



Comparative efficacy and safety among high-intensity statins. Systematic Review and Meta-Analysis

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Aim: To summarize the evidence in terms of efficacy and safety of head-to-head studies of high-intensity statins regardless of the underlying population. **Materials & methods:** A systematic review and meta-analysis was conducted to summarize the effect sizes in randomized controlled trials and cohort studies that compared high-intensity statins. **Results:** Based on 44 articles, similar effectiveness was observed across the statins in reducing LDL levels from baseline. All statins were observed to have similar adverse drug reactions (ADRs), although higher dosages were associated with more ADRs. Based on a pooled quantitative analysis of atorvastatin 80 mg versus rosuvastatin 40 mg, rosuvastatin was statistically more effective in reducing LDL. **Conclusion:** This review further confirms that high-intensity statins reduce LDL by $\geq 50\%$, favoring rosuvastatin over atorvastatin. Additional data are needed to confirm the clinical significance on cardiovascular outcomes using real-world studies.

First draft submitted: 8 September 2022; Accepted for publication: 5 December 2022; Published online: 27 February 2023

Keywords: atorvastatin • cholesterol • high intensity • HMG-CoA • hydroxymethylglutaryl-CoA reductase inhibitors • meta-analysis • rosuvastatin • statins

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide and statins remain the cornerstone of lipid-lowering therapy for the primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) events [1,2]. Statins have been shown to effectively lower low-density lipoprotein cholesterol (LDL), which is a critical marker for the primary and secondary prevention of ASCVD [3–8]. The association between LDL levels and cardiovascular events and mortality is well established in the literature and relevant guidelines, whereby the classification of high-intensity statins is based on LDL reduction of $\geq 50\%$ to reduce risk of ASCVD [9,10]. Evidence has also shown that compared with moderate- or low-intensity statins, high-intensity statins decrease CVD risk more effectively [10–12]. Additionally, high-intensity statins are recommended by the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Cholesterol Guideline, and 2018 ACC/AHA updated guideline for patients who are ≤ 75 years of age with clinical ASCVD (secondary prevention) regardless of LDL levels [9,13]. Despite this major shift in practice, many studies that evaluated the prescribing trends of statins in clinical settings found that less than half of the patients with ASCVD were prescribed high-intensity statins [14–17].

Two main statins are recommended; atorvastatin in the doses of 40–80 mg (A40–A80) and rosuvastatin between the doses of 20 and 40 mg (R20–R40). Yet it is not known which is better in reducing the ASCVD risk. Guidelines consider these two drugs to be equipotent and, thus, place them within the same category [13]. Another statin that is sometimes used at high intensity is simvastatin at a dose of 80 mg (S80), which is still recommended by the National Institute for Health and Care Excellence (NICE) 2015 guideline (updated in 2019) as well as by literature of clinical practices as a high-intensity statin [18,19].

Available evidence suggests that there is variability between the statins in reducing the LDL level, such as that observed in the VOYAGER meta-analysis, which compared atorvastatin to rosuvastatin in Caucasian subjects, whereby rosuvastatin was superior to atorvastatin [20]. The VOYAGER did not focus on high-intensity dosing but considered all doses of these two agents. Despite available evidence that high-intensity statin regimens, irrespective of dosing, are more effective than low- and moderate-intensity statins for patients with ASCVD [21], there is no clear evidence of which of the high-intensity statins is best to be used to lower CVD risk maintaining minimal adverse effects. Therefore, this systematic review, including meta-analysis, aimed at summarizing the evidence in terms of efficacy and safety of head-to-head studies covering high-intensity statins regardless of the underlying population.

Materials & methods

A systematic review of the literature was conducted following the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22]. The PROSPERO registration number of this review is CRD42021235844.

Search strategy

The databases PubMed, Cochrane Central Database, and EMBASE were comprehensively searched, in addition to searching the grey literature via the Google Scholar and ClinicalTrials.gov databases. Moreover, the references of relevant studies and reviews were manually searched to capture potential studies. The literature search was from inception until December 2021, in accordance with the Cochrane Handbook for Systematic Reviews of Interventions, Version 6.2 [23]. The search was conducted by two researchers independently (HA, MH) and was reviewed by a third researcher for accuracy (MJ).

The search strategy included terms related to three domains: drug (e.g. atorvastatin, rosuvastatin, simvastatin), dose (e.g. atorvastatin 80 mg, rosuvastatin 40 mg, simvastatin 80 mg), and high intensity (e.g. high potency, high strength). Although S80 is not recommended by the FDA as high-intensity statin due to its increased risk of adverse events, it was included in this review since it is still being recommended by the NICE 2016 guideline as well as in some clinical practices [18,19]. The detailed search strategy can be seen in [Supplementary File 1](#).

Filters that were applied to the search were randomized controlled trials (RCTs) and observational studies. Although RCTs provide a higher level of evidence, observational studies enable deeper insight into the effectiveness and safety outcomes of the study drugs since they represent real-world data [24,25]. Also as filters, the search was restricted to the English language and human subjects.

Study selection

All hits were transferred to EndNote X9.2, a reference management software. After removing duplicates, two researchers (HA and MH) independently screened the title and abstracts of identified articles. This was followed by full-text screening which was also done independently. Any disagreements were resolved through discussion with the other team members (DB and MJ). Articles were included in this review if they included at least two comparative arms of high-intensity dosing, regardless of being RCTs or observational in design. Articles were excluded if were of placebo as the only comparator, narrative articles, reviews, letters to the editor, editorials, commentaries, noncomparative research and non-English articles.

Data extraction

After including the eligible studies, the two reviewers (HA and MH) independently extracted the data using a prespecified data extraction tool using Microsoft Excel. The data extraction sheet included: characteristics of the published article (e.g. journal, year of publication), study design, objective, population characteristics, interventions with doses, main outcomes (clinical and safety outcomes), a summary of the results, and limitations/strengths of the study. Disagreements were resolved by referral to the other research reviewers (MJ and DB). The extraction was also independently re-reviewed by MJ for all the included articles.

