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Statins' Cardiovascular Benefits Outweigh their Diabetogenicity: A Direct Comparison between Number Needed to Treat and Number Needed to Harm

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Abstract

Backgrounds: Although there are several metaanalyses showing that the risk of new onset diabetes mellitus (NODM) is more increased in statin or higher dose statin users than placebos or lower dose statin users, a small increase in the risk of NODM would be outweighed by the improved cardiovascular outcomes. However, these metaanalyses are accompanied by limitations of the inclusion of the studies with confounders. The aim of this study is to elucidate the risk-benefit balance by investigating the number needed to treat (NNT) and number needed to harm (NNH) in a simultaneous comparison according to the individual trial-based criteria of NODM and cardiovascular events.

Methods: A systematic review of the literature retrieves 6 randomized controlled trials (RCTs) comparing statins vs. placebos and 5 RCTs comparing higher vs. moderate doses of statin. Only RCTs which documented the number of patients who developed DM and who experienced cardiovascular events are included.

Results: NNH is consistently larger than NNT in trials of statin use vs. placebos, or in trials of higher vs. moderate dose. Furthermore, the benefit-risk ratios are consistently greater than 1 in most trial.

Conclusions: These results suggest that the absolute risk of NODM by statin is offset by the benefit for reducing cardiovascular events. The evaluation of an individual trial-based risk-benefit balance could resolve the limitations of previous studies as well as provide further reinforced evidence that the merit of statin use for the purpose of low-density lipoprotein cholesterol lowering outweighs the NODM risk.

Keywords: Statin; Diabetes mellitus; Risk-benefit balance; Number needed to treat; Number needed to harm

Introduction

Statins have now become the most widely prescribed drugs for lowering low-density lipoprotein cholesterol, which eventually achieves protective effects against cardiovascular events. Two metaanalyses recruiting only large-size randomized trials have convincingly demonstrated that statin therapy results in a substantial reduction of cardiovascular events regardless of the risk in such events, with a good safety profile [1,2]. However, several unintended, adverse events have been recently expressed [3]. Among them, new onset diabetes mellitus (NODM) has received considerable attention, because DM *per se* confers about a 2-fold excess risk for a wide range of vascular diseases [4], and cardiovascular diseases remain the chief cause of mortality among type 2 DM patients [5]. Therefore, statin use may lead to a dilemma that the beneficial effects of statins for the prevention of cardiovascular events would in turn be superseded by a NODM and a subsequent increase in the potential risks of cardiovascular events.

There is conflicting evidence from different statin trials concerning statin-induced NODM, and if it exists, its strength is a matter of debate. Several observation studies provided evidence of positive [6,7] and neutral [8] statin-DM association. Even in RCTs, the risk of NODM was reduced by 30% with pravastatin [9], was neutral with simvastatin [10], but was nonsignificantly increased by 15% with atorvastatin [11]. Against these backgrounds, several metaanalyses [12-19] have been conducted and have yielded possible evidence of a statin-DM association. However, such evidence –the increased likelihood of NODM in statin users than nonusers or in intensive rather than moderate dose users– does not indicate whether NODM is really harmful and consequently cancels any cardioprotective benefit of statin. Furthermore, such evidence is based on the RCTs with substantial between-trial differences with regard to nonuniform criteria of NODM, varying numbers of components of metabolic syndrome, simultaneous analyses of primary and secondary prevention trials, and a wide range in age and male-to-female ratios of the participants. Such questions could be answered by carrying out simultaneous comparisons between diabetogenic risks and cardioprotective benefits under the individual trial-based diagnostic criteria of NODM and cardiovascular events in each cohort.

Accordingly, the present study considers the risk-benefit balance of statin use by focusing on a direct comparison between the number needed to treat (i.e., cardiovascular events) and the number needed to harm (i.e., statin-induced NODM) of statins in each trial. This systematic individual trial-based risk-benefit balanced analysis of the previous RCTs reduces currently raised background confounders and reinforces the opinion that the statin-induced NODM is outweighed by the reduction of cardiovascular events regardless of baseline cardiovascular event risk and statin dose.

