Systematic study of the effects of lowering low-density lipoprotein-cholesterol on regression of coronary atherosclerotic plaques using intravascular ultrasound

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Abstract

Background: Conflicting results currently exist on the effects of LDL-C levels and statins therapy on coronary atherosclerotic plaque, and the target level of LDL-C resulting in the regression of the coronary atherosclerotic plaques has not been settled.

Methods: PubMed, EMBASE, and Cochrane databases were searched from Jan. 2000 to Jan. 2014 for randomized controlled or blinded end-points trials assessing the effects of LDL-C lowering therapy on regression of coronary atherosclerotic plaque (CAP) in patients with coronary heart disease by intravascular ultrasound. Data concerning the study design, patient characteristics, and outcomes were extracted. The significance of plaques regression was assessed by computing standardized mean difference (SMD) of the volume of CAP between the baseline and follow-up. SMD were calculated using fixed or random effects models.

Results: Twenty trials including 5910 patients with coronary heart disease were identified. Mean lowering LDL-C by 45.4% and to level 66.8 mg/dL in the group of patients with baseline mean LDL-C 123.7 mg/dL, mean lowering LDL-C by 48.8% and to level 60.6 mg/dL in the group of patients with baseline mean LDL-C 120 mg/dL, and mean lowering LDL-C by 40.4% and to level 77.8 mg/dL in the group of patients with baseline mean LDL-C 132.4 mg/dL could significantly reduce the volume of CAP at follow up (SMD $-0.108 \text{ mm}^3$, 95% CI $-0.176 \sim -0.040$, \( p = 0.002 \); SMD $-0.156 \text{ mm}^3$, 95% CI $-0.235 \sim -0.078$, \( p = 0.000 \); SMD $-0.123 \text{ mm}^3$, 95% CI $-0.199 \sim -0.048$, \( p = 0.001 \); respectively).

LDL-C lowering by rosuvastatin (mean 33 mg daily) and atorvastatin (mean 60 mg daily) could significantly decrease the volumes of CAP at follow up (SMD $-0.162 \text{ mm}^3$, 95% CI $-0.234 \sim -0.081$, \( p = 0.000 \); SMD $-0.101$, 95% CI $-0.184 \sim -0.019$, \( p = 0.016 \); respectively). The mean duration of follow up was from 17 ~ 21 months.

Conclusions: Intensive lowering LDL-C (rosuvastatin mean 33 mg daily and atorvastatin mean 60 mg daily) with >17 months of duration could lead to the regression of CAP, LDL-C level should be reduced by >40% or to a target level <78 mg/dL for regression of CAP.

Keywords: Low-density lipoprotein-cholesterol, Coronary atherosclerotic plaque, Intravascular ultrasound, Coronary artery disease
Background

It is universally accepted that high serum concentrations of low-density lipoprotein cholesterol (LDL-C) can lead to atherosclerosis and accelerate the progression of atherosclerosis which is main causes of coronary artery disease [1]. Disruption of coronary atherosclerotic plaque (CAP) with subsequent thrombus formation may lead to sudden cardiac death, acute myocardial infarction, or unstable angina [2]. The evidence showed that reducing LDL-C can prevent coronary heart disease (CHD) and improve survival of CHD based on results from multiple randomized controlled trials (RCTs) [3,4].

For many years coronary angiography (CAG) has been the gold standard method for the investigation of the anatomy of coronary arteries and measure the efficacy of anti-atherosclerotic drug therapies [5,6]. But changes in CAG are measured only in the vascular lumen and not in the vessel wall [7], where the atherosclerotic process is located. Intravascular ultrasound (IVUS) is superior to angiography in the detection of early plaque formation and changes in plaque volume [8-10]. Through IVUS, Takagi et al. found that pravastatin lowered serum cholesterol levels and reduced the progression of CAP in patients with elevated serum cholesterol levels in 1997 [11]. Since then, multiple RCTs and no RCT about the effect of lowering LDL-C therapy on the regression of coronary atherosclerosis have been performed [12-16]. But the results varied with the RCTs: intensive LDL-C lowering therapy could reduce the progression of the plaques [12]; the mild LDL-C lowering did not [14-16]. The meta-analysis by Bedi et al. [17] evaluated the effects of LDL-C lowering on CAP by comparing statins with control therapy, and demonstrated that treatment with statins could slow atherosclerotic plaque progression and lead to plaque regression. The meta-analysis by Tian et al. [18] showed that CAP could be regressed in group of patients with <100 mg of LDL-C level at follow up. But so far, there are no systematic reviews of the effects of LDL-C levels on CAP, and the targets of LDL-C level that could result in the regression of the plaques have not been settled.

In this study, we conducted meta-analyses to summarize findings from the current trials on LDL-C lowering therapy retarding the progression of the CAP and to identify the targets of LDL-C resulting in the regression of the CAP for guiding the LDL-C lowering therapy. Effect of different statins on the progression of the CAP was also investigated.

Methods

Search strategy and selection criteria

An electronic literature search was performed to identify all relevant studies published in PubMed, EMBASE, and Cochrane databases in the English language from Jan. 1, 2000 to Jan. 1, 2014, using the terms “atherosclerosis” and “cholesterol blood level”. The references of the studies were also searched for relevant studies. Studies were included using the following criteria: 1) randomized controlled or prospective, blinded end-points trials in which patients with CHD were assigned to LDL-C lowering therapy or placebo, and its primary end point was CAP change detected by IVUS; 2) report of LDL-C levels at baseline and follow-up (in each arm) or the level of LDL-C which can be calculated from the data in the paper (as in the trial by Yokoyama M [15], in which the LDL-C concentrations in control arm were directly extracted from the figure); 3) data on the volume of CAP, detected in IVUS at baseline and follow-up (in each arm), and volume of CAP was calculated as vessel volume minus lumen volume; Exclusion criteria were: 1) only CAP area or volume index or percent atheroma volume were detected by IVUS; 2) the levels of LDL-C at baseline or follow-up were not provided; and 3) target plaques were unstable.

Data extraction and quality assessment

Two investigators independently reviewed all potentially eligible studies and collected data on patient and study characteristics (author, year, design, sample size, the measures of LDL-C lowering, LDL-C levels, follow-up duration, and plaque volume), and any disagreement was resolved by consensus. The primary end point of this study was progression or regression of CAP detected by IVUS. Quality assessments were evaluated with Jadad quality scale [19].

Data synthesis and analysis

Continuous variables (change of CAP volume from baseline to follow-up) were analyzed using standardized mean differences (SMD).