Quality assessment

Two reviewers (HA and MH) independently assessed the risk of bias for each study using the Crowe Critical Appraisal Tool (CCAT) [26]. The tool is considered one of the simplest and most suitable quality assessment tools that can be used for all research designs. It expresses a high degree of validity and reliability [24,25] and was previously used by the research team. The CCAT includes eight domains, i.e., preliminaries, introduction, design, sampling,

data collection, ethical matters, results, and discussion. Each domain is scored on a scale of 0–5, adding up to an overall score of 40. A higher score corresponds to better quality. The CCAT tool does not provide categorization for the overall score. Based on published literature, however, a score between 4 and 5 in most domains with an overall score of 32 (80%), or above was considered high quality; a score of 3 to 5 in most domains with an overall score of 24 (60%) or more was considered as average to good quality; and a score of ≤ 2 in most of the domains with an overall score below 24 (60%) was considered as low quality. Discrepancies between the reviewers' assessments were resolved through discussions with the research team.

Data synthesis & analysis

Data synthesis was primarily qualitatively performed by describing the available evidence. The outcomes assessed were the primary outcomes provided by the article and the focus was mainly on the change in lipid profiles. Additionally, the treatment effect data on LDL levels between atorvastatin and rosuvastatin were statistically pooled via the RevMan 5.4.1 [27] software, using the random-effect statistical model when heterogeneity between the pooled articles existed, where a significant heterogeneity is assumed at $I^2 > 50\%$. If no heterogeneity is identified in an analysis, the fixed-effect model was used. Pooled results were graphically represented using forest plot graphs. Analyzed data were continuous, where the mean difference estimate was pooled with 95% confidence interval (95% CI). Sensitivity analysis was also performed, using the leave-one-out approach, whereby one study at a time was removed from the meta-analysis, when heterogeneity existed, to determine the stability of the treatment effect. Funnel plot analysis of publication bias was generated when 10 or more independent comparisons were included in a pooled analysis.

Results

Figure 1 provides an overview of the inclusion of studies in this systematic review. A total of 3075 studies was identified from the different databases and 22 from additional sources, i.e., google scholar and manual search reference lists in included articles. After removing duplicates and screening full text, a total of 44 articles was included in this systematic review. Fourteen studies evaluated statins among patients with hypercholesteremia, eleven evaluated statins in patients with acute coronary syndrome (ACS), including myocardial infarction (MI) (ST-elevated MI, non-ST-elevated MI), four studies were conducted among patients undergoing the cardiovascular procedures percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), four were conducted among high-risk patients for coronary heart diseases, four were conducted in patients with established CVDs, three studies were conducted in patients taking statins regardless of diagnosis, while two studies were conducted among patients with diabetes, one in heart failure, and one in patients with intermediate coronary stenosis. Overall, 36 were RCTs in design, and 8 were observational cohort studies. Table 1 highlights the main characteristics and outcomes in included studies [19,28–71]. Detailed study characteristics are available in Supplementary File 2. The majority of the studies were conducted in USA ($n = 16$), with others including the Netherlands ($n = 4$), Canada ($n = 4$), India ($n = 4$), Turkey ($n = 4$) and Middle Eastern countries, constituting Lebanon ($n = 1$), Qatar ($n = 1$), and Egypt ($n = 1$). Nine studies were international, conducted in more than one country. The most common settings from which patients were recruited were clinics ($n = 19$), followed by hospitals ($n = 12$), and 14 studies did not define the study setting. With regards to patients, overall 34,196 patients were covered in this systematic review with an average age of 59.4 and 30.0% having diabetes.

A total of 31 studies compared atorvastatin to rosuvastatin and, of these, 17 compared A80 to R40, while nine studies compared different dosing of atorvastatin, and five studies compared different dosing of rosuvastatin. Eight studies included a comparison to simvastatin 80 mg. Among the 17 articles that compared A80 to R40, six included a percentage difference of LDL from baseline for each group and reported mean percentage difference with standard deviation. These studies were analyzed using a meta-analysis (Figure 2), *vide infra*.

Change in lipid profile

The primary end point in 33 studies was the change in lipid profile, primarily the change in LDL levels. Eight studies used high dose simvastatin (S80) compared with other high-intensity statins, such as a study by Meek *et al.* [19], which compared S80 to A80 in 116 patients over two years of follow-up and found no significant difference in any of the lipid profile readings (LDL, HDL, TC, TG). On the other hand, Illingworth *et al.* [59], the CHES study [66], and Karalis *et al.* [61] found A80 to be more effective than S80 against LDL, HDL, and TG levels. It is of note that Meek *et al.* used a retrospective observational study and a small sample size ($n = 116$), while

