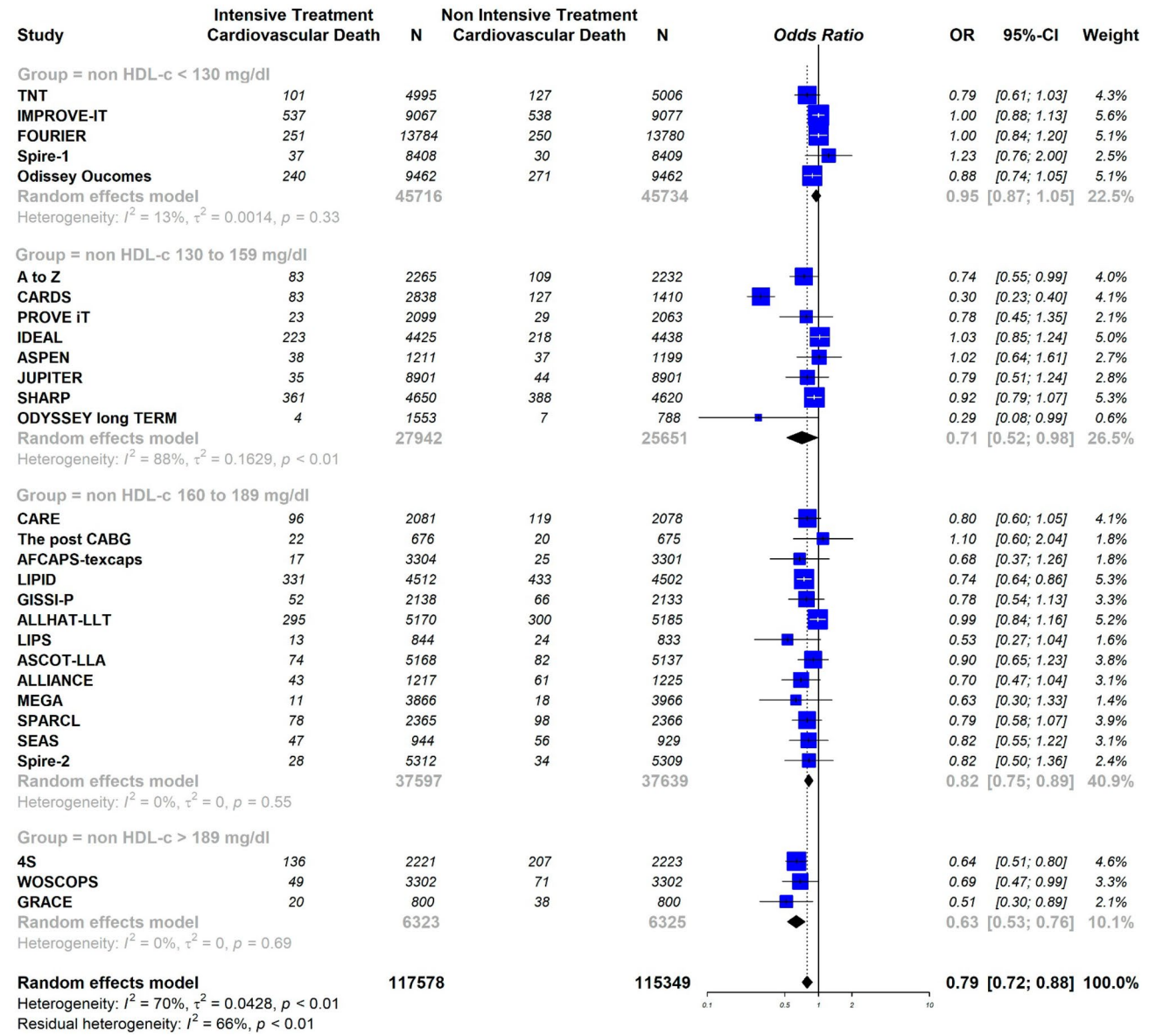


Fig. 2 Effect of lipid-lowering therapy on cardiovascular mortality. Random effects, odds ratio, 95% confidence intervals (CI) and I^2 statistics

The association between non-HDL-C and mortality was reported previously in another meta-analysis [29]. Liao et al. showed that in patients with cardiovascular disease history, high non-HDL-C level at baseline was associated with higher risk of mortality (RR: 1.24, 95% CI 1.05–1.46). Similarly, Robinson et al. reported that most lipid-modifying drugs used as monotherapy have an approximately 1:1 relationship between percent non-HDL-C lowering and cardiovascular reduction [30]. This evidence suggests that non-HDL-C, along with LDL-C, could be considered both a marker and a target of cardiovascular prevention [21].

