Relative Effect of Current Intensive Lipid-Lowering Drugs on Cardiovascular Outcomes in Secondary Prevention — A Meta-Analysis of 12 Randomized Trials —

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Background: We aimed to investigate the comparative cardiovascular benefits of high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin treatments in secondary prevention patients.

Methods and Results: We selected 12 randomized controlled trials (n=131,978 patients) using PubMed and Embase (inception–June 1, 2018). Subgroup differences were explored by meta-regression and Cochran Q test. The relative effects of high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin on major cardiovascular events (MACE), and revascularization were varied and decreased gradually, of which high-dose statin resulted in lower risk of MACE and revascularization than PCSK9 inhibitor-statin per 1 mmol/L reduction of low-density lipoprotein cholesterol (LDL-C): risk ratio (RR) for MACE, 0.86 (95% confidence interval (CI), 0.81–0.90) for high-dose statin, 0.90 (95% CI, 0.83–0.96) for ezetimibe-statin, and 0.94 (95% CI, 0.92–0.96) for PCSK9 inhibitor-statin; RR for revascularization, 0.84 (95% CI, 0.77–0.90) for high-dose statin, 0.91 (95% CI, 0.81–1.00) for ezetimibe-statin, and 0.94 (95% CI, 0.90–0.97) for PCSK9 inhibitor-statin. Similar relative effects of intensive lipid-lowering treatment were also observed in analyses of myocardial infarction and stroke, although no significant difference between groups was identified.

Conclusions: In secondary prevention patients, the relative benefits of high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin treatments were varied and decreased gradually, of which high-dose statin was significantly superior to PCSK9 inhibitor-statin for improving MACE and revascularization per 1 mmol/L reduction of LDL-C.

Key Words: Ezetimibe; Lipid-lowering drugs; PCSK9 inhibitor; Secondary prevention; Statins

Secondary prevention patients are at increased risk for recurrent cardiovascular events, and intensive lipid-lowering therapies are recommended by major clinical guidelines either as the direct treatment or as a strategy to achieve a low-density lipoprotein cholesterol (LDL-C) level ≤70 mg/dL or ≤55 mg/dL. Currently, there are several types of combination drugs available for intensive lipid-lowering treatment. High-dose statins are the most common therapy and are effective in reducing both the LDL-C level and cardiovascular risk. In addition, there are non-statin agents such as ezetimibe or proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors that are added to patients’ therapy if they are already on statins to achieve similar cardiovascular benefits as those achieved with high-dose statins. However, the comparative efficacy and safety of available intensive lipid-lowering drugs in secondary prevention patients are largely unknown.

Mendelian randomization studies have suggested that variation in the *HMGCR* gene (target of statins) has almost the same effect as variants in the *PCSK9* gene (target of PCSK9 inhibitors) and the *NPC1L1* gene (target of ezetimibe) on the risk of cardiovascular events per unit decrease in the LDL-C level. However, evidence from genetic studies may not reflect the relative effects of intensive lipid-lowering drugs used in the clinical setting. A case in point is the cholesteryl ester transfer protein (CETP) inhibitor that failed to match the clinical benefit of variants in the *CETP* gene. Clinical data, especially from randomized controlled trials (RCTs), will provide a much more robust estimate of the relative effects among intensive lipid-lowering drugs. Although the post-hoc analysis of the FOURIER trial using data from both the FOURIER trial and the Cholesterol Treatment Trialists’ (CTT) meta-analysis suggested that the benefit of PCSK9 inhibitors in reducing the risk of cardiovascular events was largely consistent with the benefit seen with statins on per 1 mmol/L of LDL-C lowering, the FOURIER trial and the trials included in the CTT meta-analysis had different baseline
characteristics of the cardiovascular risk of participants, pharmaceuticals for cardiovascular prevention, background lipid-lowering medications, follow-up duration, and placebo lipid-lowering agents. Moreover, the data for the PCSK9 inhibitors available for comparison were only from the FOURIER trial, which limited the statistical power. In this setting, the comparative effects of lipid-lowering drugs may suffer from potential bias. Recently, relevant long-term cardiovascular outcome trials have been successively released, these enrolled patients with similar baseline characteristics, thus providing us with more consistent data to analyze the comparative effect of different intensive lipid-lowering drugs.

By summarizing relevant statin and non-statin trials performed on secondary prevention patients, we respectively investigated the effects of high statin, ezetimibe-statin, and PCSK9 inhibitor-statin therapies with the same group of less lipid-lowering control drugs on cardiovascular outcomes in 3 subgroups, with the between-group differences to indirectly compare the relative benefits and harms of these intensive lipid-lowering agents.