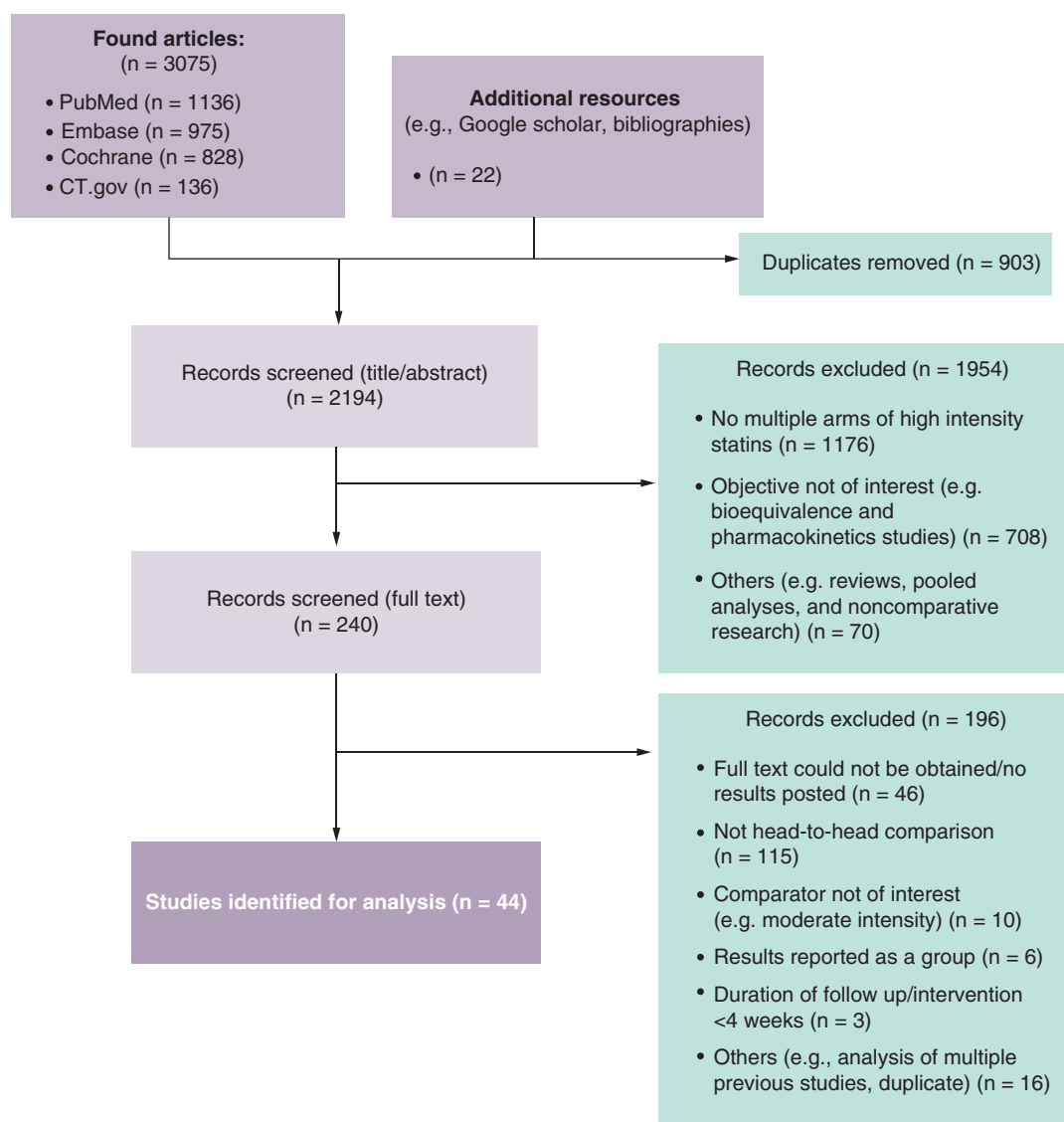


Figure 1. PRISMA flow diagram.

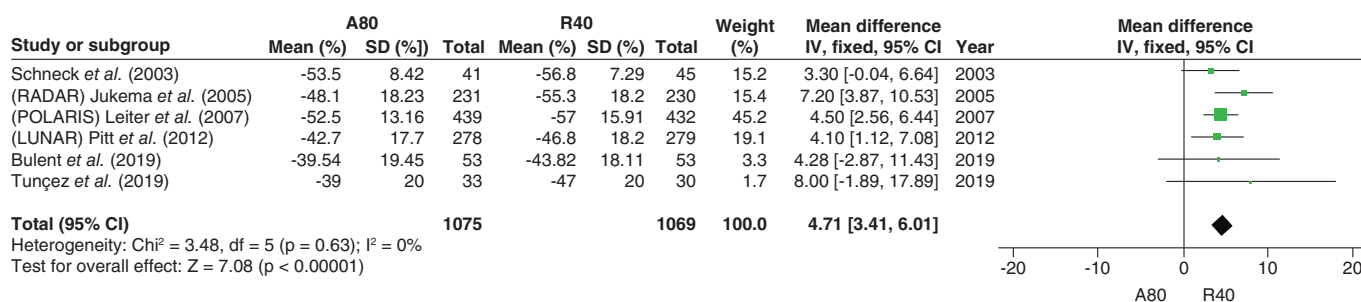


Figure 2. Forest plot.

A80: Atorvastatin 80 mg; CI: Confidence interval; R40: Rosuvastatin 40 mg; SD: Standard deviation.

Table 1. Summary of included studies.

Study (year), country	F/up [†]	DM (%)	Primary diagnosis	Treatment (n)	Lipid profile			Other outcomes	Reported ADRs	Ref.
					LDL	HDL	TC levels (mmol/l)			
Meek et al. (2011) UK	33	28.0	Regardless of diagnosis	A80 (47) S80 (69)	Median mmol/l (upper limit-lower limit) A80: 2.37 (1.78–3.19) S80: 2.37 (1.78–3.19) p = 0.385	Median mmol/l (upper limit-lower limit) A80: 1.35 (1.10–1.72) S80: 1.31 (1.05–1.78) p = 0.849	Median mmol/l (upper limit-lower limit) A80: 1.45 (1.11–2.11) S80: 1.55 (1.08–2.27) p = 0.867		d/c due to fatigue, aches and malaise, n A80: 5; S80: 9; NS	[19]
Rahhal et al. (2021) Qatar	12	47.3	ACS	A40 (475) A80 (151)	Achieved <70 mg/dl, n (%) A40 mg: 114 (24.00) A80 mg: 34 (22.50) p = 0.812			CVD associated death, non-fatal, ACS, and non-fatal stroke at one month, n (%): A40: 4 (0.80) A80: 2 (1.30) p = 0.690 at 12 months, n (%): A40: 15 (3.20) A80: 6 (4.00) p = 0.340	Myopathy, n A40: 4; A80: 1; NS Increased liver enzymes, n A40: 3; A80: 1; NS d/c due to ADRs A40: 4; A80: 0; NS	[28]
Betto et al. (2017) Lebanon	2	71.2	H.choles.	R10 (115) R20 (195) R40 (5)	Achieved patient specific target, n (%) R10: 91 (79.10%) R20: 165 (84.60%) R40: 4 (80.00%) p = 0.465	Between group differences: NR	Between group differences: NR		NR for each group	[29]
Choi et al. (2021) Korea	36	0.0	MI w/out DM	A40-A80 (1,349) R20 (872)				NOD, n (%) A40-80: 99 (7.50) R20: 70 (9.20) p = 0.550 MACE, n (%) A40-80: 149 (11.00) R20: 91 (10.40) p = 0.662		[30]

p value presented as difference between the groups.

[†] follow-up in months.