Our findings showed that the reduction of total and cardiovascular mortality with the more intensive lipid-lowering therapy was only observed when the basal non-HDL-C exceeded 130 mg/dL. Moreover, the meta-regression analysis showed that for each 40 mg/dL higher baseline non-HDL-C level, more versus less intensive lipid lowering therapy was associated with a change in ORs of 0.91 and 0.87 for cardiovascular an all-cause mortality, respectively.

Many recommendations have proposed non-HDL-C goals. However, there are not currently non-HDL-C thresholds. Our research provides information that could be used for that purpose.

The main challenge for the large use of emerging lipid-lowering drugs is their cost. Thus, the correct identification of the adequate target population for treatment is a priority.

Future recommendations should identify the patients at greatest risk who are most likely to benefit from the new

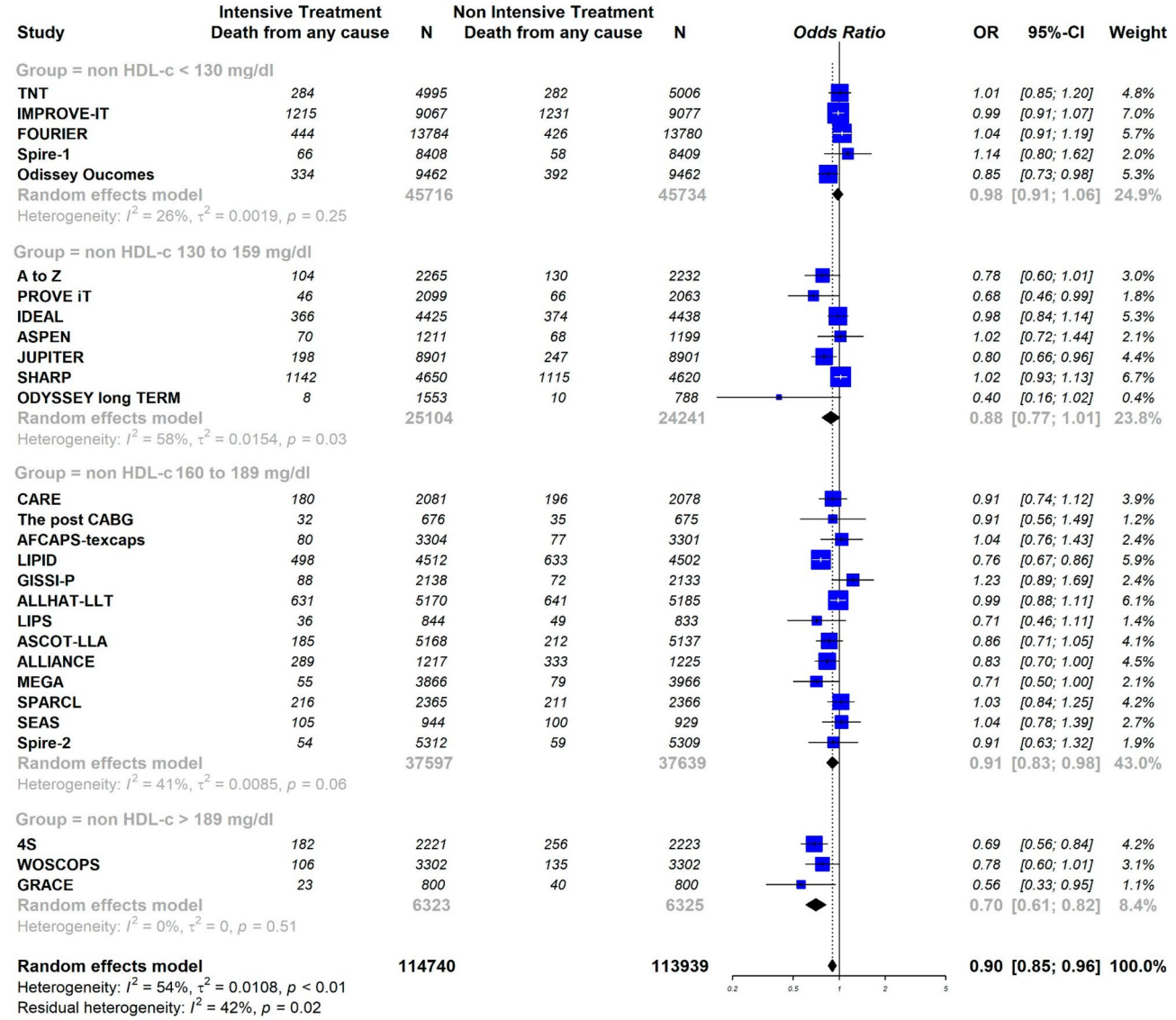


Fig. 3 Effect of lipid-lowering therapy on all-cause mortality. Random effects, odds ratio, 95% confidence intervals (CI) and I^2 statistics

and expensive lipid-lowering drugs, taking into account the financial restraints within healthcare budgets.

This meta-analysis presents several limitations. First, they are related with clinical heterogeneity (popular characteristics, different schemes of lipid-lowering therapy, different follow-up), statistical heterogeneity and potential publication bias. However, a large number of publications were included in this analysis and the results were robust when performing the sensitivity analysis. Second, the analysis included only trial-level data without having the individual data. Finally, we do not consider the analysis of other endpoints or combinations of them, because we find a great heterogeneity in the definitions.

5 Conclusion

In these meta-analyses and meta-regression, more intensive compared with less intensive non-HDL-C lowering was associated with reduction in the risk of all-cause and cardiovascular mortality when baseline non-HDL-C levels were above than 130 mg/dL. In a context of limited resources, this non-HDL-C threshold value could be considered in health decision making.