The trials may have control arm and multiple active treatment arms, changes of plaque volume in every arms were used for pooled analysis. According to the levels and the reducing percentage of LDL-C at follow-up, the arms were grouped to following groups: ≤70, >70 ≤ 100HP (>70 ≤ 100 mg and reducing percentage ≥30%), >70 ≤ 100MP (>70 ≤ 100 mg and reducing percentage ≥0 < 30%), >70 ≤ 100LP (>70 ≤ 100 mg and reducing percentage <0%), >100 mg/dL; and <0, ≥0 < 30, ≥30 < 40, >40 < 50, ≥50% respectively, to investigate the effect of different levels of LDL-C at follow up on CAPs. According to different statins, the arms were grouped to following groups: rosuvastatin, atorvastatin, pitavastatin, simvastatin, fluvastatin and pravastatin group, to investigate the effect of different statins on CAPs. The volume of CAP at follow up was compared with that at baseline to evaluate effect of LDL-C levels on regression of CAP.
Heterogeneity across trials (arms) was assessed via a standard $\chi^2$ test with significance being set at $p < 0.10$ and also assessed by means of $I^2$ statistic with significance being set at $I^2 > 50\%$. Pooled analyses were calculated using fixed-effect models, whereas random-effect models were applied in case of significant heterogeneity across studies (arms). Sensitivity analyses (exclusion of one study at one time) were performed to determine the stability of the overall effects of LDL-C levels. Additionally, publication bias was assessed using the Egger regression asymmetry test. Mean LDL-C level and follow up duration of groups were calculated by descriptive statistics. A two-sided $p$ values $< 0.05$ was considered statistically significant. Statistical analyses were performed using STATA software 12.0 (StataCorp, College Station, Texas) and Review Manager V5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

Results

Eligible studies

The flow of selecting studies for the meta-analysis is shown in Figure 1. Briefly, of the initial 647 articles, one hundred and twenty of abstracts were reviewed, resulting in exclusion of 100 articles, and 20 articles were reviewed in full text, resulting in exclusion of 10 trials and inclusion of 18 additional trials. Twenty two RCTs [12-16,20-31], [32-36] and six blinded end-points trial [37-42] were carefully evaluated. Five trials were excluded because of specific the index of plaque (volume index in TRUTH [24], trial by Kovarnik T [31], by Hattori K [42], and by Petronio AS [32]; area in LACMART [38]); GAIN [20] excluded because of no data of plaque volume at follow up; trial by Zhang X [25] excluded because of no data of LDL-C; trial by Hong Y [30] excluded because of wrong data at follow up. Sixteen RCT (ESTABLISH [14], REVERSAL [13], A-PLUS [21], ACTIVATE

Figure 1 Flow diagram of study-screening process.
Sensitivity analyses suggested that LDL-C lowering in group \( \leq 70 \) and \( >70 \leq 100\text{HP} \text{mg/dL} \) could lead to regression of CAP with reduction of the CAP volume ranged from \(-0.146 \text{ mm}^3\) (SMD, 95% CI: \(-0.238 \sim -0.054\)) when the arm of 2006 ASTEROID Ros was omitted to \(-0.167 \text{ mm}^3\) (SMD, 95% CI: \(-0.270 \sim -0.064\)) when the arm of 2011 SATURN Ros was omitted; and from \(-0.103 \text{ mm}^3\) (SMD, 95% CI: \(-0.182 \sim -0.024\)) when the arm of 2009 JAPAN-ACS Ato was omitted to \(-0.151 \text{ mm}^3\) (SMD, 95% CI: \(-0.235 \sim -0.067\)) when the arm of 2004 REVERSAL Ato was omitted. No publication bias was found, the values of \( p \) by Egger’s test for group \( \leq 70 \) and \( >70 \leq 100\text{HP} \text{mg/dL} \) were 0.835, 0.501 respectively.

In group \( >100 \text{mg/dL} \) (including eleven arms) with mean 14.6 months of follow up, the volume of CAP at follow up was not significantly increased, compared with the volumes at baseline (SMD 0.013 mm\(^3\), 95% CI \(-0.929 \sim 0.118\), \( p = 0.809\)). There was no significant heterogeneity among arms (\( \chi^2 \) for heterogeneity = 2.49, \( p = 0.991, I^2 = 0\% \)).

Sensitivity analyses suggested that LDL-C lowering to \( >100 \text{mg/dL} \) at follow up could still not lead to regression of CAP with reduction of the plaque volume ranged from \(-0.005 \text{ mm}^3\) (95% CI \(-0.136 \sim 0.126\)) when the arm of 2004 REVERSAL Pro was omitted to 0.034 mm\(^3\) (SMD, 95% CI \(-0.075 \sim 0.143\)) when 2005 Tani S Pra was omitted. No publication bias was observed from the values of \( p \) (0.566) by Egger’s test.

Mean levels of LDL-C at baseline and follow up and mean reducing percentage of LDL-C in group \( \leq 70 \), \( >70 \leq 100\text{MP} \), \( >70 \leq 100\text{LP} \), \( >70 \leq 100\text{LP} \) and \( >100 \text{mg/dL} \) were showed in Table 4.

The effect of the LDL-C reducing percentage at follow-up on regression of CAP

LDL-C lowering in group \( \geq 30 < 40 \), \( \geq 40 < 50 \), \( >50 \% \) could lead to regression of CAP, but LDL-C lowering in group \( <0 \) and \( \geq 0 < 30 \% \) could not (Figure 5, Table 3).

In group \( \geq 30 < 40 \) (including ten arms) with mean 10.3 months of follow up, and group \( \geq 40 < 50 \) (including eight arms) with mean 19.4 months of follow up, the volumes of CAP (94.3, 150.7 mm\(^3\) respectively) at follow up were significantly decreased, compared with the volumes (102.9, 157.8 mm\(^3\) respectively) at baseline (SMD \(-0.199 \text{ mm}^3\), 95% CI \(-0.314 \sim -0.085\), \( p = 0.001\); SMD \(-0.108 \text{ mm}^3\), 95% CI \(-0.176 \sim -0.040\), \( p = 0.002\); respectively). There was no significant heterogeneity among arms (\( \chi^2 \) for heterogeneity = 3.10, \( P = 0.960, I^2 = 0\% \); \( \chi^2 \) for heterogeneity = 2.50, \( P = 0.927, I^2 = 0\% \); for group \( \geq 30 < 40 \), and group \( \geq 40 < 50 \) respectively).

Sensitivity analyses showed that LDL-C lowering in group \( \geq 30 < 40 \) and group \( \geq 40 < 50 \) could still lead to regression of CAP with reduction of the plaque volume ranged from \(-0.166 \text{ mm}^3\) (95% CI \(-0.295 \sim -0.038\)) when the arm of 2009 JAPAN-ACS Ato was omitted.

The effect of the levels of LDL-C at follow-up on regression of coronary atherosclerotic plaque

LDL-C lowering in group \( \leq 70 \) and \( >70 \leq 100\text{HP} \text{mg/dL} \) could lead to regression of CAP, but LDL-C lowering in group \( >70 \leq 100\text{MP} \), \( >70 \leq 100\text{LP} \), \( >70 \leq 100\text{LP} \) and \( >100 \text{mg/dL} \) could not (Figure 4, Table 3).