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Methods

Data extraction

A computerized English literature search between 1992 and January 2015 was conducted in PubMed with "statin" and "diabetes" as keywords. As of January 2015, 4482 publications were initially extracted. Filters activated by "metaanalysis" or "systematic review" then retrieved 266 publications. Subsequently, those articles which were not apparently metaanalyses or systematic reviews from their titles/abstracts were excluded. Additional review articles that were considered pertinent were sought by manual search through reference lists in the retrieved publications. By these procedures, 24 metaanalyses and systematic review articles [12-35] were considered eligible sources of RCTs. Following a thorough review of the 73 RCTs included in these 24 metaanalyses and systematic reviews, 6 RCTs of statin use vs. placebos [10,11,36-39] and 5 RCTs of intensive vs. moderate doses of statin use (reviewed in ref.19) were finally judged as qualifying because of their reported actual number of NODM and cardiovascular events in the same cohort, in which participants were restricted to be without DM at the baseline.

NNT and NNH calculations

The number needed to treat (NNT) is defined as the number of patients needed to achieve one cardiovascular event prevention by statin use or intensive dose statin therapy. In the same sense, the number needed to harm (NNH) is defined as the number of patients needed by which one NODM patient appears. By definition, therefore, when NNH is larger than NNT, the cardiovascular benefit of statin treatment outweighs the diabetogenic harm. Actually, the absolute benefit gain is expressed by a difference of cardiovascular event rates between statin or intensive dose statin users and placebos or moderate dose statin users. The absolute risk increase is expressed by a difference of rate of NODM between the two groups. NNT or NNH is then respectively calculated by a reciprocal of the absolute benefit gain or a reciprocal of the absolute risk increase [40,41].

Benefit-risk ratio

In this study, cardiovascular event rates of reference and experimental arms are respectively expressed as p1 and p2. Similarly, rates of NODM in experimental and reference arms are respectively expressed as q1 and q2. Since NNT and NNH would be usable only when p1>p2 and q1>q2, the trials of p1<p2 and/or q1<q2, if any, could not be a subject of NNT and NNH calculations. This leads to a loss of information even in the valuable studies. To avoid this information loss, the benefit-risk ratio is calculated to evaluate benefit-risk balance. Where the benefit and risk ratios are respectively defined as p1/p2 and q1/q2, the benefit-risk ratio is then expressed by (p1/p2)/ (q1/q2). If this ratio is >1, then benefit outweighs the risk.

Results

The characteristics of the selected 11 RCTs are summarized in Tables 1,2. The trial design (primary or secondary prevention), definition of NODM, and predefined primary endpoint were different between trials.

Table 3 demonstrates each NNT, NNH, and benefit-risk ratio

Trial name (reference)	Trial design	Statin and doses(mg)	Number of patients		Male(%)/ Female(%)	Age (year)	Follow-up (year)	Definition	
			Total	non DM/DM				Endpoint	NODM
JUPITER [36]	1°	Ros20 vs. placebo	17802	17802/0	62/38	median 66	median 1.9	Nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, death from cardiovascular causes	Physician-reported
ASCOT-LLA [11]	1°+2°	Ato10 vs. placebo	10305	7773/2532	81/19	mean 63	median 3.3	Nonfatal MI and fatal CHD	Self-reported history and receiving any treatment
HPS [10]	2°	Sim40 vs. placebo	20536	14573/5963	75/25	more than 70	mean 5	Major vascular events (major coronary events, strokes, and revascularizations)	Initiation of oral hypoglycemic or insulin treatment, or specific report of new diabetes
GISSI-HF [37]	2°	Ros10 vs. placebo	4574	3378/1196	77/23	mean 68	median 3.9	Time to death or time to death or admission to hospital for cardiovascular reasons	NA
LIPID [38]	2°	Pra40 vs. placebo	9014	6997/2017†	83/17	median 62	mean 6.1	Nonfatal MI and fatal CHD	FBG>=7mmol/l or reported use of oral hypoglycemic or insulin treatment
AURORA [39]	2°	Ros10 vs. placebo	2773	2042/731	62/38	mean 64	mean 3.2	Time to major cardiovascular event (nonfatal MI, nonfatal stroke, death from cardiovascular causes)	NA

1°: primary prevention, 2°: secondary prevention, Ros: rosuvastatin, Ato: atorvastatin, Sim: simvastatin, Pra: pravastatin, PBO: placebo, NODM: new onset diabetes mellitus. MI: myocardial infarction, CHD: coronary heart disease, NA: not available, FBG: fasting blood glucose
†including impaired fasting glucose
Table 1: Study characteristics included in this study. Statins vs. placebos.