**Methods**

This meta-analysis was conducted in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement.20

**Data Sources and Searches**

We searched the PubMed and Embase databases for relevant trials, from database inception date through to June 1, 2018. An additional search was performed by manually scrutinizing the reference lists of relevant reviews and meta-analyses, and abstracts from major cardiovascular conferences held in the past 2 years. Potential trials were identified using the following search terms: (“lipid-lowering treatment” OR “lipid-lowering agents” OR “statin” OR “ezetimibe” OR “PCSK9 inhibitor”) and (“cardiovascular disease” OR “coronary heart disease” OR “myocardial infarction” OR “cerebrovascular disease” OR “stroke” OR “peripheral artery disease”). Trials were limited to RCTs, with no language restriction. We excluded trials published before 2000 because the pharmaceuticals for cardiovascular prevention before that time may be different from those prescribed in the latest lipid-lowering trials.

**Study Selection**

Two investigators independently searched and screened the retrieved studies. Any discrepancy was resolved by discussing with a third investigator. The inclusion criteria were as follows: (1) ≥60% participants were secondary prevention patients (defined by a history of atherosclerosis cardiovascular disease (CVD), i.e., coronary artery disease [CAD], cerebrovascular disease, or peripheral artery disease); (2) included 1,000 patient-years in each randomized group; (3) compared more intensive lipid-lowering therapy with less-intensive statin therapy; and (4) reported one of the interesting outcomes listed below. Trials that compared non-statin drugs with placebo, but had 80% or more patients using statins at background during the trial, were also eligible. Interesting outcomes included major cardiovascular events (MACE), myocardial infarction (MI), stroke, coronary revascularization, all-cause death, and cardiovascular death. Studies were excluded if: (1) the trial was performed in patients with significant competing risks (i.e., heart failure or chronic kidney disease); and (2) the non-statin drugs reduced LDL-C not by upregulation of LDL receptor expression or inhibition of LDL receptor degradation.

**Data Extraction and Quality Assessment**

Two investigators independently extracted the data using a predefined structured form. Two investigators independently appraised the accuracy of the abstractions and resolved any discrepancy by discussing with a third investigator. The following information was extracted: publication year, sample size, mean or median follow-up duration, demographic characteristics, history of diabetes mellitus, background use of lipid-lowering therapy, the definition of each interesting outcome, the number of events for each outcome, and lipid-lowering interventions, baseline LDL-C level and reduction of LDL-C in both more intensive and less-intensive lipid-lowering groups. Two investigators independently assessed the potential risks of bias of the included trials according to the Cochrane Collaboration’s risk of bias tool. Any discrepancy on bias assessment was then reported and summarized as Cohen’s Kappa.

**Data Synthesis and Analysis**

A random-effects model (DerSimonian and Laird) was used to calculate summary risk ratio (RR) and its 95% confidence interval (CI). We standardized the analyses to a 1 mmol/L reduction in LDL-C because we were inter-
estimated in the proportional effects of lowering LDL-C by 1 mmol/L, and because the trials varied in the relative intensity of LDL-C lowering achieved because of differences in lipid-lowering strategies. Standardized analyses were conducted by multiplying the log of the summary statistic of each trial (and its standard error) by 1/d, where d was the average LDL-C reduction in that trial. Heterogeneity was estimated using the I² statistic; I² > 50% represented significant heterogeneity.

Meta-analyses were performed according to predefined subgroups stratified by the type of drugs in the more intensive lipid-lowering groups, including high statin (high-dose statins), ezetimibe-statin, and PCSK9 inhibitor-statin. Additional stratified analyses were conducted stratifying according to potential confounding factors of baseline LDL-C level (<100 and ≥100 mg/dL). Meta-regression was used to investigate the association of different types of intensive lipid-lowering strategies on the trial RRs for all outcomes. Sensitivity analyses were conducted by using an adjusted model in which patient-year instead of the total number of patient-months was used to investigate the association of different types of intensive lipid-lowering strategies on the trial RRs for all outcomes.