In group \( \leq 70 \text{mg/dL} \) (including seven arms) with mean 18.6 months of follow up and group \( >70 \leq 100\text{HP} \text{mg/dL} \) (including eleven arms) with mean 17.4 months of follow up, the volumes of CAP (125.9, 123.8 mm\(^3\) respectively) at follow up were significantly decreased, compared with the volumes (177.1, 129.7 mm\(^3\) respectively) at baseline (SMD \(-0.156 \text{ mm}^3\), 95% CI (confidence interval) \(-0.235 \sim -0.078\), \( p = 0.000\); SMD \(-0.123 \text{ mm}^3\), 95% CI \(-0.199 \sim -0.048\), \( p = 0.001\); respectively). There was no significant heterogeneity among arms (\( \chi^2 \) for heterogeneity = 0.57, \( p = 0.997, I^2 = 0\% \) for group \( \leq 70 \text{mg/dL} \); \( \chi^2 \) for heterogeneity = 6.83, \( p = 0.741, I^2 = 0\% \) for group \( >70 \leq 100\text{HP} \text{mg/dL} \).
| Authors and trial name | Trial type and location | Objective | Year | N T/C | Study population | LDL-C at follow up | LDL-C reducing percentage | Treatments | Follow up | Main Results or Conclusion |
|------------------------|------------------------|-----------|------|-------|------------------|-------------------|--------------------------|------------|----------|-----------------------------|
| Okazaki S [14]; ESTABLISH | RCT: prospective, open-label, randomized, single center study. Japan | Effects of statins on changes in plaque by IVUS | 2004 | 24/24 | ACS | 70/119 | -44/-0.004 | Ato 20 vs Diet | 6 | Plaque volume was significantly reduced in the Ato group compared with the control group. |
| Nissen SE [13]; REVERSAL | RCT: Double-blind, randomized active control multicenter trial; USA | Effects of statins (intensive or moderate) on changes in plaque by IVUS | 2004 | 253/249 | CAD | 79/110 | -46/-25 | Ato 80 vs Pra40 | 18 | Ato reduced progression of coronary plaque compared with Pra. Compared with baseline values, Ato had no change in atheroma burden, whereas patients treated with Pra showed progression of coronary plaque. |
| Tardif JC [21]; A-PLUS | RCT: international, multicenter, double-blind, placebo-controlled, randomized trial. Canada, USA | Effects of different dosage of avasimibe on changes in plaque by IVUS | 2004 | 108/98/117/109 | CAD | 100/102/101/91 | 7.8/9.1/10.9/1.7 | Ava50, 250, and 750 vs Placebo on the basis of LDL-C<125 | 18 | Avasimibe did not favorably alter coronary atherosclerosis as assessed by IVUS. |
| Jensen LO [39] | Open non placebo controlled serial investigation; blinded end-points. Denmark | To investigate the effect of lipid lowering by simvastatin on coronary atherosclerotic plaque volumes and lumen. | 2004 | 40 | CAD | 85 | -46.3 | Sim 40 | 15 | Lipid-lowering therapy with Sim is associated with a significant plaque regression in coronary arteries. |
| Yokoyama M [15] | RCT: randomized, single center. Japan | Effects of statins on changes in plaque by IVUS | 2005 | 29/30 | Stable angina | 87/124 | -35/-0.075 | Ato 10 vs Diet | 6 | Treatment with Ato may reduce volumes of coronary plaques. |
| Kawasaki M [16] | RCT: randomization, open-label, single-center study. Japan | Effects of statins on changes in plaque by IVUS | 2005 | 17/18/17 | Stable angina | 95/102/149 | -39/-32/-0.02 | Ato 20, Pra 20 vs Diet | 6 | Treatment with Ato and Pra may not significantly reduce volumes of coronary plaques. |
| Tani S [33] | RCT: a prospective, single-center, randomized, open trial. Japan | Investigated the effects of pravastatin on the serum levels of MDA-LDL and coronary atherosclerosis. | 2005 | 52/23 | Stable angina | 104/120 | -20/-2.4 | Pra 10-20 vs con | 6 | Plaque volume was significantly reduced in the Pra group compared with the control group. |
| Nissen SE [22]; ACTIVATE | RCT: randomized, multicenter. USA | Effects of pactimibe on changes in plaque by IVUS | 2006 | 206/202 | CAD | 91/86 | -9.6/-14.9 | Pac100 vs Placebo | 18 | Pac is not an effective strategy for limiting atherosclerosis and may promote atherogenesis. |
Table 1 Features of participating trials (Continued)

| Study                  | Design                      | Objectives                                                                 | Year | Patients | CAD, DM | Effect on LDL-C | Ros | Therapy Details                                                                                           |
|------------------------|-----------------------------|-----------------------------------------------------------------------------|------|----------|---------|-----------------|-----|----------------------------------------------------------------------------------------------------------|
| Nissen SE [37]; ASTEROID | Prospective, open-label blinded end-points. USA, Germany, France, Canada | Effects of Statins with different levels of LDL-C on changes in plaque by IVUS | 2006 | 349      | 61      | -53.2           |     | Therapy using Ros can result in significant regression of atherosclerosis.                                |
| Yamada T [26]; REACH   | RCT: open-labeled, randomized, multicenter study. Japan                     | Evaluate the effect of marked reduction of LDL-C in patients with CHD on progression of atherosclerosis. | 2007 | 26/32    | Stable angina 83/115 | -43/0 | Ato 5 vs Con                                                                                            |
| Nissen SE [23]; ILLUSTRATE | RCT: prospective, randomized, multicenter, double-blind clinical trial. North America or Europe | Effects of CETP inhibitor on changes in plaque by IVUS                       | 2007 | 446/464  | CAD     | 87/70           | 6.6/-13.3 | Ato 10-80 vs Ato+Tor 60 on the basis of LDL-C≤100 by Ato                                                  |
| Nissen SE [36]; PERISCOPE | RCT: prospective, randomized, multicenter, double-blind clinical trial. USA | To compare the effects of pioglitazone, and glimepiride on the progression of coronary atherosclerosis in patients with type 2 diabetes and CAD | 2008 | 181/179  | CAD, DM | 96.1/95.6     | 1.8/2.2   | Gli 1-4 mg vs Pio 15-45 mg on bases of statins therapy                                                  |
| Nissen SE [35]; STRADIVARIUS | RCT: Randomized, double-blinded, placebo-controlled, 2-group, parallel-group trial. North America, Europe, and Australia | The effect of rimonabant on regression of coronary disease in patients with the metabolic syndrome and CAD | 2008 | 335/341  | CAD, Obesity | 87.6/86.3 | -4.7/-3.6 | Rim 20 mg vs Placebo on bases of statins therapy                                                       |
| Hiro T [12]; JAPAN-ACS | RCT: prospective, randomized, open-label, parallel group, multicenter. Japan | Effects of statins on changes in plaque by IVUS                              | 2009 | 127/125  | ACS     | 84/81           | -36/-36   | Ato 20 vs Pit 4                                                                                         |
| Takayama T; COSMOS [40] | Prospective, open-label blinded end-points multicenter trial. Japan        | Evaluate the effect of rosuvastatin on plaque volume in patients with stable CAD, including those receiving prior lipid-lowering therapy | 2009 | 126      | Stable angina | 83       | -38.6           | Ros <20                                                                                                 |