A10: Atorvastatin 10 mg; A20: Atorvastatin 20 mg; A40: Atorvastatin 40 mg; A80: Atorvastatin 80 mg; ACS: Acute coronary syndrome; ADR: Adverse drug reaction; AKI: Acute kidney injury; AMI: Acute myocardial infarction; ASCVD: Atherosclerotic cardiovascular diseases; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CHD: Coronary heart disease; CI: Confidence interval; CPK: Creatinine phosphokinase; CVD: Cardiovascular disease; D/c: Discontinue; DM: Diabetes mellitus; Ez10: Ezetimibe 10 mg; H.choles: Hypercholesterolemia; HDL: High-density lipoprotein; HH: Heterozygous familial hypercholesterolemia; IVUS: Intravascular ultrasound; LDL: Low-density lipoprotein; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVEFV: Left ventricular end systolic volume; MACCE: Major adverse cardiovascular and cerebrovascular events; MACE: Major adverse cardiac events; MI: Myocardial infarction; NODM: New onset diabetes mellitus; NR: Not reported; NS: Not significantly different; PCI: Percutaneous coronary intervention; PON-1: paraoxonase-1; R10: Rosuvastatin 10 mg; R20: Rosuvastatin 20 mg; R40: Rosuvastatin 40 mg; R80: Rosuvastatin 80 mg; RCT: Randomized controlled trial; S40: Simvastatin 40 mg; S80: Simvastatin 80 mg; STEMI: ST-elevation myocardial infarction; TC: Total cholesterol; TG: Triglycerides; URTI: Upper respiratory tract infection; w/out: Without.

Table 1. Summary of included studies (cont.).

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Study (year), country	F /up [†] (%)	DM (%)	Primary diagnosis	Treatment (n)	Lipid profile			Other outcomes		Reported ADRs	Ref.	
					LDL	HDL	TC levels (mmol/l)	TG levels (mmol/l)				
Roy et al. (2020) India	12	39.2	Post-PCI	A80 (321) R40 (621)					None of the post-PCI patients died. One acute MI occurred in each group. Repeated hospitalization for angina/stroke, n (%) A80: 7 (2.18) R40: 18 (2.9) NS Revascularization A80 2 (0.62%) R40 2 (0.32%) NS	Measured at 3 months post-PCO Myalgia, n A80: 0; R40: 1; NS Increased liver enzymes levels, n A80: 2; R40: 7; NS Increased CPK, n A80: 6; R40: 8; NS D/c or dose reduction due to ADRs, n A80: 3; R40: 13; NS	[31]	
Schneck et al. (2003) Canada and USA	1.5	NR	H.choles w/out active arterial disease	R5 (38) R10 (45) R20 (39) R40 (45) R80 (42) A10 (43) A20 (39) A40 (42) A80 (41)	Mean % change from baseline (SE) R20: -51.70 (0.90) R40: -56.80 (1.10) R80: -61.90 (1.40) A40: -48.40 (1.10) A80: -53.50 (1.30) p < 0.001	Mean % change from baseline (SE) R20: +9.10 (1.80) R40: +12.30 (1.70) R80: +9.60 (1.70) A40: +4.10 (1.70) A80: +2.10 (1.80) p < 0.05	Mean % change from baseline (SE) R20: -37.20 (0.70) R40: -41.10 (0.80) R80: -45.00 (1.10) A40: -36.30 (0.80) A80: -40.20 (1.00) p < 0.001	Mean % change from baseline (SE) R20: -18.40 (4.60) R40: -25.70 (4.30) R80: -19.70 (4.40) A40: -27.20 (4.40) A80: -34.50 (4.50) NS	Any ADR, n (%) R20: 15 (38.50%); R40: 21 (46.70); R80: 28 (66.70) A40: 26 (61.90); A80: 23 (56.10) Pharyngitis, n (%) R20: 1 (2.60); R40: 1 (2.20); R80: 8 (19.00); A40: 4 (9.50); A80: 4 (9.80) Headache, n (%) R20: 2 (5.10); R40: 5 (11.10); R80: 4 (9.50); A40: 4 (9.50); A80: 2 (4.90); NS	[32]		
POLARIS (2007) USA, Canada and Europe	6.5	39.2	High-risk with known CHD, CHD-risk equivalents, or established atherosclerosis and H.choles.	R40 (432) A80 (439)	Mean % change from baseline (CI) R40: -57.00 (-58.50, -55.50) A80: -52.50 (-53.90, -51.10) p < 0.001	Mean % change from baseline (CI) R40: +11.00 (9.10, 12.90) A80: +6.20 (4.60, 7.70) p < 0.001	Mean % change from baseline (CI) R40: -41.20 (-42.40, -40.10) A80: -39.30 (-40.50, -38.20) NS	Mean % change from baseline (CI) R40: -23.70 (-26.80, -20.70) A80: -27.70 (-30.50, -24.80) p < 0.05	Nasopharyngitis, n (%) R40: 27 (6.30); A80: 17 (3.90) Arthralgia, n (%) R40: 25 (5.80); A80: 18 (4.10) Myalgia, n (%) R40: 22 (5.10); A80: 26 (5.90) URTI, n (%) R40: 20 (4.60); A80: 17 (3.90) Backpain, n (%) R40: 18 (4.20); A80: 21 (4.80) Sinusitis, n (%) R40: 17 (3.90); A80: 8 (1.80) UTI, n (%) R40: 15 (3.50); A80: 25 (5.70) Diarrhea, n (%) R40: 15 (3.50); A80: 16 (3.60)	[33]		

p value presented as difference between the groups.

[†] follow-up in months.

A10: Atorvastatin 10 mg; A20: Atorvastatin 20 mg; A40: Atorvastatin 40 mg; A80: Atorvastatin 80 mg; ACS: Acute coronary syndrome; ADR: Adverse drug reaction; AKI: Acute kidney injury; AMI: Acute myocardial infarction; ASCVD: Atherosclerotic cardiovascular diseases; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CHD: Coronary heart disease; CI: Confidence interval; CPK: Creatinine phosphokinase; CVD: Cardiovascular disease; D/c: Discontinue; DM: Diabetes mellitus; Ez10: Ezetimibe 10 mg; H.choles: Hypercholesteremia; HDL: High-density lipoprotein; HFH: Heterozygous familial hypercholesteremia; IVUS: Intravascular ultrasound; LDL: Low-density lipoprotein; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end systolic volume; MACCE: Major adverse cardiovascular and cerebrovascular events; MACE: Major adverse cardiac events; MI: Myocardial infarction; NODM: New onset diabetes mellitus; NR: Not reported; NS: Not significantly different; PCI: Percutaneous coronary intervention; PON-1: paraoxonase-1; R10: Rosuvastatin 10 mg; R20: Rosuvastatin 20 mg; R40: Rosuvastatin 40 mg; R80: Rosuvastatin 80 mg; RCT: Randomized controlled trial; S40: Simvastatin 40 mg; S80: Simvastatin 80 mg; STEMI: ST-elevation myocardial infarction; TC: Total cholesterol; TG: Triglycerides; URTI: Upper respiratory tract infection; w/out: Without.