### Table 1. Baseline Characteristics of Included Trials

| Study and date | Duration, year | Sample size | Female, % | Mean age, years | DM, % | Participants |
|----------------|----------------|-------------|-----------|----------------|-------|--------------|
| PROVE-IT (2004)⁹ | 2.0 | 2,099/2,063 | 21.9 | 58.2 | 17.6 | ACS |
| A to Z (2004)⁴ | 2.0 | 2,266/2,232 | 24.5 | 61.0 | 23.5 | ACS |
| TNT (2005)⁶ | 4.9 | 4,995/5,006 | 19.0 | 61.0 | 15.0 | Stable coronary disease |
| IDEAL (2005)⁶ | 4.8 | 4,439/4,449 | 19.2 | 61.7 | 12.1 | MI |
| SEARCH (2010)⁵ | 6.7 | 6,031/6,033 | NR | 64.2 | NR | MI |
| IMPROVE-IT (2015)⁸ | 6.0 | 9,067/9,077 | 24.3 | 63.6 | 27.2 | ACS |
| ODYSSEY LONG TERM (2015)¹⁵ | 1.5 | 1,550/786 | 37.7 | 62.8 | 34.5 | 69% CAD |
| HIJ-PROPER (2017)¹⁶ | 3.9 | 864/857 | 24.5 | 65.6 | 30.2 | ACS |
| SPIRE2 (2017)¹⁷ | 0.8 | 5,312/5,309 | 34.6 | 62.4 | 46.8 | CVD |
| FOURIER (2017)⁹ | 2.2 | 13,784/13,780 | 24.5 | 62.5 | 36.6 | CVD |
| ODYSSEY OUTCOMES (2018)¹⁸ | 2.8 | 9,482/9,482 | NR | NR | NR | ACS |
| REAL-CAD (2018)¹⁸ | 3.0 | 6,199/6,214 | 15.0 | 68.1 | 40.1 | Stable coronary disease |

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| A to Z (2004)⁴ | 2.0 | 2,266/2,232 | 24.5 | 61.0 | 23.5 | ACS |
| TNT (2005)⁶ | 4.9 | 4,995/5,006 | 19.0 | 61.0 | 15.0 | Stable coronary disease |
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⁹A to Z Placebo titrated to simvastatin 20 mg, ¹⁰Alirocumab 150 mg subcutaneously every 2 weeks, ¹¹Bococizumab 150 mg every 2 weeks, ¹²Simvastatin 40 mg plus ezetimibe 10 mg, ¹³High-dose statin with or without ezetimibe. A to Z. Phase Z of the A to Z trial. FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk. HIJ-PROPER, Heart Institute of Japan Proper level of lipid lowering with Pitavastatin and Ezetimibe in acute coronary syndrome trial. IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering Study Group. IMPROVE-IT, The Improved Reduction of Outcomes: Vytorin Efficacy International Trial. ODYSSEY LONG TERM, Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled With Their Lipid Modifying Therapy. ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab. PROVE-IT, Pravastatin or Atorvastatin Evaluation and Infection Therapy. SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine. SPIRE2, Studies of PCSK9 Inhibition and the Reduction of Vascular Events program 2. TNT, Treating to New Targets. REAL-CAD, High-Dose Versus Low-Dose Pitavastatin in Japanese Patients With Stable Coronary Artery Disease. CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NR, not reported.
Relative Effect of Intensive Lipid-Lowering

Results

The process of study selection is shown in Figure 1. Of the 2,256 citations initially identified, 840 were duplicates, 1,309 were excluded based on title/abstract screening, and 95 did not meet the inclusion criteria. A total of 12 studies were identified by screening previous meta-analyses and reviews, and abstracts of the latest cardiovascular conferences.

Table 1 describes the baseline characteristics of the included trials. The more intensive lipid-lowering drugs were high-dose statins in 6 trials, ezetimibe-statin in 2 trials, and PCSK9 inhibitor-statin in 4 trials. The less-intensive lipid-lowering drugs were less-intensive statins or placebo plus background statin.

A Cochran Q test was used to explore subgroup differences. A two-sided P<0.05 represented statistical significance. All the intensive lipid-lowering drugs were all compared with the same control group, subgroup differences in our study would represent the different effects of the 3 intensive lipid-lowering drugs on cardiovascular outcomes or on deaths. For a certain outcome, if the Cochran Q test found a significant difference between group A and group B, and the estimated RR of the intensive lipid-lowering drugs in group A as compared with control drugs was smaller/larger than that of the intensive lipid-lowering drugs in group B (no matter whether the CIs of both groups overlapped or not), we deemed that the intensive lipid-lowering drugs in group A were significantly superior/inferior to the intensive lipid-lowering drugs in group B for improving this outcome. Publication bias was assessed by constructing a “funnel plot” in which the SE of the log RR was plotted against the log RR. The asymmetry of the plot was examined visually and additionally examined by Begg’s test. All the analyses were performed by Review Manager, version 5.3 (Cochrane Collaboration, Copenhagen, Denmark), and Stata 12.0 (StataCorp. LP).