Gao et al. BMC Cardiovascular Disorders 2014, 14:60
Table 1 Features of participating trials (Continued)

| Study | Design | Country | Study Objective | Comparison | Year | Number | Event | Baseline | Change | Follow-up | Result |
|-------|--------|---------|----------------|------------|------|--------|-------|---------|--------|-----------|--------|
| Rodés-Cabau; ERASE [34] | RCT: multicenter randomized placebo-controlled. Canada | Evaluate the early effects of newly initiated statin therapy on coronary atherosclerosis as evaluated by IVUS | 2009 | 38/36 | ACS | 77/63 | 8.5/-37 | Before ACS vs After ACS | <2 | Newly initiated statin therapy is associated with rapid regression of coronary atherosclerosis. |
| Nasu K [41] | Prospective and multicenter study with nonrandomized and non-blinded design, but blinded end. Japan | Evaluate the effect of treatment with statins on the progression of coronary atherosclerotic plaques of a nonculprit vessel by serial IVUS | 2009 | 40/39 | Stable angina | 98.1/121 | -32.3/-1.1 | Flu 60 vs Con | 12 | One-year lipid-lowering therapy by Flu showed significant regression of plaque volume. |
| Hong MK [27] | RCT: randomized control trial. Korea. | Evaluated the effects of statin treatments for each component of coronary plaques. | 2009 | 50/50 | Stable angina | 78/64 | -34.5/-44.8 | Sim 20 vs Ros 10 | 12 | Statin treatments might be associated with significant changes in necrotic core and fibrofatty plaque volume. |
| Nicholls SJ; SATURN [28] | RCT: a prospective, randomized, multicenter, double-blind clinical trial. USA | Compare the effect of these two intensive statin regimens on the progression of coronary atherosclerosis. | 2011 | 519/520 | CHD | 70.2/62.6 | -41.5/-47.8 | Ato 80 vs Ros 40 | 24 | Maximal doses of Ros and Ato resulted in significant regression of coronary atherosclerosis. |
| Lee CW [29]; ARTMAP | RCT: a prospective, single-center, open-label, randomized comparison trial. Korea. | Compared the effects of atorvastatin 20 mg/day versus rosuvastatin 10 mg/day on mild coronary atherosclerotic plaques. | 2012 | 143/128 | Stable angina | 56/53 | -47/-49 | Ato 20 vs Ros 10 | 6 | Usual doses of Ato and Ros induced significant regression of coronary atherosclerosis in statin-naive patients. |

Abbreviations: RCT, randomized controlled trials; T, treatment group; C, control group IVUS, Intravascular ultrasound; CAD, Coronary artery disease; ACS, Acute coronary syndrome; CHD, Coronary heart disease; Ato, Atorvastatin; Ros, Rosuvastatin; Pra, Pravastatin; Pit, Pitavastatin; Sim, Simvastatin; Flu, Fluvastatin; Con, Control; Pac, Pactimibe; Tor, Torcetrapib, Ava 50, 250, 750, Avasimibe 50, 250, 750 mg; T/C, Treat/Control; Gli, Glimepiride; Pio, Pioglitazone; Rim, Rimonabant.
| Authors | Trial name | Management in each arm | N  | LDL-C level At Baseline | LDL-C level At Follow-up |
|---------|------------|------------------------|----|------------------------|--------------------------|
| Tardif JC | A-PLUS | Avasimibe50 | 108 | 92.8 ± 1.7 | 100* |
| Tardif JC | A-PLUS | Avasimibe250 | 98 | 93.4 ± 1.6 | 101.9* |
| Tardif JC | A-PLUS | Avasimibe750 | 117 | 91.4 ± 1.6 | 101.4* |
| Tardif JC | A-PLUS | Placebo | 109 | 89.6 ± 1.6 | 91.1* |
| Okazaki S | ESTABLISH | Control | 24 | 123.9 ± 35.3 | 1194 ± 24.6 |
| Okazaki S | ESTABLISH | Atorvastatin | 24 | 124.6 ± 34.5 | 70.0 ± 25.0 |
| Yokoyama M | Control | Control | 30 | 131.5 ± 23# | 124.5 ± 24.1# |
| Yokoyama M | Control | Atorvastatin | 29 | 133 ± 13 | 87 ± 29 |
| Nissen SE | REVERSAL | Atorvastatin | 253 | 150.2 ± 27.9 | 78.9 ± 30.2 |
| Nissen SE | REVERSAL | Pravastatin | 249 | 150.2 ± 25.9 | 110.4 ± 25.8 |
| Nissen SE | ACTIVATE | Pactimibe | 206 | 101.4 ± 27.7 | 91.3 |
| Nissen SE | ACTIVATE | Placebo | 202 | 101.5 ± 31.1 | 86.4 |
| Nissen SE | ILLUSTRATE | Atorvastatin | 446 | 84.3 ± 18.9 | 87.2 ± 22.6 |
| Nissen SE | ILLUSTRATE | Atorvastatin & torcetrapib | 464 | 83.1 ± 19.7 | 70.1 ± 25.4 |
| Kawasaki M | Control | Control | 17 | 152 ± 20 | 149 ± 24 |
| Kawasaki M | Pravastatin | Pravastatin | 18 | 149 ± 19 | 102 ± 13 |
| Kawasaki M | Atorvastatin | Atorvastatin | 17 | 155 ± 22 | 95 ± 15 |
| Hiro T | JAPAN-ACS | Pitavastatin | 125 | 130.9 ± 33.3 | 81.1 ± 23.4 |
| Hiro T | JAPAN-ACS | Atorvastatin | 127 | 133.8 ± 31.4 | 84.1 ± 27.4 |
| Nissen SE | ASTEROID | Rosuvastatin | 349 | 130.4 ± 34.3 | 60.8 ± 20.0 |
| Takayama T | COSMOS | Rosuvastatin | 126 | 140.2±31.5 | 82.9±18.7 |
| Lee CW | ARTMAP | Atorvastatin | 143 | 110 ± 31 | 56 ± 18 |
| Lee CW | ARTMAP | Rosuvastatin | 128 | 109 ± 31 | 53±18 |
| Yamada T | REACH | Atorvastatin | 26 | 123 ± 17 | 83 ± 22 |
| Yamada T | REACH | Control | 32 | 115 ± 14 | 115 ± 30 |
| Nasu K | Control | Fluvastatin | 40 | 144.9 ± 31.5 | 98.1 ± 12.7 |
| Nasu K | Control | Control | 39 | 122.3 ± 18.9 | 121.0 ± 21.2 |
| Nicholls SJ | SATURN | Atorvastatin | 519 | 1199.9 ± 28.9 | 702 ± 1.0 |
| Nicholls SJ | SATURN | Rosuvastatin | 520 | 1200 ± 27.3 | 62.6 ± 1.0 |
| Hong MK | Simvastatin | Simvastatin | 50 | 119 ± 30 | 78 ± 20 |
| Hong MK | Rosuvastatin | Rosuvastatin | 50 | 116 ± 28 | 64 ± 21 |
| Tani S | Pravastatin | Pravastatin | 52 | 130 ± 38 | 104 ± 20 |
| Tani S | Control | Control | 23 | 123 ± 28 | 120 ± 30 |
| Rodés-C Bef | ERASE | Statins before ACS | 38 | 71 ± 23 | 77 ± 25 |
| Rodés-C Aft | ERASE | Statins after ACS | 36 | 100 ± 30 | 63 ± 17 |
| Jensen LO | Simvastatin | Simvastatin | 40 | 158.7 ± 30.6 | 85.1 ± 22.1 |
| Nissen SE | PERISCOPE | Statins+Gli | 181 | 94.4 ± 32.9 | 96.1 ± 30.4 |
| Nissen SE | PERISCOPE | Statins+Pio | 179 | 93.5 ± 30.7 | 95.6 ± 28.9 |
| Nissen SE | STRADIVARIUS | Statins+Rim | 335 | 91.9 ± 27.9 | 87.6 ± 30.5 |
| Nissen SE | STRADIVARIUS | Statins+Con | 341 | 89.5 ± 32.2 | 86.3 ± 30.3 |