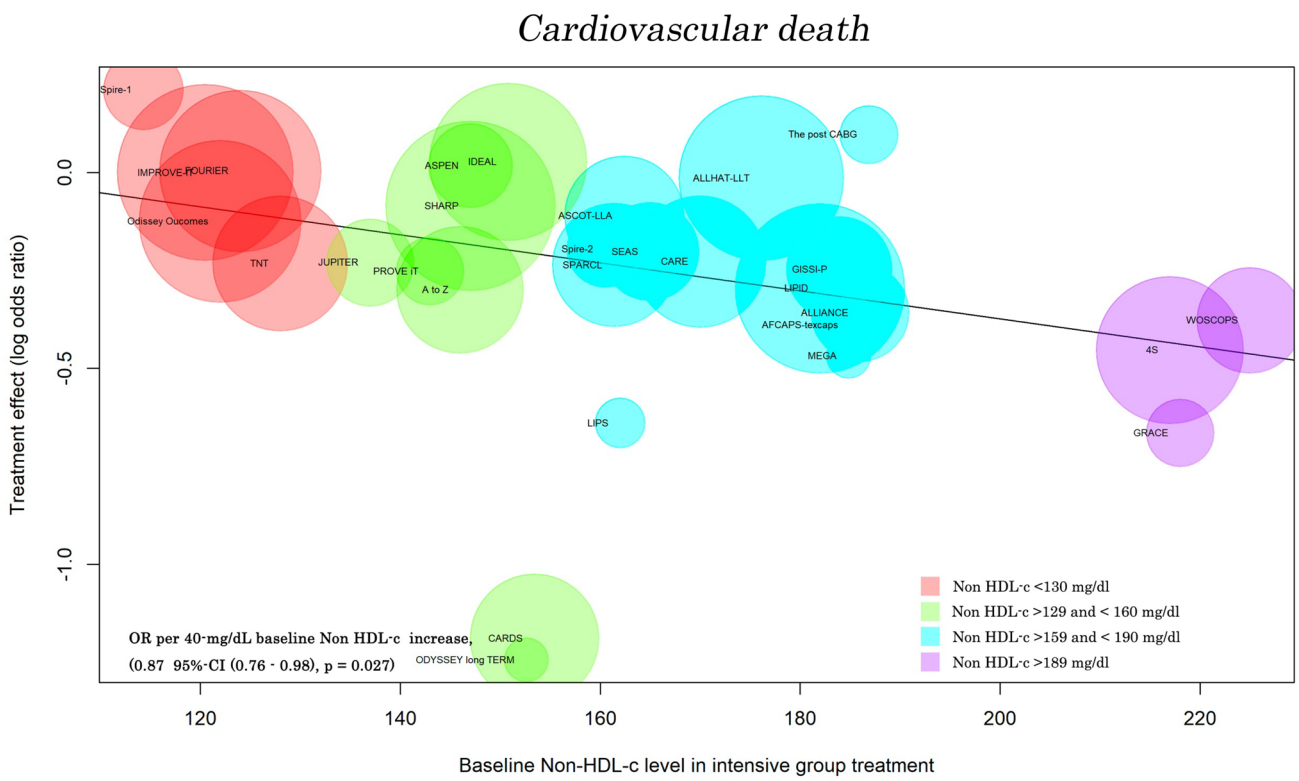


Fig. 4 Random-effects meta-regression analyses: association between baseline non-HDL-C levels and cardiovascular mortality