Figure 2. Meta-regression analysis of major cardiovascular events and revascularization procedures by type of intensive lipid-lowering drugs. Change in rate ratios (RRs) per 1 mmol/L reduction of low-density lipoprotein cholesterol (LDL-C) and 95% confidence intervals (CIs) of more intensive vs. less-intensive lipid-lowering therapies plotted against type of more intensive lipid-lowering drugs. Circle size is proportional to the weight in the meta-regression. The solid and dotted lines respectively represent the meta-regression slope of the change in RR per 1 mmol/L reduction of LDL-C and its 95% CI for treatment across different types of more lipid-lowering drugs.
lipid-lowering group (range 87.0–134.8 mg/dL), and the mean baseline LDL-C was 107.1 mg/dL in the less-intensive lipid-lowering group (range 87.0–134.6 mg/dL). (To convert LDL-C values to mmol/L, multiply by 0.0259.)

trials in patients with a history of MI\(^6\), and 3 trials\(^{15,17,19}\) in patients with mixed CVDs but with some patients (<31%) probably without a history of CVD. The mean follow-up was 3.4 years (range 0.8–6.7 years), the mean baseline LDL-C was 107.1 mg/dL in the more intensive lipid-lowering group (range 87.0–134.8 mg/dL), and the mean baseline LDL-C was 107.1 mg/dL in the less-intensive lipid-lowering group (range 87.0–135.6 mg/dL). (To convert LDL-C values to mmol/L, multiply by 0.0259.)
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Table 2. Sources of Statistical Heterogeneity in Subgroup Analyses

| Subgroup (Analysis by type of more intensive lipid-lowering drug) | No. of trials | Sample size | No. of patients with event/total no. (%) | Risk ratio [95% CI] | Interaction P value |
|---------------------------------------------------------------|--------------|-------------|----------------------------------------|---------------------|--------------------|
| **MACE** (Analysis by type of more intensive lipid-lowering drug) |              |             |                                        |                     |                    |
| High-dose statin                                              |              |             |                                        |                     |                    |
| Baseline LDL-C <100 mg/dL                                     | 3            | 35,119      | 2,177/17,552 (12.40%)                  | 0.82 [0.73, 0.92]   | 0.29               |
| Baseline LDL-C ≥100 mg/dL                                     | 3            | 17,547      | 1,312/8,803 (14.90%)                   | 0.88 [0.82, 0.93]   |                    |
| Ezetimibe-statin                                              |              |             |                                        |                     |                    |
| Baseline LDL-C <100 mg/dL                                     | 1            | 18,144      | 2,572/9,067 (28.37%)                   | 0.90 [0.82, 0.97]   | 0.93               |
| Baseline LDL-C ≥100 mg/dL                                     | 1            | 1,721       | 241/864 (27.89%)                      | 0.91 [0.71, 1.10]   |                    |
| PCSK9 inhibitor-statin                                        |              |             |                                        |                     |                    |
| Baseline LDL-C <100 mg/dL                                     | 2            | 46,488      | 2,242/23,246 (9.65%)                   | 0.94 [0.92, 0.96]   | >0.99              |
| Baseline LDL-C ≥100 mg/dL                                     | 2            | 12,959      | 251/862 (3.66%)                       | 0.94 [0.86, 1.03]   |                    |
| **Revascularization procedure (Analysis by type of more intensive lipid-lowering drugs)** |              |             |                                        |                     |                    |
| High-dose statin                                              |              |             |                                        |                     |                    |
| Baseline LDL-C <100 mg/dL                                     | 2            | 25,118      | 1,099/12,557 (8.75%)                  | 0.83 [0.71, 0.95]   | 0.90               |
| Baseline LDL-C ≥100 mg/dL                                     | 3            | 17,547      | 1,040/8,803 (11.81%)                  | 0.84 [0.74, 0.95]   |                    |
| Ezetimibe-statin                                              |              |             |                                        |                     |                    |
| Baseline LDL-C <100 mg/dL                                     | 1            | 18,144      | 1,871/9,067 (20.64%)                  | 0.93 [0.85, 1.01]   | 0.33               |
| Baseline LDL-C ≥100 mg/dL                                     | 1            | 1,721       | 225/864 (26.04%)                      | 0.82 [0.64, 1.00]   |                    |
| PCSK9 inhibitor-statin                                        |              |             |                                        |                     |                    |
| Baseline LDL-C <100 mg/dL                                     | 2            | 46,488      | 1,488/23,246 (6.40%)                  | 0.93 [0.89, 0.97]   | 0.14               |
| Baseline LDL-C ≥100 mg/dL                                     | 2            | 12,959      | 88/6,862 (1.28%)                      | 1.00 [0.91, 1.08]   |                    |
| **MI (Analysis by type of more intensive lipid-lowering drugs)** |              |             |                                        |                     |                    |
| High-dose statin                                              |              |             |                                        |                     |                    |
| Baseline LDL-C <100 mg/dL                                     | 3            | 35,119      | 1,563/17,552 (8.90%)                  | 0.77 [0.55, 0.98]   | 0.35               |
| Baseline LDL-C ≥100 mg/dL                                     | 3            | 17,547      | 557/8,803 (6.33%)                     | 0.89 [0.80, 0.98]   |                    |
| Ezetimibe-statin                                              |              |             |                                        |                     |                    |
| Baseline LDL-C <100 mg/dL                                     | 1            | 18,144      | 1,322/9,067 (14.58%)                  | 0.88 [0.79, 0.97]   | 0.79               |
| Baseline LDL-C ≥100 mg/dL                                     | 1            | 1,721       | 224/864 (25.93%)                      | 0.91 [0.71, 1.11]   |                    |
| PCSK9 inhibitor-statin                                        |              |             |                                        |                     |                    |
| Baseline LDL-C <100 mg/dL                                     | 2            | 46,488      | 1,092/23,246 (4.70%)                  | 0.92 [0.86, 0.97]   | 0.24               |
| Baseline LDL-C ≥100 mg/dL                                     | 2            | 12,959      | 108/6,862 (1.57%)                     | 0.85 [0.75, 0.95]   |                    |