Note: * calculated on the bases of baseline levels and change percentage at follow up [21].
# calculated according to Figure 2 in the paper [15].
to −0.214 mm³ (SMD, 95% CI −0.342 ~ −0.085) when 2009 COSMOS Ros was omitted; from −0.093 mm³ (95% CI −0.174 ~ −0.011) when the arm of 2011 SATURN Ros was omitted to −0.126 mm³ (SMD, 95% CI −0.200 ~ −0.053) when 2004 REVERSAL Ato was omitted respectively. Publication bias analysis suggested the values of \( p \) by Egger’s test were 0.024, 0.605 for group \( \geq 30 < 40 \), and group \( \geq 40 < 50 \) respectively.

In group \( < 0 \) with mean 19.6 months of follow up and group \( \geq 0 < 30 \% \) with mean 18.3 months of follow up, the volume of CAP at follow up was not significantly decreased, compared with the volumes at baseline (SMD −0.034 mm³, 95% CI −0.111 ~ 0.044, \( p = 0.396 \); SMD −0.032 mm³, 95% CI −0.093 ~ 0.030, \( p = 0.315 \) respectively). There was no significant heterogeneity among arms (\( \chi^2 \) for heterogeneity = 1.55, \( p = 0.981 \), \( I^2 = 0 \% \) for group \( < 0 \% \); \( \chi^2 \) for heterogeneity = 4.59, \( p = 0.970 \), \( I^2 = 0 \% \) for group \( \geq 0 < 30 \% \)).

Sensitivity analyses showed that LDL-C lowering in group \( < 0 \% \) could not still significantly decrease the volume of CAP at follow up, compared with the volumes at baseline (SMD −0.010 mm³, 95% CI: −0.080 ~ 0.061) when the arm of 2007 ILLUSTRATE Ato + Tor was omitted to −0.042 mm³ (SMD, 95% CI: −0.108 ~ 0.024) when the arm of 2004 REVERSAL Pro was omitted. No publication bias was found, the values of \( p \) by Egger’s test for group \( < 0 \) were 0.537.

Mean levels of LDL-C at baseline and follow up, mean reducing percentage of LDL-C in group \( < 0 \% \), \( \geq 0 < 30 \% \), \( \geq 30 < 40 \% \), \( \geq 40 < 50 \% \) and \( \geq 50 \% \), were showed in Table 4.

The effect of lowering LDL-C by statins on regression of coronary atherosclerotic plaque

LDL-C lowering by rosuvastatin, atorvastatin and pitavastatin in group \( \leq 70 \) and >70 ≤100 HP mg/dL could lead to regression of CAP, but LDL-C lowering by simvastatin, fluvastatin and pravastatin could not (Figure 6, Table 5).

LDL-C lowering by rosuvastatin (mean 33.3 mg daily for mean 20 months), atorvastatin (mean 60.3 mg daily for mean 17 months) and pitavastatin (4 mg daily for 8 ~ 12 months) in group \( \leq 70 \) and >70 ≤100 HP mg/dL could significantly decrease the volumes of CAP at follow up, compared with the volumes at baseline (SMD −0.162 mm³, 95% CI: −0.234 ~ −0.081, \( p = 0.000 \); SMD −0.101, 95% CI: −0.184 ~ −0.019, \( p = 0.016 \); SMD −0.304 mm³, 95% CI: −0.553 ~ −0.055, \( p = 0.017 \); respectively). There was no significant heterogeneity among arms (\( \chi^2 \) for heterogeneity = 0.37, \( p = 0.985 \), \( I^2 = 0 \% \) for rosuvastatin; \( \chi^2 \) for heterogeneity = 4.44, \( p = 0.072 \), \( I^2 = 0 \% \) for atorvastatin).

Sensitivity analyses suggested that lowering LDL-C by rosuvastatin could lead to regression of CAP with reduction of the plaque volume ranged from −0.153 mm³ (SMD, 95% CI: −0.249 ~ −0.056) when the arm of 2006 ASTEROID Ros was omitted to −0.178 mm³ (SMD, 95%...
CI: \(-0.287 \sim -0.069\) when the arm of 2011 SATURN Ros was omitted. Lowering LDL-C by atorvastatin could, but not significantly, lead to regression of CAP when the arm of 2009 JAPAN-ACS Ato was omitted (SMD: \(-0.075 \text{ mm}^3\), 95% CI: \(-0.162 \sim 0.012\)). No publication bias was found, the values of \(p\) by Egger’s test for rosuvastatin and atorvastatin group were 0.770, 0.582 respectively (Table 5).

Intensity of lowering LDL-C by different statins was shown in Table 6. Rosuvastatin and atorvastatin could reduce LDL-C by more than 40%.

**Discussion**

**Feature of this meta-analysis**

This meta-analysis broke though the limit of single trial, and pooled arms together according to the levels of LDL-C at follow up in the arms, regardless of the measures of lowering LDL-C: treating arm (statins, ACAT inhibitor, CETP inhibitor, decreasing obesity drug, and glucose-lowering agents) and control arms (dietary restriction, moderate LDL-C lowering by statin); intensive and moderate LDL-C lowering. The volumes of CAP at follow up were compared with those at baseline in the same arms to evaluate the regression of the CAPs, this meta-analysis really reflected the change of the plaques volume with the change of LDL-C levels.