in each RCT comparing statin vs. placebos. Among them, p2>p1 and q2>q1 was respectively found in one [37] and two trials [38,39]. Therefore, the calculation of NNT and NNH was accurate in the other three RCTs [10,11,36]. The number needed to treat in order to prevent 1 primary endpoint was 18-83. The number needed to treat to cause 1 case of NODM was 165-213. Therefore, NNT was found to be consistently smaller than NNH across these three trials. Benefit-risk ratio was consistently greater than 1 except one trial [37]. This consistency was reserved both in primary and secondary prevention trials.

Table 4 demonstrates each NNT, NNH, and benefit-risk ratio in each intensive vs. moderate dose statin trial. Again, NNT was found to be smaller than NNH in 4 of 5 trials and benefit-risk ratio was greater than 1 in 3 of 5 trials.

Discussion

This is the first report of a direct comparison between individual trial-based NNT and NNH under each diagnostic criterion of NODM and cardiovascular events. This analysis differs from the previous metaanalyses in that it simultaneously addresses two parameters (NNT and NNH) of clinical concern about the risk-benefit balance according to each diagnostic criterion of NODM and cardiovascular events. This approach elucidates that NNH is larger than NNT in statin users than placebos, or in population using intensive rather than moderate doses

Authors	Trial design	Statin and doses(mg)	Number of patients		Male(%)/ Female(%)	Age (year)	Follow-up (year)	Definition	
			Total	non DM/DM				primary endpoint	NODM
Cannon CP	2°	Ato80 vs. Sim40	4162	3428/734	78/22	mean 58	mean 2	Death from any cause, MI, unstable angina, revascularization, and stroke	NA
de Lemos JA	2°	Sim80 vs. Sim20	4497	3438/1059	76/24	median 61	up to 2	Cardiovascular death, nonfatal MI, admission for acute coronary syndrome, stroke	NA
LaRosa JC	2°	Ato80 vs. Ato20	10001	8500/1501	81/19	mean 61	median 4.9	Death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke	NA
Pedersen TR	2°	Ato80 vs. Sim20	8888	7819/1069	81/19	mean 62	median 4.8	Coronary death, nonfatal MI, cardiac arrest with resuscitation	NA
Armitage J	2°	Sim80 vs. Sim20	12064	NA	83/17	mean 64	mean 6.7	Coronary death, MI, stroke, arterial revascularization	NA

2°: secondary prevention, Ato: atorvastatin, Sim: simvastatin, NODM: new onset diabetes mellitus. MI: myocardial infarction, CHD: coronary heart disease, NA: not available.

Table 2: Study characteristics included in this study. Intensive vs. moderate doses of statins. References are listed in a review article [19].

Trial name	Number of non DM patients at study entry		Number of patients with primary endpoint		Rates of primary endpoint		NNT	Number of patients with NODM		Rates of NODM		NNH	Benefit-risk ratio
	PBO	Statin	PBO	Statin	PBO (p1)	Statin (p2)	1/(p1-p2)	Statin	PBO	Statin (q1)	PBO (q2)	1/(q1-q2)	
JUPITER [36]	8901	8901	251	142	0.028	0.016	81.7	270	216	0.030	0.024	164.8	1.41
ASCOT-LLA [11]	3863	3910	108	62	0.028	0.016	82.6	154	134	0.039	0.035	212.9	1.55
HPS [10]	7282	7291	1837	1432	0.252	0.196	17.9	335	293	0.046	0.040	175.1	1.12
GISSI-HF [37]	1718	1660	919	908	0.535	0.547	NA	225	215	0.136	0.125	96.2	0.90
LIPID [38]	3501	3496	507	395	0.145	0.113	31.4	126	138	0.036	0.039	NA	1.40
AURORA [39]	1041	1001	272	261	0.261	0.261	1824.9	10	14	0.010	0.013	NA	1.35

PBO: placebo, NNT: number needed to treat, NNH: number needed to harm, NODM: new onset diabetes mellitus. Benefit-risk ratio is calculated by (p1/p2)/(q1/q2).

Table 3: NNT and NNH in trials of statin versus placebos.

