Elevated low-density lipoprotein (LDL) cholesterol has been established as one of the major risk factors for adverse cardiovascular events [1], and accumulating evidence has indicated LDL-lowering with statins is the most essential therapeutic component for primary and secondary prevention in coronary artery disease (CAD) [2,3]. Despite a large body of evidence regarding a higher intensity LDL-lowering strategy with the notion "the lower, the better" and recommendations by U.S. and European guidelines of lipid management [4,5], the efficacy of higher intensity statin therapy in Asian populations has been rarely investigated, although there was one large-scale placebo-controlled study of pravastatin involving 7,832 Japanese patients without a history of cardiovascular disease that examined primary prevention of cardiovascular disease with pravastatin in Japan (MEGA) trial [6]. A guideline by the American College of Cardiology and American Heart Association (ACC/AHA) indicated that doses lower than those used in Western countries may be appropriate in Asians, which is a recommendation similar to that for patients who have a history of hemorrhagic stroke [4,5]. However, as a consequence of obviously insufficient evidence, discussion regarding Asians in ACC/AHA and European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) lipid management guidelines is very limited. In fact, only one sentence addresses this issue in each guideline, despite the recent growth in Asian populations in these areas (https://www.census.gov/main/www/cprs.html). Furthermore, although "high intensity" statin therapy is recommended in the ACC/AHA guideline for secondary prevention based on findings in previous studies, including the safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes (A to Z) [7], treating new targets (TNT) [8], incremental decrease in end points through aggressive lipid lowering (IDEAL) [9], and pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22 (PROVE-IT TIMI22) [10], the doses of statins in "high intensity" in these trials, such as atorvastatin 40 mg or 80 mg/day or rosuvastatin 20 mg or 40 mg/day, are excessively higher than those approved and covered by insurance in Japan. In contrast, "high-intensity or high-dose statins" in Japan, such as pravastatin 40-80 mg, atorvastatin 10-20 mg, rosuvastatin 5-10 mg, and pitavastatin 2-4 mg are listed within the "moderate-intensity" statin group in the ACC/AHA guideline [5]. Since no previous large-scale randomized trial anywhere in the world has demonstrated the superiority of such moderate-intensity statin therapy compared to low-intensity statin therapy, no sufficient evidence has been obtained for the treatment. Therefore, prospective endpoint trials for the prognostic benefit of higher-intensity statin therapy, although it has been previously considered as "moderate-intensity", have been warranted to establish evidence particularly for Asians, who may need lower doses of statins compared to non-Asian patients in Western countries.

Two large-scale randomized trials enrolling Japanese patients of less- and more-intensive statin therapy have recently been published. One is a primary study and the other is a secondary prevention study. The EMPATHY study is an intention-to-treat analysis evaluating the efficacy of "intensive" LDL-C lowering therapy targeting less than 70 mg/dl. (n=2518) in serum LDL-C, compared to the "standard" one targeting 100-120 mg/dl. (n=2524) in high-risk primary prevention. Patients with diabetic retinopathy in addition to dyslipidemia, but without a history of cardiovascular disease, were enrolled [11]. The REAL-CAD study addressed the prognostic superiority of higher-dose pitavastatin (4 mg/day, "moderate intensity" in U.S. guideline) (n=6526) compared to low-dose (1 mg/day) (n=6528) in secondary prevention [12]. The protocols, study demographics and results in these two studies are summarized in Figure 1 and Table 1 [13,14]. In the EMPATHY study, the primary endpoint was a "cardiovascular (CV) event", a composite of wider range cardiovascular, cerebral and renal events than other endpoint studies in this field, such as CV death, myocardial infarction (MI), unstable angina (UA) requiring hospitalization or coronary revascularization, ischemic stroke, cerebral revascularization, deterioration of renal function including initiation of hemodialysis, and aortic and peripheral diseases including aortic dissection, critical limb ischemia and peripheral revascularization. In contrast, the primary endpoint in the REAL-CAD study was a composite of rather focused events, which is generally defined as 4P-MACE, including CV death, non-fetal MI and stroke and hospitalization for UA. In the EMPATHY study, intensive LDL-C lowering therapy by statins was indicated to achieve LDL-C<70 mg/dl, but the mean LDL-C level was 76.5 mg/dl at 3 years after randomization, indicating a substantial population did not achieve the target LDL-C level. As a result, intention to treat...
analysis showed intensive statin therapy did not reduce the cumulative incidence of the primary endpoint. However, in post-hoc analysis limited to patients who actually achieved the target LDL-C level, a limited to patients who achieved the target LDL-C level, a

These two studies provide important evidence. First, they, the REAL-CAD study in particular, demonstrated moderate-intensity statin therapy to be effective for better outcomes as compared to low-intensity statin therapy, which have rarely been investigated in previous large-scale randomized trials [15]. Furthermore, these studies were the first to establish evidence of higher intensity statin therapy in high-risk primary and secondary prevention for Asian populations.

The incidence of CV events in Japanese was substantially lower than that in Western countries. For instance, the overall primary endpoint rate in the TNT study, the study design of which was similar to that of the REAL-CAD study, was 9.8%, while 4.6% in the REAL-CAD study, although the definition of the primary endpoint is slightly different between the two studies. Nevertheless, higher intensity statin therapy, even though it was "moderate intensity" in Western guidelines, was associated with a reduced risk of adverse cardiovascular events. The findings in these two studies indicate the need for moderate intensity statin therapy in Asians as secondary and high-risk primary prevention, and may have an impact on future recommendations in the guidelines of not only Asian countries, but also those of the United States and European countries.

References
2. [No authors listed]. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 344: 1383-1389. [Crossref]