Our meta-analysis results indicated that intensive lowering LDL-C in group \(\leq 70, >70 \leq 100\) mg/dL (mean follow up LDL-C, mean duration of follow up: 60.6 mg/dL, 18.6 months; 77.8 mg/dL, 17.4 months respectively), \(\geq 30 < 40, \geq 40 < 50\) and \(\geq 50\) (mean LDL-C reducing, mean
| Group | Included arms (case) | CAP Volume at Baseline (mm³) | CAP Volume at Follow up (mm³) | Pooled SMD (95% CI, p) | Heterogeneity test \( \chi^2 \) test (p) | I² | Lower SMD (95% CI) | Upper SMD (95% CI) | Sensitivity analyses | Egger's test |
|-------|---------------------|-----------------------------|-----------------------------|------------------------|-----------------------------|-----|-------------------|-------------------|-------------------|-------------|
| ≤70 mg | 7 (1250)            | 177.1±41.9                  | 125.9±38.6                  | -0.156 (-0.235-- -0.078, 0.000) | 0.57 (0.997)                 | 0   | -0.146 (-0.238-- -0.054) | -0.167 (-0.270-- -0.064) | Without 2006 ASTEROID Ros Without 2011 SATURN Ros | 0.835       |
| >70≤100HP mg | 11 (1352)            | 129.7±72.3                  | 123.8±69.8                  | -0.123 (-0.199-- -0.048, 0.001) | 6.83 (0.741)                 | 0   | -0.103 (-0.182-- -0.024) | -0.151 (-0.235-- -0.067) | Without 2009 JAPAN-ACS Ato Without 2004 REVERSAL Ato | 0.501       |
| >70≤100MP mg | 5 (1548)             | 195.8±2.3                   | 191.8±4.7                   | -0.045 (-0.115-- -0.026, 0.215) | 1.59 (0.811)                 | 0   | -0.016 (-0.103-- -0.066) | -0.061 (-0.140-- -0.019) | Without 2007 ILLUSTRATE Ato+Tor Without 2008 STRADIVARIUS Con | 0.500       |
| >70≤100LP mg | 6 (1061)             | 201.2±15.1                  | 197.3±15.0                  | -0.045 (-0.130-- -0.040, 0.301) | 1.14 (0.950)                 | 0   | -0.024 (-0.136-- 0.087) | -0.059 (-0.148-- 0.031) | Without 2007 ILLUSTRATE Ato Without 2004 A-PLUS Ava 50 | 0.241       |
| >100 mg | 10 (669)             | 175.9±86.4                  | 178.7±89.1                  | 0.017 (-0.090--0.124, 0.757) | 2.37 (0.984)                 | 0   | -0.000 (-0.135-- 0.136) | -0.039 (-0.073-- 0.151) | Without 2004 REVERSAL Pro Without 2005 Tani S Pra | 0.692       |
| <0%    | 8 (1276)             | 201.2±13.8                  | 198.3±13.8                  | -0.034 (-0.111--0.044, 0.396) | 1.55 (0.981)                 | 0   | -0.012 (-0.109-- 0.084) | -0.044 (-0.125-- 0.037) | Without 2007 ILLUSTRATE Ato Without 2004 A-PLUS Ava 50 | 0.087       |
| >0≤30% | 13 (2014)            | 188.6±51.7                  | 186.3±52.7                  | -0.032 (-0.093--0.030, 0.315) | 4.59 (0.970)                 | 0   | -0.010 (-0.080-- 0.061) | -0.042 (-0.108-- 0.024) | Without 2007 ILLUSTRATE Ato+Tor Without 2004 REVERSAL Pra | 0.537       |
| >30≤50% | 10 (594)             | 102.9±96.9                  | 94.3±90.4                   | -0.199 (-0.314-- -0.085, 0.001) | 3.10 (0.960)                 | 0   | -0.166 (-0.295-- -0.038) | -0.214 (-0.342-- -0.085) | Without 2009 JAPAN-ACS Ato Without 2009 COSMOS Ros | 0.024       |
| >40≤50% | 8 (1677)             | 157.8±37.8                  | 150.7±36.3                  | -0.108 (-0.176-- -0.040, 0.002) | 2.50 (0.927)                 | 0   | -0.093 (-0.174-- -0.011) | -0.126 (-0.200-- -0.053) | Without 2011 SATURN Ros Without 2004 REVERSAL Ato | 0.605       |
| >50%   | 1 (349)              | 212.2±81.3                  | 197.5±79.1                  | -0.183 (-0.332-- -0.035, 0.016) |                         |     |                     |                   | Without 2004 REVERSAL Ato | 0.846       |
duration of follow up: 36.1%, 10.3 months; 45.4%, 19.4 months; 53.2%, 24 months respectively) could lead to the regression of CAP; that moderate lowering LDL-C in group >70 ≤ 100 MP mg/dL (mean LDL-C reducing by 9.1%, mean 19.8 months of follow up), >100 (mean follow up LDL-C 110.0 and mean 14.6 months of follow up) mg/dL and ≥ 0 < 30% (mean LDL-C reducing by 10.6%, mean 18.3 months of follow up) could not lead to the regression; and that intensive lowering LDL-C, by mean 48% with rosuvastatin, and by mean 42% with atorvastatin, could regress CAP. The sensitivity analysis confirmed the effect of the LDL-C change on the volume of the plaque. The importance of intensive lowering LDL-C on regression of CAP and LDL-C target of this meta-analysis

In the trials that evaluated the effects of LDL-C lowering on atheroma progression by IVUS, the effects varied with level of LDL-C at follow up. In group ≤ 70 mg, ≥ 30 < 40% and ≥ 40 < 50%, the LDL-C at baseline in most trials (including ESTABLISH [14], REVERSAL [13], JAPAN-ACS [12], ASTEROID [37], COSMOS [40], trial by Kawasaki M [16] and by Nasu K [41]) were >120 mg. In ASTEROID [37], COSMOS [40], JAPAN-ACS [12] trial and fluvastatin arm of the trial by Nasu K [41] with respective the mean LDL-C level 60.8 mg, 82.9 mg, 81-84 mg and 98 mg (53.2%, 38.6%, 36% and 32.3% reduction of level of LDL-C) at follow up, it was showed that CAP could be regressed with intensive statin therapy. In ESTABLISH [14] and REVERSAL [13], the mean reducing percent of LDL-C at follow up in the statin treatment arms were 44% and 46% respectively, the volumes of CAPs at follow up were not significantly decreased, compared with those in baseline. In the trials by Yokoyama M [15] and Kawasaki M [16], mean reducing percentage of LDL-C at follow up was 35% for atorvastatin arm of the trial by Yokoyama M [15], 32% for pravastatin arm of the trial by Kawasaki M [16] and 39% for atorvastatin arm of the trial by Kawasaki M [16], the volume of CAPs at follow up were also not significantly decreased, compared with that at baseline. Pooled these arms with follow up LDL-C ≤ 70 mg or reducing > 30% together, these meta-analysis showed that the CAPs could be regressed in group ≤ 70 mg, ≥ 30 < 40% and ≥ 40 < 50%. Because of publication bias in group ≥ 30 < 40% (Table 3), the level of LDL-C in this group could not be recommended for regressing CAP. Based on the mean level and reducing percentage at follow up in the arms were below 30% because the levels of LDL-C at baseline were <95 mg/dL. In ILLUSTRATE trial [23], after treatment with atorvastatin to reduce levels of LDL-C to less than 100 mg/dL, patients were randomly assigned to receive either atorvastatin monotherapy or atorvastatin plus 60 mg of torcetrapib daily. After 24 months, the reduction of LDL-C in both arms was <24% and the progression of CAP was not halted. In trial [34,35] with statins treatment and baseline LDL-C < 110 mg, if the LDL-C lowering percentage at follow up were <24%, the CAP was also not regressed. The meta analysis with six arms in group >70 ≤ 100 MP mg/dL and five arms in group >70 ≤ 100 MP mg/dL did not show that only >70 ≤ 100 mg/dL of LDL-C level but <30% reduction at follow up could lead to regression of CAP, which further confirmed the importance of intensively lowering LDL-C in regression of CAP. Though LDL-C at follow up in some trials [13,15,16,26,27,39] of LDL-C lowering by statins was >70 ≤ 100 mg/dL and