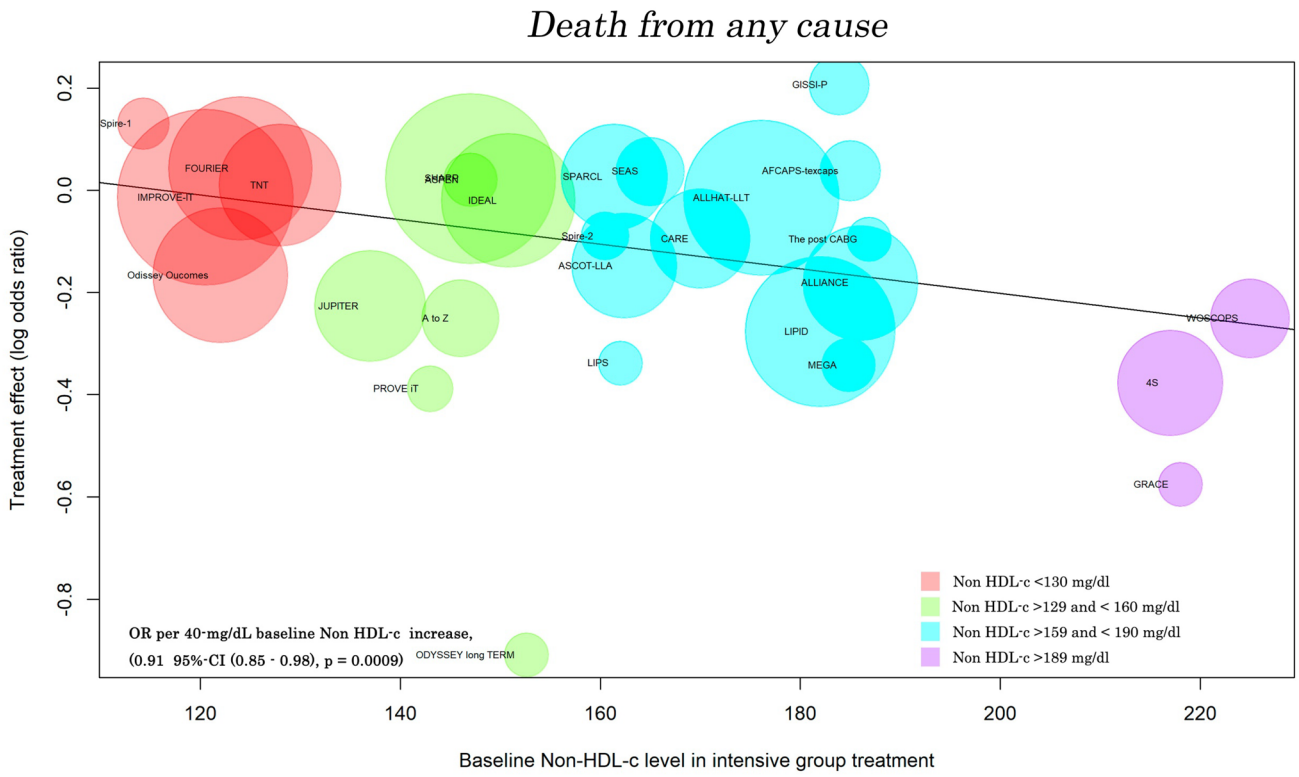
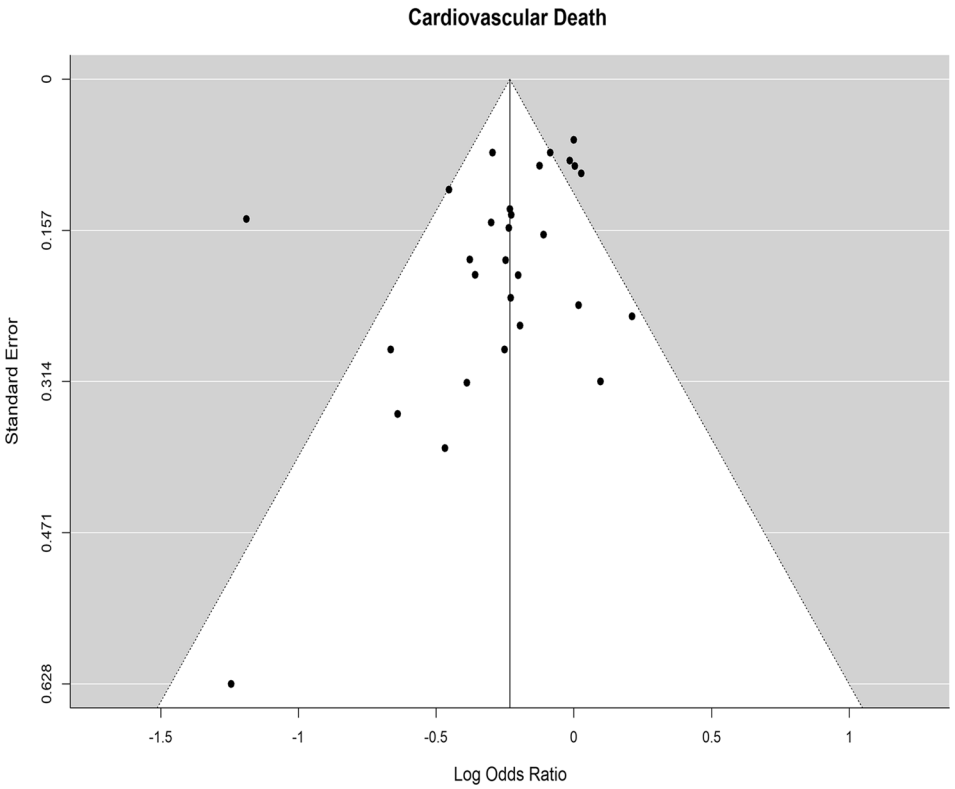


Fig. 5 Random-effects meta-regression analyses: association between baseline non-HDL-C levels and all-cause mortality