(Table 2 continued the next page.)
was associated with an RR of 0.84 (95% CI, 0.77–0.90), 0.91 (95% CI, 0.81–1.00), and 0.94 (95% CI, 0.90–0.97) per 1 mmol/L reduction of the LDL-C level, respectively, in the subgroups with high-dose statins, ezetimibe-statin, and PCSK9 inhibitor-statin as the intervention (Figure 3). In pair-wise comparisons, only high-dose statin was significantly better than PCSK9 inhibitor-statin in reducing the risk of revascularization (P_between-group_difference = 0.01, Figure 3) per 1 mmol/L reduction of the LDL-C level; findings were generally unchanged stratified by baseline LDL-C level (Table 2).

MI
Overall, 4,866 of 66,394 patients (7.33%) receiving the more intensive lipid-lowering drugs vs. 5,528 of 65,584 (8.43%) receiving the less-intensive drugs experienced a MI during follow-up. The overall risk reduction in MI with more vs. less-intensive therapy across all trials was 0.88 (95% CI, 0.84–0.92) per 1 mmol/L reduction of the LDL-C level, and did not vary by the type of intensive lipid-lowering drugs (P_regression = 0.515; Supplementary Figure 2; P_subgroup heterogeneity = 0.79, Figure 4). In the predefined subgroup analyses, MI risk was associated with an RR of 0.85 (95% CI, 0.74–0.95), 0.88 (95% CI, 0.80–0.96), and 0.90 (95% CI, 0.85–0.95) per 1 mmol/L reduction of the LDL-C level, respectively, in the subgroups with high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin as the intervention (Figure 4); findings were generally unchanged stratified by baseline LDL-C level (Table 2).

Stroke
Overall, 1,404 of 66,394 patients (2.11%) receiving the more intensive lipid-lowering drugs vs. 1,659 of 65,584 (2.53%) receiving the less-intensive drugs experienced a stroke during follow-up. The overall risk reduction in stroke with more vs. less-intensive therapy across all trials was 0.90 (95% CI, 0.86–0.94) per 1 mmol/L reduction of the LDL-C level, and did not vary by the type of intensive lipid-lowering drugs (P_regression = 0.299; Supplementary Figure 2; P_subgroup heterogeneity = 0.38, Figure 4). In the predefined subgroup analyses, stroke risk was associated with an RR of 0.86 (95% CI, 0.76–0.95), 0.83 (95% CI, 0.66–0.99), and 0.93 (95% CI, 0.85–1.02) per 1 mmol/L reduction of the LDL-C level, respectively, in the subgroups with high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin as the intervention (Figure 4); findings were generally unchanged stratified by baseline LDL-C level (Table 2).
**Relative Effect of Intensive Lipid-Lowering**