### Table 4 Levels and reducing percentage of LDL-C and duration in each group

| Group     | N   | Mean LDL-C at Baseline (mg) | Mean LDL-C at Follow up (mg) | Mean Reducing percentage | Actual range of reducing percentage | Duration (month) |
|-----------|-----|-----------------------------|-------------------------------|--------------------------|-------------------------------------|------------------|
| ≤ 70 mg   | 1250| 120.0±8.2                   | 60.8±3.5                     | 48.8±3.3                 | 37~53.2                             | 18.6±8.2         |
| >70 ≤ 100 MP mg | 1352 | 132.4±12.9                  | 77.8±7.0                     | 40.4±4.0                 | 32.3~46.7                           | 17.4±5.9         |
| >70 ≤ 100 LP mg | 1548 | 91.3±6.9                    | 82.4±8.2                     | 9.1±4.5                  | 3.6~14.9                            | 19.8±2.7         |
| >70 ≤ 100 MP mg | 1061 | 88.5±5.5                    | 91.5±5.4                     | -4.7±2.5                 | -1.7~8.5                            | 19.9±4.5         |
| >100 mg   | 699  | 125.1±24.4                  | 110.0±9.3                    | 8.3±15.6                 | -10.9~32                            | 14.6±5.1         |
| <0%       | 1276 | 89.1±5.3                    | 93.2±6.2                     | -5.6±3.1                 | -1.7~10.9                           | 19.6±4.2         |
| 0 ≤ 30%   | 2014 | 102.4±22.1                  | 89.7±15.7                    | 10.6±7.3                 | 0~25                                | 18.3±4.5         |
| >30 ≤ 40% | 594  | 132.6±11.4                  | 83.3±7.7                     | 36.1±1.9                 | 32~39                               | 10.3±3.1         |
| >40 ≤ 50% | 1677 | 123.7±13.4                  | 66.8±8.0                     | 45.4±2.8                 | 41.5~49                             | 19.4±6.9         |
| >50%      | 349  | 130.4±34.3                  | 60.8±20.0                    | 53.2                     | 53.2                                | 24               |
reducing >30%, the CAP in the trials was also not regressed. Included eleven arms with baseline LDL-C > 130.0 mg/dL, follow up LDL-C >70 ≤100 mg/dL and LDL-C reducing >30% (in group >70 ≤100 HP mg), this meta-analysis suggested that LDL-C reducing >40% or to target 77.8 mg could regress CAP (Table 4). The meta-analysis in group >70 ≤100 MP and >70 ≤100 LP mg/dL indicated that LDL-C reducing percentage, not lowering absolute value of LDL-C at follow up, was important for regressing CAP.

Although rosuvastatin, atorvastatin, pitavastatin, simvastatin, and fluvasatatin in some trials could reduce LDL-C level to ≤100 mg by or >30%, the meta-analysis indicated that rosuvastatin, atorvastatin and pitavastatin (mean lowering LDL-C by 48.4%, 42.3% and 36.2% respectively) could regress the CAPs, and simvastatin with mean lowering LDL-C by 39.9% could not. The role of pitavastatin in regressing CAPs remains to be verified because the role was from only one RCT with 125 cases [12]. Pravastatin with mean lowering LDL-C by 24.6% could not regress the CAPs either. Fluvastatin with mean lowering LDL-C by 32.3% in the blinded endpoint trial with 40 patients can regress the CAP [41], but meta-analysis indicated that fluvastatin could not regress the CAP. The reason that pravastatin and fluvastatin in this meta-analysis can not regress the CAPs might be attributed to their low-intensity of lowering LDL-C and low dosage which can not reduce LDL-C by >40%.

Taken all the results of meta-analysis together, it was recommended that LDL-C level should be reduced by >40% or to a target level <78 mg/dL for regressing CAP.
The difference in LDL-C target level between this meta-analysis and current guidelines

The patients included in this meta-analysis were coronary heart disease. According to 2004 the guideline of the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program [43] and 2011 ESC/EAS Guidelines for the management of dyslipidaemias [1], this group of patients belongs to very high risk category, and the recommended targets of LDL-C should be less than 70 mg/dL or 30-40% reduction from baseline in 

Table 5 Results of meta-analysis in different statins groups

| Group    | Included arms (and case) | Pooled SMD (95% CI, p) | Heterogeneity test | Sensitivity analyses | Egger's test |
|----------|--------------------------|------------------------|-------------------|---------------------|--------------|
|          |                          |                        |                   | Lower SMD (95% CI)  | Upper SMD (95% CI) |             |
|          |                          |                        |                   |                      |              |             |
| Rosuvastatin | 5 (1173)                  | -0.162 (-0.234~ -0.081, 0.000) | 0.37 (0.985) | -0.153 (-0.249~ -0.056) | -0.178 (-0.287~ -0.060) | 0.770 |
|           |                          |                        |                   | Without 2006 ASTEROID Ros | Without 2011 SATURN Ros |             |
| Atorvastatin | 8 (1138)                  | -0.101 (-0.184~ -0.019, 0.016) | 4.44 (0.728) | -0.075 (-0.162~ -0.012) | -0.132 (-0.225~ -0.038) | 0.582 |
|           |                          |                        |                   | Without 2009 JAPAN-ACS Ato | Without 2004 REVERSAL Ato |             |
| Pitavastatin | 1 (125)                   | -0.304 (-0.553~ -0.055, 0.017) |             |                      |              |             |
| Fluvastatin | 1 (40)                    | -0.169 (-0.608~ -0.270, 0.450) |             |                      |              |             |
| Simvastatin | 2 (90)                    | -0.10 (-0.393~ 0.192, 0.501) | 0.04 (0.846) | -0.074 (-0.467~ -0.318) | -0.133 (-0.572~ -0.360) | 0.000 |
|           |                          |                        |                   | Without 2004 Jensen LO Sim | Without 2009 Hong MK Sim |             |
| Pravastatin | 3 (319)                   | -0.008 (-0.163~ -0.147, 0.020) | 1.86 (0.395) | -0.005 (-0.165~ -0.154) | 0.039 (-0.131~ -0.028) | 0.528 |
|           |                          |                        |                   | Without 2005 Kawasaki M Pra | Without 2005 Tani S Pra |             |
ATP III, and less than 70 mg/dL or a ≥50% reduction in 2011 ESC/EAS Guidelines. The target levels for subjects at very high risk in the both guidelines are extrapolated from several clinical trials [43], mainly from the meta-analysis by Cholesterol Treatment Trialists’ Collaborators [44], which indicated that absolute benefit of LDL-C lowering related chiefly to the absolute reduction of LDL-C, and the risk reductions are proportional to the absolute LDL-C reductions, but the meta-analysis did not provide target level of LDL-C for the benefit in terms of cardiovascular disease reduction [44]. According to 2013 ACC/AHA blood cholesterol guideline [45], this group of patients should be treated with high-intensity statin (atorvastatin 40–80 mg daily or rosuvastatin 20–40 mg daily), which was the intensity of statin suggested in this meta-analysis (Table 6).