Table 1. Summary of included studies (cont.).

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Study (year), country	F/up [†]	DM (%)	Primary diagnosis	Treatment (n)	Lipid profile			Other outcomes		Reported ADRs	Ref.
					LDL	HDL	TC levels (mmol/l)	TG levels (mmol/l)			
GRAVITY (2013) USA, South America and Europe	3	NR	High risk ASCVD >20%	R10 + Ez10 (214)	Mean % change from baseline (SD)	Mean % change from baseline (SD)	Mean % change from baseline (SD)	p < 0.001	p < 0.005	p < 0.001	[34]
				R20 + Ez10 (214)	R20+Ez10: -63.50 (16.70)	R20+Ez10: 7.50 (16.40)	R20+Ez10: -46.60 (12.80)				
				S40 + Ez 10 (202)	S80+Ez10: -57.40 (20.50)	S80+Ez10: 4.30 (12.60)	S80+Ez10:-41.70 (15.20)				
				S80+ Ez 10 (203)	p < 0.005	R20+Ez10 vs S80+ Ez10	R20+Ez10 vs S80+ Ez10				
Agrawal et al. (2018) India	6	0	History of ASCVD	A40 (120) A80 (120)	Mean % change from baseline (SD)	Mean % change from baseline (SD)	Mean % change from baseline (SD)				[35]
					A40: -50.03 (18.06)	A40: +11.36 (28.62)	A40: 24.11 (16.14)				
					A80: -52.30 (13.72)	A80: +9.02 (27.47)	A80: 26.15 (21.30)				
					p = 0.149	p = 0.269	p = 0.214				
Aydin et al. (2015) Turkey	1	21.5	STEMI	A80 (59) R20 (61)	Mean % change from baseline (SD)	Mean % change from baseline (SD)	Mean % change from baseline (SD)				[36]
					A80: -52.00 (15.00)	A80: +0.90 (22.00)	A80: -36.00 (14.00)				
					R20: -52.00 (14.00)	R20: +7.60 (26.00)	R20: 16.00 (54.00)				
					p = 0.900	p = 0.07	p = 0.590				
PLANET I (2015) International	13	100	DM and progressive renal disease	R10 (107) R40 (116) A80 (102)	Between group differences: NR	Between group differences: NR	Between group differences: NR				[37]
							Urine protein: urine creatinine ratio A80 vs R40: -8.50% (-25.00 to 11.70) p = 0.38				
							Any ADR, n (%) R40: 79 (64.20); A80: 63 (57.30) Any serious ADR, n (%): R40: 20 (16.30); A80: 21 (19.10) Any renal ADR, n (%) R40: 12 (9.80); A80: 5 (4.50) Creatinine doubling, n (%) R40: 6 (4.90); A80: 0 Acute renal failure, n (%) R40: 5 (4.10); A80: 1 (0.90) Death, n (%) R40: 1 (0.80); A80: 0				
p value presented as difference between the groups. [†] follow-up in months.											
A10: Atorvastatin 10 mg; A20: Atorvastatin 20 mg; A40: Atorvastatin 40 mg; A80: Atorvastatin 80 mg; ACS: Acute coronary syndrome; ADR: Adverse drug reaction; AKI: Acute kidney injury; AMI: Acute myocardial infarction; ASCVD: Atherosclerotic cardiovascular diseases; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CHD: Coronary heart disease; CI: Confidence interval; CPK: Creatinine phosphokinase; CVD: Cardiovascular disease; D/c: Discontinue; DM: Diabetes mellitus; Ez10: Ezetimibe 10 mg; H.choles: Hypercholesterolemia; HDL: High-density lipoprotein; HFH: Heterozygous familial hypercholesterolemia; IVUS: Intravascular ultrasound; LDL: Low-density lipoprotein; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end systolic volume; MACCE: Major adverse cardiovascular and cerebrovascular events; MACE: Major adverse cardiac events; MI: Myocardial infarction; NODM: New onset diabetes mellitus; NR: Not reported; NS: Not significantly different; PCI: Percutaneous coronary intervention; PON-1: paraoxonase-1; R10: Rosuvastatin 10 mg; R20: Rosuvastatin 20 mg; R40: Rosuvastatin 40 mg; R80: Rosuvastatin 80 mg; RCT: Randomized controlled trial; S40: Simvastatin 40 mg; S80: Simvastatin 80 mg; STEMI: ST-elevation myocardial infarction; TC: Total cholesterol; TG: Triglycerides; URTI: Upper respiratory tract infection; w/out: without.											

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Table 1. Summary of included studies (cont.).

