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 |           |                  |            |
| JUPITER [36]            | 1°          | Ros20 vs. placebo    | 17802             | 62/38  |           | median 66 | median 1.9       | Nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, death from cardiovascular causes |
|                         |             |                      | 17802/0          |        |           |           |                  |            |
| ASCOT-LLA [11]          | 1°+2°       | Ato10 vs. placebo    | 10305             | 81/19  |           | mean 63   | median 3.3       | Nonfatal MI and fatal CHD |
|                         |             |                      | 7773/2532        |        |           |           |                  |            |
| HPS [10]                | 2°          | Sim40 vs. placebo    | 20536             | 75/25  |           | more than 70 | mean 5        | Major vascular events (major coronary events, strokes, and revascularizations) |
|                         |             |                      | 14573/5963       |        |           |           |                  |            |
| GISSI-HF [37]           | 2°          | Ros10 vs. placebo    | 4574              | 77/23  |           | mean 68   | median 3.9       | Time to death or time to death or admission to hospital for cardiovascular reasons |
|                         |             |                      | 3378/1196        |        |           |           |                  |            |
| LIPID [38]              | 2°          | Pra40 vs. placebo    | 9014              | 83/17  |           | mean 62   | mean 6.1        | Nonfatal MI and fatal CHD |
|                         |             |                      | 6997/2017†       |        |           |           |                  |            |
| AURORA [39]             | 2°          | Ros10 vs. placebo    | 2773              | 62/38  |           | mean 64   | mean 3.2        | Time to major cardiovascular event (nonfatal MI, nonfatal stroke, death from cardiovascular causes) |
|                         |             |                      | 2042/731         |        |           |           |                  |            |

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 3 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 |
|---------|--------------|----------------------|--------------------|---------|-----------|------------|-----------------|------------|
| 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 |
|------------|-----------------------------------------|----------------------------------------|--------------------------|-----|------------------------------|----------------|-----|------------------|
| JUPITER [36] | PBO 8901 | Statin 8901 | PBO (p1) 8901 | Statin (p2) 8901 | 1/(p1-p2) | Statin PBO | Statin (q1) PBO (q2) | 1/(q1-q2) | 1.41 |
| ASCOT-LA [11] | 3683 | 3910 | 108 62 | 0.028 0.016 82.6 154 134 | 0.039 0.035 212.9 1.04 |
| 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) | Intensive | Moderate (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 | 567 | 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.

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