The results of our meta-analysis imply that the patients with CHD should be intensively treated with statins (rosuvastatin 33 mg or atorvastatin 60 mg daily) to reduce the level of LDL-C by >40% or to a target level <78 mg/dL for regressing CAP, which have a little different to the guidelines. These different target levels of LDL-C might be due to different observational index: cardiovascular events for both guidelines, CAP volume for this meta-analysis. Moreover, our target is directly from meta-analysis, the target of 2011 ESC/EAS Guidelines is from extrapolation of meta-analysis, not a direct data. Our meta-analysis revealed the relation between the regression of coronary artery disease and LDL-C level from the view of pathological anatomy. Published meta-analysis [17,18] about CAP by IVUS did not review the relationship between LDL-C level and CAP.

### Study limitation

The results of this analysis were obtained by pooling data from twenty clinical trials. As with any meta-analysis, this study has some limitations. Firstly, though no publication bias was observed by Egger’s test there may be a potential of publication bias because only published data were included. Secondly, the methodology used for measurement of coronary atheroma might not be the same in the studies. The plaques volume may be calculated from slices with 1 mm apart for a length of 10 mm vessel in some trials [13,15,22,23,27–29,37], or 0.1–0.3 mm-apart for a length of 10–50 mm vessel in other trials [12,21,33,39,40], which might affect accuracy of plaque measurement. There were some differences in selecting plaque: some trials assessed the plaque in non-culprit vessel, while others assessed non-culprit plaque in a culprit vessel [12,14,34], which assured the plaque was stable. Our study focus on target plaque change, i.e. plaque regression or progression, those differences in measurements and plaque selection did not affect the change of the target plaque with LDL-C levels. So, it has little effect on homogeneous of studies, and this detection bias was very much limited from values of 

### Table 6 Levels and reducing percentage of LDL-C, dosage and duration in different statin group

| Group       | N   | Age  | Mean LDL-C at Baseline (mg) | Mean LDL-C at Follow up (mg) | Mean Reducing percentage | Statin dosage (mg) | Duration (month) |
|-------------|-----|------|----------------------------|-----------------------------|-------------------------|-------------------|-----------------|
| Rosuvastatin| 1173| 58±1.8| 123.9±8.6                  | 63.3±7.4                    | 48.4±4.2                | 33.3±11.6         | 20.5±6.3        |
| Atorvastatin| 1138| 58±2.5| 128.0±14.0                 | 73.0±8.7                    | 42.3±3.7                | 60.3±28.6         | 17.5±7.1        |
| Pitavastatin| 125 | 62.5±11.5| 130.9±33.3                | 81.1±23.4                   | 36.2±19.5              | 4                | 8–12            |
| Fluvastatin | 40  | 63.0±10.0| 144.9±31.5                | 98.1±12.7                   | 32.3                    | 60               | 12              |
| Simvastatin | 90  | 57.9±0.1| 136.6±5.3                 | 81.2±3.5                    | 39.6±1.1               | 28.9±10.0        | 17.8±6.5        |
| Pravastatin | 319 | 58.2±3.2| 146.8±7.4                 | 108.9±2.9                   | 24.6±2.6               | 34.8±9.9         | 15.4±5.0        |
major adverse cardio- and cerebrovascular events. Furthermore, high level of LDL-C plays a crucial role in the formation of atherosclerotic plaque, but LDL-C level is not unique risk factor for atherosclerotic plaque. Hypertension is another important risk factor for the formation of plaque [48,49]. Smoking cessation, administrating β-blockers, anti-hypertension therapy might play some role in slowing progression of CAP [48,50-52]. The trend of CAP regression in group <0% might attribute to these non-LDL-C reducing factors.

Conclusions
Atherosclerotic plaque extension and disruption are basic mechanism of atherosclerotic cardio- and cerebrovascular disease. Stabling and regressing atherosclerotic plaque play an important role in preventing cardio- and cerebrovascular disease. Pooled the twenty trials with CAP detected by gold standard: IVUS, this systemic review demonstrated that intensive lowering LDL-C (rosuvastatin mean 33 mg daily and atorvastatin mean 60 mg daily) with >17 months of duration could lead to the regression of coronary atherosclerotic plaque, LDL-C level should be reduced by >40% or to a target level <78 mg/dL for regressing CAP.

Abbreviations
LDL-C: Low-density lipoprotein cholesterol; CAP: Coronary atherosclerotic plaque; CHD: Coronary heart disease; RCT: Randomized controlled trial; CAG: Coronary angiography; MUS: Intravascular ultrasound; SMD: Standardized mean differences; ACS: Acute coronary syndrome; ACAT: Acyl–coenzyme A:cholesterol acyltransferase; CETP: Cholesterol ester transfer protein; CI: Confidence interval; ATP III: Adult Treatment Panel III; CAD: Coronary artery disease.

Competing interests
The authors declare that they have no competing interests. This study was not funded.

Authors' contributions
GWQ, FQZ and LYF carried out data extraction, participated in the analysis and drafted the manuscript. LXY and LCY participated in the design of the study and helped to draft the manuscript. HY, CYM and YB conceived the study, and participated in its statistical analysis. All authors read and approved the final manuscript.

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Received: 2 January 2014 Accepted: 25 April 2014
Published: 2 May 2014

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doi:10.1186/1471-2261-14-60
Cite this article as: Gao et al.: Systematic study of the effects of lowering low-density lipoprotein-cholesterol on regression of coronary atherosclerotic plaques using intravascular ultrasound. BMC Cardiovascular Disorders 2014 14:60.