Study (year), country	F/up [†] (%)	DM (%)	Primary diagnosis	Treatment (n)	LDL	HDL	Lipid profile		Other outcomes	Reported ADRs	Ref.
					Absolute difference from baseline, mg/dl (SD)	Absolute difference from baseline, mg/dl (IQR)	Absolute difference from baseline, mg/dl (SD)	Absolute difference from baseline, mg/dl (IQR)	TG levels (mmol/l)		
Kilit <i>et al.</i> (2016) Turkey	1	23.6	AMI	A80 (31) R40 (24)	A80: -76.00 (36.00) R40: -65.00 (34.00) p = 0.277	A80: -2.00 (-10.00 – 2.00) R40: 1.00 (-4.00 – 5.00) p = 0.012	A80: -78.00 (37.00) R40: -67.00 (44.00) p = 0.342	A80: 22.00 (-45.00 – 59.00) R40: 2.00 (-52.00 – 48.00) p = 0.374	Total oxidant status Absolute difference, μ mol H2O2 Eq/L (IQR) A80: -2.90 (-6.00 – -1.10) R40: -2.30 (-4.40 – -0.50) p = 0.375 Total antioxidant status mmol Trolox Eq/L (SD) A80: 0.04 (0.21) R40: 0.01 (0.30) p = 0.701 Serum Paraoxonase-1, U/L (IQR) A80: 16.00 (1.00–46.00) R40: 18.00 (3.00–40.00) p = 0.982 Serum Arylesterase, U/L (SD) A80: 59.00 (206.00) R40: 36.00 (111.00) p = 0.645 Oxidative stress index arbitrary unit (SD) A80: -0.34 (0.59) R40: -0.28 (0.40) p = 0.621		[38]
RADAR (2005) Netherlands	4.5	NR	Any established CVD	A80 (231) R40 (230)	Mean % change from baseline (SE) A80: -48.10 (1.20) R40: -55.30 (1.20) p < 0.001	Mean % change from baseline (SE) A80: +2.70 (1.10) R40: +4.70 (1.10) NS	Mean % change from baseline (SE) A80: -39.50 (0.90) R40: -44.70 (0.90) p < 0.001	Mean % change from baseline (SE) A80: -31.60 (1.80) R40: -35.40 (1.80) NS		Increased creatinine kinase, n A80: 2; R40: 0 Myalgia, % A80: 8.00; R40: 7.00	[39]
Li <i>et al.</i> (2018) China	12	80.5	STEMI and underwent PCI	A40 (59) A80 (59)						MACE, n (%) A40: 31 (52.54) A80: 4 (6.78) p < 0.05	[40]
Crouse <i>et al.</i> (1999) USA	3	NR	H.choles.	S40 (202) A20 (210) S80 (215) A40 (215)	Mean % change from baseline (SE) S80: -49.20 (0.80) A40: -51.10 (0.80) NS	Mean % change from baseline (SE) S80: 6.60 (0.80) A40 3.00 (0.80) p < 0.001	Mean % change from baseline (SE) S80: -25.20 (1.60) A40: -29.60 (1.40) p < 0.001	Mean % change from baseline of ApoA-I (SE) S80: 5.90 (0.90) A40: 0.00 (0.90) p < 0.001			[41]

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[†] follow-up in months.

A10: Atorvastatin 10 mg; A20: Atorvastatin 20 mg; A40: Atorvastatin 40 mg; A80: Atorvastatin 80 mg; ACS: Acute coronary syndrome; ADR: Adverse drug reaction; AKI: Acute kidney injury; AMI: Acute myocardial infarction; ASCVD: Atherosclerotic cardiovascular diseases; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CHD: Coronary heart disease; CI: Confidence interval; CPK: Creatinine phosphokinase; CVD: Cardiovascular disease; D/c: Discontinue; DM: Diabetes mellitus; Ez10: Ezetimibe 10 mg; H.choles: Hypercholesterolemia; HDL: High-density lipoprotein; HFH: Heterozygous familial hypercholesterolemia; IVUS: Intravascular ultrasound; LDL: Low-density lipoprotein; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end systolic volume; MACCE: Major adverse cardiovascular and cerebrovascular events; MACE: Major adverse cardiac events; MI: Myocardial infarction; NODM: New onset diabetes mellitus; NR: Not reported; NS: Not significantly different; PCI: Percutaneous coronary intervention; PON-1: paraoxonase-1; R10: Rosuvastatin 10 mg; R20: Rosuvastatin 20 mg; R40: Rosuvastatin 40 mg; R80: Rosuvastatin 80 mg; RCT: Randomized controlled trial; S40: Simvastatin 40 mg; S80: Simvastatin 80 mg; STEMI: ST-elevation myocardial infarction; TC: Total cholesterol; TG: Triglycerides; URTI: Upper respiratory tract infection; w/out: Without.

Table 1. Summary of included studies (cont.).

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Study (year), country	F/up [†] (%)	DM (%)	Primary diagnosis	Treatment (n)	Lipid profile			Other outcomes		Reported ADRs	Ref.
					LDL	HDL	TC levels (mmol/l)	TG levels (mmol/l)			
Stein et al. (2003) USA	4.5	NR	HFH	A80 (187) R80 (435)	Mean % change from baseline (SE) R80: -57.90% (0.90) A80: -50.40 (1.20) p < 0.001	Mean % change from baseline (SE) R80: +12.40 (1.00) A80: +2.90 (1.30) p < 0.001	Mean % change from baseline (SE) R80: -46.40 (0.80) A80: -42.10 (1.00) p < 0.001	Mean % change from baseline (SE) R80: -27.80 (1.50) A80: -31.60 (2.00) NS	Mean % change from baseline of Apo B (SE) R80: -50.20 (0.90) A80: -44.40 (1.10) p < 0.001 Mean % change from baseline of Apo A-I (SE) R80: +5.90 (0.90) A80: -2.30 (1.20) p < 0.001	Abdominal pain n (%) R80: 13 (3.00); A80: 2 (1.00) Headache n (%) R80: 7 (2.00); A80: 5 (3.00) Hypertonia n (%) R80: 4 (1.00); A80: 5 (3.00) Insomnia n (%) R80: 10 (2.00); A80: 4 (2.00) Myalgia n (%) R80: 16 (4.00); A80: 5 (3.00) Nausea n (%) R80: 10 (2.00); A80: 1 (<1.00) D/c due to ADRs n (%) R80: 13 (3.00); A80: 4 (2.00)	[42]
STELLAR (2003) USA	1.5	7.0	History of ASCVD	R10 (158) R20 (164) R40 (158) R80 (163) A10 (158) A20 (156) A40 (160) A80 (167) S10 (167) S20 (164) S40 (159) S80 (165) P10 (162) P20 (166) P40 (164)	Mean % change from baseline R20: -52.40 R40: -55.00 A40: -47.80 A80: -51.10 S80: -45.80 A40 vs R20 p < 0.002 A40 vs R40 p < 0.001 A80 vs R20 p = 0.363 A80 vs R40 p = 0.006 S80 vs R20 p < 0.001 S80 vs R40 p < 0.001	Mean % change from baseline R20: +9.50 R40: +9.60 A40: +4.40 A80: +2.10 S80: +6.80 A40 vs R20 p < 0.001 A40 vs R40 p < 0.001 A80 vs R20 p < 0.001 A80 vs R40 p < 0.001	Mean % change from baseline R20: -37.60 R40: -40.20 A40: -35.80 A80: -38.90 S80: -32.90 A40 vs R40 p < 0.001	Mean % change from baseline R20: -23.70 R40: -26.10 A40: -26.80 A80: -28.20 S80: -18.20 NS		Myalgia, % R80: 7.30; A80: 5.40; R40: <2 Increased liver enzymes, n A80: 2; S80: 1 Increased creatine kinase, n R80: 1	[43,44]
p value presented as difference between the groups. †follow-up in months.											
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Table 1. Summary of included studies (cont.).