In the predefined subgroup analyses, all-cause death risk was associated with an RR of 0.90 (95% CI, 0.79–1.00), 0.86 (95% CI, 0.55–1.17), 0.98 (95% CI, 0.92–1.04) per 1 mmol/L reduction of the LDL-C level, respectively, in the subgroups with high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin as the intervention (Figure 5); findings were generally unchanged.

**All-Cause Death**

Overall, 4,057 of 64,844 patients (6.26%) receiving the more intensive lipid-lowering drugs vs. 4,246 of 64,796 (6.55%) receiving the less-intensive drugs died during follow-up. The overall risk reduction in all-cause death with more vs. less-intensive therapy across all trials was 0.94 (95% CI, 0.89–0.99) per 1 mmol/L reduction of the LDL-C level, and did not vary by the type of intensive lipid-lowering drugs (P-regression=0.502; Supplementary Figure 2: P-subgroup heterogeneity=0.46, Figure 5). In the predefined subgroup analyses, all-cause death risk was associated with an RR of 0.90 (95% CI, 0.79–1.00), 0.86 (95% CI, 0.55–1.17), 0.98 (95% CI, 0.92–1.04) per 1 mmol/L reduction of the LDL-C level, respectively, in the subgroups with high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin as the intervention (Figure 5); findings were generally unchanged.

**Figure 4.** Meta-analysis of myocardial infarction (A) and stroke (B) stratified by type of intensive lipid-lowering drugs. See Figure 3 for explanations.
1 mmol/L reduction of the LDL-C level, and did not vary by the type of intensive lipid-lowering drugs (P_regression = 0.347; Supplementary Figure 2; P_subgroup heterogeneity = 0.38, Figure 5).

In the predefined subgroup analyses, cardiovascular death risk was associated with an RR of 0.88 (95% CI, 0.75–1.00), 0.99 (95% CI, 0.85–1.14), and 0.99 (95% CI, 0.93–1.04) per 1 mmol/L reduction of the LDL-C level, respectively, in the subgroups with high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin as the interven-

stratified by baseline LDL-C level (Table 2).

**Cardiovascular Death**
Overall, 2,017 of 66,394 patients (3.04%) receiving the more intensive lipid-lowering drugs vs. 2,099 of 65,584 (3.20%) receiving the less-intensive drugs died of cardiovascular causes during follow-up. The overall risk reduction in cardiovascular death with more vs. less-intensive therapy across all trials was 0.95 (95% CI, 0.89–1.01) per 1 mmol/L reduction of the LDL-C level, and did not vary by the type of intensive lipid-lowering drugs (P_regression = 0.347; Supplementary Figure 2; P_subgroup heterogeneity = 0.38, Figure 5).

In the predefined subgroup analyses, cardiovascular death risk was associated with an RR of 0.88 (95% CI, 0.75–1.00), 0.99 (95% CI, 0.85–1.14), and 0.99 (95% CI, 0.93–1.04) per 1 mmol/L reduction of the LDL-C level, respectively, in the subgroups with high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin as the interven-

**Figure 5.** Meta-analysis of all-cause (A) and cardiovascular (B) death stratified by type of intensive lipid-lowering drugs. See Figure 3 for explanations.
tion (Figure 5); findings were generally unchanged stratified by baseline LDL-C level (Table 2).

Additional Analyses

In the sensitivity analysis, we addressed the influence of each trial, investigating whether omitting the studied trial would significantly alter the pooled results of the meta-analysis. When each trial was deleted one by one, the original overall estimates did not show any deviations, which meant that our findings were robust (Supplementary Table 3). In further sensitivity analyses by adjusting the follow-up duration of each trial, the overall effect of each lipid-lowering group and the difference between groups were not significantly changed (Supplementary Table 4). A further analysis limited to trials with follow-up duration >2 years, trials with a low risk of bias (had ≤2 unclear or high risk of bias in quality assessment) or trials without participants who possibly had no history of CVD also confirmed the same results (Supplementary Table 4).