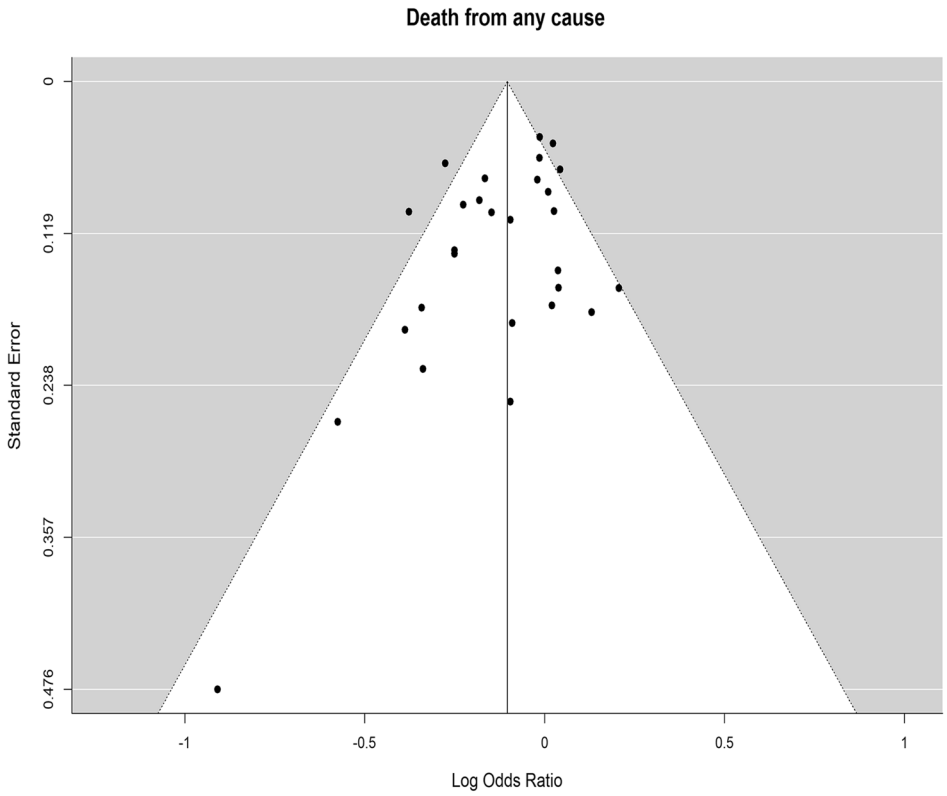


Fig. 6 Funnel plot using standard error for log odds ratio of all-cause and cardiovascular mortality