Study (year), country	F/up [†] (%)	DM (%)	Primary diagnosis	Treatment (n)	Lipid profile			TG levels (mmol/l)	Other outcomes		Reported ADRs	Ref.
					LDL	HDL	Mean % change from baseline		TC levels (mmol/l)	Mean % change from baseline		
CORALL (2005) Netherlands	4.5	100	DM and H.choles.	R40 (131) A80 (131)	Mean % change from baseline R40: -53.60 A80: -47.80 p < 0.001	Mean % change from baseline R40: -1.10 A80: -2.80 NS	Mean % change from baseline R40: -39.60 A80: -36.00 p < 0.05	Mean % change from baseline R40: -22.70 A80: -23.70 NS	Absolute change of ApoA-I g/L from baseline R40: -2.70 A80: -2.10 NS	Mean % change of ApoB from baseline R40: -40.50 A80: -36.30 p < 0.05	Serious ADRs, % R40: 5.00; A80: 2.00 D/c due to ADRs, % R40: 7.00; A80: 8.00 Myalgia, % R40: 5.00; A80: 11.00 Increased liver enzymes, n A80: 1	[45]
Stein et al. (2020) USA	35	32.9	Veteran population regardless of diagnosis	A40: 4,910 A80: 942 R20: 3,342 R40: 823							Overall ADRs, n (%) R20-40: 121 (2.91); A40-80: 269 (4.59); p < 0.05 R20: 112 (3.35); R40: 9 (1.09); p < 0.05 R20: 112 (3.35); A40: 201 (4.09); p < 0.05 A80: 68 (7.22); R40: 9 (1.09); p < 0.05 Increased liver enzymes, n (%) R20-40: 58 (1.39); A40-80: 234 (3.99); p < 0.05 R20: 53 (1.59); R40: 4 (0.49); p < 0.05 A40: 198 (4.03); R20: 53 (1.59); p < 0.05 A80: 36 (3.82); R40: 4 (0.49); p < 0.05 Statin-associated muscle symptoms, n (%) R20-40: 21 (0.50); A40-80: 0; p < 0.05 R20: 21 (0.63); R40: 53 (1.59); p < 0.05 Elevated creatine kinase, n (%) R20-40: 16 (0.38); A40-80: 20 (0.34); NS Overall ADRs, n (%) A80: 68 (7.22); R40: 201 (4.09); p < 0.01 Increased liver enzymes, n (%) A40: 198 (4.03); A80: 36 (3.82) Statin associated muscle symptoms NS in subgroups Elevated creatine kinase NS in subgroups Myalgia, n (%) A40: 56 (1.14); R20: 21 (0.63); p < 0.05 A80: 11 (1.16); R40: 0; p < 0.05	[46]

p value presented as difference between the groups.

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Study (year), country	F /up [†]	DM (%)	Primary diagnosis	Treatment (n)	Lipid profile			TG levels (mmol/l)	Other outcomes	Reported ADRs	Ref.
					LDL	HDL	TC levels (mmol/l)				
CENTAURUS (2010) International	3	18.5	ACS	R20 (437) A80 (450)	Between group differences: NR	Between group differences: NR	Between group differences: NR	Mean % change in from baseline of apoB /apoA-1 R20: -44.40 A80: -44.40 NS	Increased liver enzymes, n (%) R20: 3 (0.70); A80: 10 (2.30) Increased serum creatine, n (%) R20: 1 (0.20); A80: 1 (0.20)	[47]	
CURE-ACS (2013) India	3	35.7	ACS	A40 (116) A80 (120)	Mean % change from baseline A80: -27.50 A40: -19.04 p = 0.024	NS	Mean % change from baseline A80: -15.34 A40: - 10.05 p < 0.05	NS	Myalgia, n A80: 1	[48]	
Marais <i>et al.</i> (2008) USA and South America	1.5	NR	HFH	R80 (22) A80 (22)	Mean % change from baseline (SE) R80: -19.10 (1.90) A80: -18.00 (1.90) p = 0.670	Mean % change from baseline (SE) R80: +2.50 (4.60) A80: - 4.90 (4.60) p = 0.24	Mean % change from baseline (SE) R80: -17.60 (1.60) A80: -17.90 (1.60) p = 0.910	Mean % change from baseline (SE) R80: -6.30 (4.40) A80: -13.90 (4.40) p = 0.21	Mean % change of ApoB from baseline R80: -11.40 (2.00) A80: -11.70 (2.00) p = 0.90 Mean % change of Apo A-I from baseline R80: +4.10 (2.30) A80: -7.50 (4.40) p = 0.001	All ADRs, n R80: 15; A80: 6 Serious ADRs, n R80: 2; A80: 0	[49]
El Saïd <i>et al.</i> (2020) Egypt	6	37.6	Heart failure	A80 (42) R20 (43)	NS				Mean % change of LVEF A40: 20.42 R20: 10.26 p < 0.001 Mean % change of LVEDV: A40: -7.07 R20: -7.20 p = 0.913 Mean % change of LVESV: A40: -16.61 R20: -14.81 p = 0.16 Mean % change of NT pro-BNP: A40: -12.68 R20: -7.74 p = 0.176	Mean % change of liver function tests (AST) from baseline A40: 7.61; R20: 5.00; p = 0.031 Mean % change of liver function tests (ALT) from baseline A40: 12.06; R20: 8.57; p = 0.018	[50]