Discussion

Our study used meta-regression and stratified analyses to compare the relative effect of current intensive lipid-lowering drugs in secondary prevention patients, and found that (1) the relative benefits of high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin therapy on the risks of MACE and revascularization were varied and decreased gradually, of which only high-dose statin was associated with significantly lower risks of these events than PCSK9 inhibitor-statin per 1 mmol/L reduction in the LDL-C level; (2) similar relative effects among the drugs regarding MI and stroke were also observed, but no significant difference between high-dose statin and PCSK9 inhibitor-statin was identified; and (3) only high-dose statin was associated with borderline significant reduction of all-cause and cardiovascular death while ezetimibe-statin and PCSK9 inhibitor-statin were not.

Although statins, ezetimibe, and PCSK9 inhibitors have specific roles in the guidelines, the selection of lipid-lowering drugs for lipid-lowering management does not remain unchanged, and has in fact shifted over time. Current major guidelines recommend the individual role of each lipid-lowering drug, only considering the aspects of the intensity of lipid-lowering, side effects, treatment response and price, without the relative cardiovascular benefits of lipid-lowering drugs. The current meta-analysis compared the relative effects among current intensive lipid-lowering drugs, intending to provide guidance and optimization in the use of guidelines from the aspect of the relative effects of the agents. We used standardized analyses to compare the relative effect among high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin, because taking into account the different levels of LDL-C reduction in the effect of trials by standardizing the cardioprotective effect as cardiovascular events per unit reduction of LDL-C can avoid the possible impact on the comparison results caused by differences in the intensity of lipid-lowering. The findings in our study may not change future guidelines, but they further support the recommendations in current guidelines that statin treatment is the cornerstone of intensive lipid-lowering therapy, supplemented by non-statin lipid-lowering drugs to address statin intolerance or failure to reach LDL-C target. Additionally, these findings should improve our understanding of the hypothesis of “the lower the better”; that is, the use of statin and non-statin therapies may not be associated with similar cardiovascular risk reduction per unit change in LDL-C.

Our study and the post-hoc analysis of the FOURIER trial both respectively investigated the effect of lipid-lowering drugs in different subgroups, and used the between-group difference to compare the relative effect among lipid-lowering therapies. Our analysis found that high-dose statin was associated with significantly lower risks of MACE and revascularization than PCSK9 inhibitor-statin per 1 mmol/L reduction in the LDL-C level whereas the post-hoc analysis of the FOURIER trial showed that PCSK9 inhibitor had similar cardiovascular effects on cardiovascular outcome as statins per 1 mmol/L reduction in the LDL-C level. Contrary to that analysis, the comparisons in the current study were based on trials with more uniform basic characteristics across different subgroups. The first is that our study only included trials performed on secondary prevention patients, thus maintaining a similar cardiovascular risk profile of the participants across each subgroup. Second, we excluded RCTs published before 2000; by this procedure, the pharmaceuticals used for cardiovascular prevention in each included trial came from the same era and were therefore largely the same. Third, as the background lipid-lowering drugs possibly interacted with intervention lipid-lowering drugs, our study considered this confounding factor by treating background lipid-lowering drugs as part of the intensive treatment and compared different combinations of lipid-lowering drugs instead of different single lipid-lowering therapies. Fourth, our study further considered the difference of follow-up duration of each trial in the analysis by conducting a sensitivity analysis that used person-year instead of total patients to pool all estimates. Finally, we select trials with less lipid-lowering control as placebo, so the relative effects of different intensive lipid-lowering agents could be compared based on the same reference. In addition, our studies included the latest large-scale cardiovascular outcomes trials, which provided a large number of patients and events for us to analyze the relative effects of different intensive lipid-lowering drugs. Through these procedures, the comparative effect high-dose statin and PCSK9 inhibitor-statin reflected by our study was not only less likely to be influenced by potential bias from baseline characteristics, but also was capable of robust statistical power.

In addition, recent meta-analyses have shown that the benefits of lipid-lowering are influenced by baseline LDL-C level, so we conducted further subgroup analysis stratified by baseline LDL-C level (<100 mg/dL and ≥100 mg/dL) to investigate the effect of this baseline characteristic on our findings. Positively, no significant difference between the group with baseline LDL-C <100 mg/dL and the group with baseline LDL-C ≥100 mg/dL was presented in all outcomes, which suggested that our results were probably because the RR in our study was not affected by baseline LDL-C level. In line with our study, the CTT meta-analysis also found no influence of baseline LDL-C on the benefit of lipid-lowering. The discordant findings between our analysis and the recent analyses were probably because the RR in our study considered the absolute reduction of LDL-C in each trial whereas the recent studies did not. Because LDL-C reduction was positively associated with the benefit of lipid-lowering, if the absolute LDL-C reduction was different between the high and low baseline LDL-C groups, using the RR without adjustment of the absolute LDL-C reduc-
tion may show an interaction between baseline LDL-C level and the benefit of lipid-lowering.