Authors	Number of non DM patients at study entry		Number of patients with primary endpoint		Rates of primary endpoint		NNT	Number of patients with NODM		Rates of NODM		NNH	Benefit-risk ratio
	Moderate	Intensive	Moderate	Intensive	Moderate (p1)	Intensive (p2)	1/(p1-p2)	Intensive	Moderate	Intensive (q1)	Moderate (q2)	1/(q1-q2)	
Cannon CP	1688	1707	355	315	0.210	0.185	38.8	101	99	0.059	0.059	1927.4	1.13
de Lemos JA	1736	1768	234	212	0.135	0.120	67.2	65	47	0.037	0.027	103.2	0.83
LaRosa JC	3797	3798	830	647	0.219	0.170	20.7	418	358	0.110	0.094	63.4	1.10
Pedersen TR	3724	3737	917	776	0.246	0.208	25.9	240	209	0.064	0.056	123.5	1.04
Armitage J	5399	5398	1214	1184	0.225	0.219	181.3	625	587	0.116	0.109	141.6	0.96

PBO: placebo, NNT: number needed to treat, NNH: number needed to harm, NODM: new onset diabetes mellitus
Benefit-risk ratio is calculated by (p1/p2)/(q1/q2).

Table 4: NNT and NNH in trials of intensive vs. moderate doses of statin. References are listed in a review article [19].

of statin. In addition, benefit-risk ratio is mostly greater than 1 in both primary and secondary prevention trials or intensive dose statin use. These results suggest that the statins' advantage outweighs the statins' diabetogenicity regardless of statin dose and cardiovascular event risk at baseline.

Although there are many RCTs reporting statins' benefit for cardiovascular health, only 11 studies were considered pertinent in the present study. This is attributable to the fact that a NODM was not initially considered as a potential adverse event of statins, so that NODM was less likely to become a main topic and was not a primary endpoint. Therefore, many previous RCTs recruited patients both with and without DM at entry, and the incidence of a cardiovascular endpoint was analyzed in this mixed population with a different ability for glycemic control. In addition, even in the subanalysis studies, the information was very limited concerning the actual number of patients developing DM as well as with cardiovascular events among participants restricted to be without DM at entry. This may further make the selection of pertinent publications difficult for the purpose of carrying out a statin risk-benefit balance simultaneously.

Several confounders could be pointed out in previous observational studies and metaanalyses when considering the increased chance of statin-induced NODM than nonstatin users. First, the diagnostic criteria of NODM were different between studies, with some including an initiation of pharmacotherapy and some including personal or a physician report [12-14]. Second, patients carrying a higher number of risk factors for DM are more susceptible to statin-induced NODM than those carrying a smaller number of risk factors for DM [42-44]. This consideration is important since statin users may adopt a less healthy lifestyle than nonstatin users. Given that the risk factors of hyperlipidemia, such as increased body weight, excess calorie intake, less daily exercise habit, sedentary lifestyle, and further components of metabolic syndrome are equivalent to DM, statin may push predisposing individuals toward the development of DM or simply hasten the DM that would have developed anyway by these risk factors regardless of whether or not the person took statin. This context is relevant to the third confounder –a selection bias– in which choice and dose of statin may influence the statin-DM association [14,19]. Strong statin at higher doses may be more likely to be prescribed to those patients with severer metabolic syndrome. It is conceivable that patients with multiple components of metabolic syndromes are both at risk of developing DM [44] and liable to receive higher doses of statin. Fourth, participants in RCTs at different baseline cardiovascular risk –primary or secondary prevention trial– may also lead to a different risk-benefit outcome, because cardioprotective effects of statins are more prominent in secondary prevention than primary prevention. Fifth, the age of participants may also comprise a confounder. Statin appears to increase the risk of NODM in older patients [14]. The risk of DM by pravastatin was increased by 32% in PROSPER [14] in which the patients were aged 70-82 years, while it was decreased by 30% in WOSCOPS in which the mean age of participants was 55 years [9]. Finally, observational studies are unavoidably susceptible to detection bias. Statin users are more likely to have health concerns which lead to a doctor visit, subsequently having more frequent health checks and more chances to detect DM.