Compliance with Ethical Standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Skalen K, Gustafsson M, Rydberg EK, Hultén LM, Wiklund O, Innerarity TL, et al. Subendothelial retention of atherogenic lipoproteins in early atherosclerosis. Nature. 2002;417:750–4.
2. Libby P, Loscalzo J, Ridker PM, Farkouh ME, Hsue PY, Fuster V, et al. Inflammation, immunity, and infection in atherothrombosis: JACC review topic of the week. J Am Coll Cardiol. 2018;72:2071–81.
3. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383–9.
4. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20.536 high risk individuals: a randomized placebo-controlled trial. Lancet. 2002;360:7–22.
5. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016;374:2021–31.
6. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195–207.
7. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol. 2006;82:438–45.
8. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.
9. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J. 2016;37:2999–3058.
10. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol. 2018;73:e285–350.
11. Volpe M, Volpe R, Gallo G, Presta V, Tocci G, Folco E, et al. 2017 Position paper of the Italian Society for Cardiovascular Prevention (SIPREC) for an updated clinical management of hypercholesterolemia and cardiovascular risk: executive document. High Blood Press Cardiovasc Prev. 2017;24:313–29.
12. Reiner Z. Managing the residual cardiovascular disease risk associated with HDL-cholesterol and triglycerides in statin-treated patients: a clinical update. Nutr Metab Cardiovasc Dis. 2013;23:799–807.
13. Sampson UK, Fazio S, Linton MF. Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges. Curr Atheroscler Rep. 2012;14:1–10.
14. Su X, Kong Y, Peng D. Evidence for changing lipid management strategy to focus on non-high density lipoprotein cholesterol. Lipids Health Dis. 2019;18(1):134. https://doi.org/10.1186/s12944-019-1080-x.
15. Navarese EP, Robinson JG, Kowalewski M, Kolodziejczak M, Andreotti F, Bliden K, et al. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. JAMA. 2018;319:1566–79.
16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Br Med J. 2009;339:b2700.
17. R Core Team. R: a language and environment for statistical computing [Internet]. 2018. R Foundation for Statistical Computing, Vienna. https://www.R-project.org/. Accessed 1 Apr 2019.
18. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010;36:1–48.
19. Castelli WP. Epidemiology of coronary heart disease: the Framingham study. Am J Med. 1984;76:4–12.
20. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267–78.
21. Cicero AFG, Landolfo M, Ventura F, Borghi C. Current pharmacotherapeutic options for primary dyslipidemia in adults. Expert Opin Pharmacother. 2019;20:1277–88.
22. Sniderman A, McQueen M, Contois J, Williams K, Furberg CD. Why is non-high-density lipoprotein cholesterol a better marker of the risk of vascular disease than low-density lipoprotein cholesterol? J Clin Lipidol. 2010;4:152–5.
23. Verbeek R, Hovingh GK, Boekholdt SM. Non-high-density lipoprotein cholesterol: current status as cardiovascular marker. Curr Opin Lipidol. 2015;26:502–10.
24. Suzuki K, Oikawa T, Nochioka K, Miura M, Kasahara S, Sato M, et al. Elevated serum non-HDL (high-density lipoprotein) cholesterol and triglyceride levels as residual risks for myocardial infarction recurrence under statin treatment. Arterioscler Thromb Vasc Biol. 2019;39:934–44.
25. Adhyaru BB, Jacobson TA. Roles of non-statins, LDL-C, thresholds, and special population consideration: a look at the updated 2016 ACC Consensus Committee recommendations. Curr Atheroscler Rep. 2017;19:29.
26. Landmesser U, Chapman MJ, Farnier M, Gencer B, Gielen S, Hovingh GK, et al. European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk. Eur Heart J. 2017;38:2245–55.
27. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379:2097–107.
28. Parhofer KG. Increasing HDL-cholesterol and prevention of atherosclerosis: a critical perspective. Atheroscler Suppl. 2015;18:109–11.
29. Liao P, Zeng R, Zhao X, Guo L, Zhang M. Prognostic value of non-high-density lipoprotein cholesterol for mortality in patients with coronary heart disease: a systematic review and meta-analysis. Int J Cardiol. 2017;227:950–5.
30. Robinson JG, Wang S, Smith BJ, Jacobson TA. Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. J Am Coll Cardiol. 2009;53:316–22.
31. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med. 1995;333:1301–7.
32. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after

myocardial infarction in patients with average cholesterol levels. N Engl J Med. 1996;335:1001–9.
33. Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. N Engl J Med. 1997;336:153–62.
34. Downs JR, Clearfield M, Weis S, Shapiro DR, Beere PA, Langendorfer A, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA. 1998;279:1615–22.
35. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;339:1349–57.
36. GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? Ital Heart J. 2000;1:810–20.
37. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002;288:2998–3007.
38. Athyros VG, Papageorgiou AA, Mercouris BR, Athyrou VV, Symeonidis AN, Basayannis EO, et al. Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention: the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Curr Med Res Opin. 2002;18:220–8.
39. Serruys PW, de Feyter P, Macaya C, Kokott N, Puel J, Vrolix M, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002;287:3215–22.
40. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003;361:1149–58.
41. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004;292:1307–16.
42. Koren MJ, Hunninghake DB, ALLIANCE Investigators. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the alliance study. J Am Coll Cardiol. 2004;44:1772–9.
43. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364:685–96.
44. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350:1495–504.
45. La Rosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352:1425–35.
46. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study. JAMA. 2005;294:2437–45.
47. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care. 2006;29:1478–85.
48. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota TN, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006;368:1155–63.
49. Amarenco P, Bogousslavsky J, Callahan A III, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355:549–59.
50. Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med. 2008;359:1343–56.
51. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377:2181–92.
52. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–97.
53. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1489–99.
54. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376:1713–22.
55. Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, et al. Cardiovascular efficacy and safety of bococizumab in high-risk patients. N Engl J Med. 2017;376:1527–39.