The superiority of high-dose statins over PCSK9 inhibitor-statin in reducing the risks of MACE and revascularization was possibly explained by the pleiotropic effects of statins. It has been shown that statins improve endothelial function by preserving eNOS in endothelial cells, and thus may lead to an improvement in cardiovascular outcomes after percutaneous coronary intervention. What’s more, statins reduce the process of inflammation and induce lowering of high-sensitivity C-reactive protein, which appears to be associated with reduced cardiovascular events following percutaneous coronary intervention.

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Intensive lipid-lowering treatment with high-dose statins was also seemingly associated with lower risks of MI and stroke than treatment with PCSK9 inhibitor-statin per 1 mmol/L reduction in the LDL-C level, but no significant difference between these treatments was observed. Considering that the number of these outcome events was smaller than that of MACE and revascularization events, it was probably because the number of events available for analyzing these outcomes was too small thus were unable to show a between-group difference with statistical significance.

Only high-dose statin treatment was associated with borderline significant reduction of all-cause and cardiovascular deaths in our study and neither ezetimibe-statin nor PCSK9 inhibitor-statin showed this association. Consistent with our study, the previous meta-analysis by Koskinas and colleagues also showed no effect of non-statin agents on reduction of all-cause and cardiovascular deaths. As half of the non-statin trials included in our study had baseline LDL-C levels <100 mg/dL and moreover the recent meta-analysis by Navarese and colleagues shown that lipid-lowering initiated at a baseline LDL-C level <100 mg/dL was not associated with reductions in all-cause and cardiovascular death, it appears that a low baseline LDL-C level might account for the neutral effect of ezetimibe-statin and PCSK9 inhibitor-statin on all-cause and cardiovascular deaths. However, this speculation is tempered by the results of 2 recent large RCTs in which lipid-lowering with either statin or non-statin drugs reduced all-cause deaths in patients with mean baseline LDL-C <100 mg/dL. In that setting, the hypothesis that the neutral effect of ezetimibe-statin and PCSK9 inhibitor-statin on all-cause death is related to low baseline LDL-C level does not make sense. Based on previous studies, we speculate that the underlying reason is possibly related to the pleiotropic effects of statins, as statins are reported to also reduce cancer deaths, but non-statin agents are not reported to have a similar effect. With this advantage, high-dose statin is likely to be better than ezetimibe-statin and PCSK9 inhibitor-statin for improving survival. Nevertheless, it should be noted that current understanding of the pleiotropic effects of non-statin agents is limited; whether the lack of survival benefit of ezetimibe-statin and PCSK9 inhibitor-statin is truly because of a lack of a role in reducing cancer deaths still requires further investigation.

Study Limitations

First, our meta-analysis was at the trial level rather than the individual level; individuals’ data may allow us to perform detailed subgroup analysis to explore the source of heterogeneity among treatment groups. Second, we only investigated the relative effect of different intensive lipid-lowering drugs in secondary prevention patients; whether our conclusions also apply to primary prevention patients remains unknown. Third, because of the design of current lipid-lowering trials, we only obtained data that compared the relative effects among high-dose statins, ezetimibe-statin, and PCSK9 inhibitor-statin on cardiovascular outcomes; the comparative benefits and harms among statins, ezetimibe, and PCSK9 inhibitors are not yet known.

Conclusions

We newly found that the beneficial effects of high-dose statin, ezetimibe-statin, and PCSK9 inhibitor-statin on the risks of cardiovascular events were varied and decreased gradually in secondary prevention patients, for whom high-dose statin was significantly better than PCSK9 inhibitor-statin against MACE and revascularization per 1 mmol/L reduction in the LDL-C level. High-dose statin was also superior to ezetimibe-statin and PCSK9 inhibitor-statin for improvement in all-cause and cardiovascular deaths. These findings may inform clinicians to select high-dose statins as first-line lipid-lowering drugs for secondary prevention of CVD.

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Conflict of Interest

None declared.

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**Supplementary Files**

Please find supplementary file(s); [http://dx.doi.org/10.1253/circj.CJ-18-1321](http://dx.doi.org/10.1253/circj.CJ-18-1321)