Against these backgrounds, several attempts have been made to explore the risk-benefit balance by comparing statin vs. placebo, intensive vs. moderate statin doses, and primary vs. secondary prevention. Cannon et al. estimated that the benefit of preventing total vascular events was 9 times higher than the risk of NODM [45]. Intensive dose statin documented a 16% absolute risk reduction of cardiovascular disease risk with a 12% absolute increase in DM risk [19]. In the primary prevention of statins, the magnitude of the increased risk of NODM is estimated to be 50 times smaller than the absolute cardiovascular benefit [2]. However, even these calculations still cannot avoid bias because they are based on metaanalyses in which the included RCTs have between-trial differences as mentioned above. Such limitations motivate the individual trial-based NNT and NNH comparison under the same diagnostic criteria of NODM and cardiovascular events in each cohort. The present study could resolve the aforementioned limitations of between-trial confounders, thereby providing evidence that statins' diabetogenicity can be canceled and outweighed by the more protective effects of cardiovascular events regardless of different baseline risks of cardiovascular events or statin dose.

Despite the strength, the relatively shorter observation period of the studies recruited in the present one could still render limitations. A glycemic disorder begins long before DM diagnosis [46], and type 2 DM requires a long latency period until cardiovascular events become manifest. In fact, major cardiovascular event rates cumulatively increased in proportion to the length of observation period [47,48]. On the other hand, the mean or median observation period of the studies in the present study is only between 1.9 and 6.1 years, suggesting that a firm conclusion concerning the statins' risk-benefit balance awaits further investigation. It should be noted that valsartan-induced DM occurs more frequently in the later period of its use [49]. Another limitation of concern is whether the present results, derived from studies in which most participants were Caucasians, could be extrapolated to Asian ethnicity. The increase of type 2 DM patients in Asian countries is an epidemic –the prevalence of type 2 DM has tripled or quintupled over the past 30 years in some Asian countries, a higher rate than in the USA where it doubled during the past 40 years. Since DM in Asian countries developed in a much shorter time, in a younger group, and in people with much lower BMI [50], further investigations are required concerning the NNT/NNH comparison in particular in Asian ethnicity.

As statins are consequently prescribed to the overwhelmingly majority of patients with hyperlipidemia, a specific investigation of the risk-benefit balance of statin treatment is merited and the present trial-based findings deserve clinical consideration. The present analyses add insight into the probable cardioprotective advantage of statins rather than their diabetogenic harm.

References

1. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, et al. (2005) Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 366: 1267-1278.

2. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, Blackwell L, Keech A, et al. (2012) The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 380: 581-590.

3. Macedo AF, Taylor FC, Casas JP, Adler A, Prieto-Merino D, et al. (2014) Unintended effects of statins from observational studies in the general population: systematic review and meta-analysis. BMC Med 12: 51.

4. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. (2010) Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 375: 2215-2222.

5. Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, et al. (2011) Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 364: 829-841.

6. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, et al (2013) Risk of incident diabetes among patients treated with statins: population based study. BMJ 346: f2610.

7. Dormuth CR, Filion KB, Paterson JM, James MT, Teare GF, et al. (2014) Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. BMJ 348: g3244.

8. Ko DT, Wijeysundera HC, Jackevicius CA, Yousef A, Wang J, et al. (2013) Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins. Circ Cardiovasc Qual Outcomes 6: 315-322.

9. Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, et al. (2001) Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation 103: 357-362.

10. Collins R, Armitage J, Parish S, Sleigh P, Peto R, et al. (2003) Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 361: 2005-2016.

11. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, et al. (2003) 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. 361: 1149-1158.

12. Coleman CI, Reinhart K, Kluger J, White CM. (2008) The effect of statins on the development of new-onset type 2 diabetes: a meta-analysis of randomized controlled trials. Curr Med Res Opin 24: 1359-1362.

13. Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, et al. (2009) Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes Care 32: 1924-1929.

14. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, et al. (2010) Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 375: 735-742.

15. Mills EJ, Wu P, Chong G, Ghement I, Singh S, et al. (2011) Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. QJM 104: 109-124.

16. Naci H, Brugts J, Ades T (2013) Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. Circ Cardiovasc Qual Outcomes 6: 390-399.

17. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, et al. (2013) Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 1: CD004816.

18. Navarese EP, Buffon A, Andreotti F, Kozinski M, Welton N, et al. (2013) Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. Am J Cardiol 111: 1123-1130.

19. Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, et al. (2011) Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 305: 2556-2564.

20. Ray KK, Seshasai SR, Erqou S, Sever P, Jukema JW, et al. (2010) Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. Arch Intern Med 170: 1024-1031.

21. 21. Naci H, Brugts JJ, Fleurence R, Tsoi B, Toor H, et al. (2013) Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. Eur J Prev Cardiol 20: 641-657.

22. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, et al. (2013) Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 1: CD004816.

23. Petretta M, Costanzo P, Perrone-Filardi P, Chiariello M (2010) Impact of gender in primary prevention of coronary heart disease with statin therapy: a meta-analysis. Int J Cardiol 138: 25-31.

24. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. (2010) Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 376: 1670-1681.

25. Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, et al. (2009) The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ 338: b2376.

26. Cai R, Yuan Y, Zhou Y, Xia W, Wang P, et al. (2014) Lower intensified target LDL-c level of statin therapy results in a higher risk of incident diabetes: a meta-analysis. PLoS One 9: e104922.

27. Chang YH, Hsieh MC, Wang CY, Lin KC, Lee YJ (2013) Reassessing the benefits of statins in the prevention of cardiovascular disease in diabetic patients--a systematic review and meta-analysis. Rev Diabet Stud 10: 157-170.

28. Swerdlow DI, Preiss D, Kuchenbaecker KB, Holmes MV, Engmann JE, et al. (2015) HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. Lancet 385: 351-361.

29. Tonelli M, Lloyd A, Clement F, Conly J, Husereau D, et al. Efficacy of statins for primary prevention in people at low cardiovascular risk: a meta-analysis. CMAJ 183: E1189-1202.

30. Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, et al. (2008) Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. J Am Coll Cardiol 52: 1769-1781.

31. Thavendiranathan P, Bagai A, Brookhart MA, Choudhry NK (2006) Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. Arch Intern Med 166: 2307-2313.

32. Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB (2012) Meta-analysis of statin effects in women versus men. J Am Coll Cardiol 59: 572-582.

33. Gould AL, Davies GM, Alemao E, Yin DD, Cook JR (2007) Cholesterol reduction yields clinical benefits: meta-analysis including recent trials. Clin Ther 29: 778-794.

34. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD (1998) Cholesterol reduction yields clinical benefit: impact of statin trials. Circulation 97: 946-952.

35. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD (1995) Cholesterol reduction yields clinical benefit. A new look at old data. Circulation 91: 2274-2282.

36. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, et al. (2008) Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 359: 2195-2207.

37. Gissi-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, et al. (2008) Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 372: 1231-1239.

38. Keech A, Colquhoun D, Best J, Kirby A, Simes RJ, et al. (2003) Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. Diabetes Care 26: 2713-2721.

39. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, et al. (2009) Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 360: 1395-1407.

40. Mancini GB, Schulzer M (1999) Reporting risks and benefits of therapy by use of the concepts of unqualified success and unmitigated failure: applications to highly cited trials in cardiovascular medicine. Circulation 99: 377-383.

41. Schulzer M, Mancini GB (1996) 'Unqualified success' and 'unmitigated failure': number-needed-to-treat-related concepts for assessing treatment efficacy in the presence of treatment-induced adverse events. Int J Epidemiol 25: 704-712.

42. Waters DD, Ho JE, Boekholdt SM, DeMicco DA, Kastelein JJ, et al. (2013) Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes. J Am Coll Cardiol 61: 148-152.

43. Sattar N, McConnachie A, Shaper AG, Blauw GJ, Buckley BM, et al. (2008) Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. Lancet 371: 1927-1935.

44. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ (2012) Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet 380: 565-571.

45. Cannon CP (2010) Balancing the benefits of statins versus a new risk-diabetes. Lancet 375: 700-701.

46. Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, et al. (2009) Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. Lancet 373: 2215-2221.

47. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, et al. (1999) Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. Diabetes Care 22: 920-924.

48. Oizumi T, Daimon M, Jimbu Y, Wada K, Kameda W, et al. (2008) Impaired glucose tolerance is a risk factor for stroke in a Japanese sample--the Funagata study. Metabolism 57: 333-338.

49. Aksnes TA, Kjeldsen SE, Rostrup M, Omvik P, Hua TA, et al. (2007) Impact of new-onset diabetes mellitus on cardiac outcomes in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial population. Hypertension 50: 467-473.

50. Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, et al. (2006) Epidemic obesity and type 2 diabetes in Asia. Lancet 368: 1681-1688.