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Study (year), country	F/up [†] (%)	DM (%)	Primary diagnosis	Treatment (n)	Lipid profile				Other outcomes	Reported ADRs	Ref.
					LDL	HDL	TC levels (mmol/l)	TG levels (mmol/l)			
Hoogerbrugge et al. (1999) Netherlands	3	NR	H.choles.	A40 (40) A80 (40)	Mean % change from baseline A40: -44.00 A80: -50.50 p < 0.050	Mean % change from baseline A40: +6.50 A80: +9.00 NS	Mean % change from baseline A40: -38.50 A80: -44.00 p < 0.05	Mean % change from baseline A40: -34.50 A80: -35.50 NS	Mean % change of ApoB from baseline A40: -46.00 A80: -51.00 p < 0.05		[51]
PRATO-ACS-2 (2020) Italy	12	28.5	Non-STEMI ACS	A40 (354) R20 (355)					Incidence of AKI, n (%): R20: 29 (8.20) A40: 27 (7.60) p = 0.45	All-cause death, n (%) R20: 13 (3.70); A40: 12 (3.40); p = 0.84 Nonfatal MI, n (%) R20: 7 (2.00); A40: 8 (2.30); p = 0.79 Cumulative ADRs, n (%) R20: 20 (5.60); A40: 20 (5.60); p = 0.99	[52]
Analysis of STELLAR (2016) USA	1.5	7.8	Women with H.choles.	R10 (73) R20 (99) R40 (75) A10 (78) A20 (76) A40 (80) A80 (83) S10 (92) S20 (74) S40 (77) S80 (87) P10 (89) P20 (70) P40 (80)	Mean % change from baseline R20: -53.00 R40: -57.00 A40: -47.00 A80: -51.00 S80: -48.00 A40 vs R20 p < 0.002 A40 vs R40 p < 0.002 S80 vs R40 p < 0.002	Mean % change from baseline R20: +9.00 R40: +7.10 A40: +3.10 A80: +1.60 S80: +5.80 A40 vs R20 p < 0.002 A80 vs R20 p < 0.002 A80 vs R240 p < 0.002	Mean % change from baseline R20: -22.00 R40: -25.00 A40: -24.00 A80: -28.00 S80: -21.00			[53]	
Pierri et al. (2016) Italy	1	39.8	CAD undergoing CABG	A40 (111) A80 (101)					Incidence of post operative atrial fibrillation, n (%) A40: 26 (23.60) A80: 16 (16.00) NS	Death, n (%) A40: 3 (2.70); A80: 1 (1.00); All ADRs, n (%) A40: 42 (38.20); A80: 33 (32.70) Bleeding needing surgery revision, n (%) A40: 3 (2.70); A80: 2 (2.00) Perioperative myocardial infarction, n (%) A40: 2 (1.80); A80: 4 (4.00) Renal failure, n (%) A40: 5 (4.50); A80: 4 (4.00) Atrial fibrillation, n (%) A40: 26 (23.60); A80: 16 (15.80)	[54]

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Study (year), country	F/up [†]	DM (%)	Primary diagnosis	Treatment (n)	Lipid profile			Other outcomes	Reported ADRs	Ref.	
					LDL	HDL	TG levels (mmol/l)				
ROMA II (2013) Italy	12	42.5	Stable angina undergoing elective PCI	R40 (175) A80 (175)				Overall incidence of MACCE (%) R40: 11.40% A80: 12.00% NS		[55]	
Schwartz et al. (2004) USA and Canada	6	14.6	H.choles. and a high risk of CHD	A80 (94) R80 (215)	Number of patients who achieved <100 mg/dl at 18 weeks: R20: 92/127 R40: 113/128 A40: 77/127 p = 0.035 R40 vs A40 p < 0.01 At week 24 R80: 215/255 A80: 94/127 p = 0.03	Absolute change from baseline mg/dl R20: -0.50 A40: -1.10 p = 0.8	Absolute change from baseline mg/dl R20: -31.00 A40: -19.00 p = 0.50	Absolute change from baseline mg/dl R20: -61.00 A40: -48.00 p = 0.091	Absolute change in ApoA-I (mg/dl) from baseline R20: +3.00 A40: -2.40 p = 0.18 Absolute change from baseline in ApoB (mg/dl) R20: -36.00 A40: -34.00 p = 0.700 IVUS: NS	Myalgia, n (%) R20-40: 14 (5.50); A40-80: 7 (5.60) Elevated creatine kinase, n R5: 1; R80: 5 Elevated liver enzymes, n R5: 1; R80: 3; A80: 1	[56]
Hong et al. (2011) South Korea	11	24.0	Intermediate coronary stenosis	R20 (65) A40 (63)	Absolute change from baseline mg/dl R20: -60.00 A40: -47.00 p = 0.057						[57]
Khurana et al. (2015) India	1	NR	ACS	A40 (50) R20 (50)	Mean % change from baseline A40: 37.06 R20: 39.16 p = 0.54	Mean % change from baseline A40: 0.78 R20: 0.68 p = 0.24	Mean % change from baseline A40: 2.28 R20: 3.18 p = 0.51	Mean % change from baseline A40: 26.40 R20: 28.36 p = 0.21	Mean % change of CRP from baseline A40: 34.84 R20: 44.54 p = 0.02 Mean % change of ESR from baseline A40: 12.38 R20: 11.50 p = 0.96	Constipation, n (%) A40: 5 (10.00); R20: 4 (8.00) Dyspepsia, n (%) A40: 4 (8.00); R20: 4 (8.00) Abdominal pain, n (%) A40: 1 (2.00); R20: 2 (4.00) Myalgia, n (%) A40: 1 (2.00); R20 (2.00)	[58]
p value presented as difference between the groups. † follow-up in months.											
A10: Atorvastatin 10 mg; A20: Atorvastatin 20 mg; A40: Atorvastatin 40 mg; A80: Atorvastatin 80 mg; ACS: Acute coronary syndrome; ADR: Adverse drug reaction; AKI: Acute kidney injury; AMI: Acute myocardial infarction; ASCVD: Atherosclerotic cardiovascular diseases; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CHD: Coronary heart disease; CI: Confidence interval; CPK: Creatinine phosphokinase; CVD: Cardiovascular disease; D/c: Discontinue; DM: Diabetes mellitus; Ez10: Ezetimibe 10 mg; H.choles: Hypercholesterolemia; HDL: High-density lipoprotein; HFH: Heterozygous familial hypercholesterolemia; IVUS: Intravascular ultrasound; LDL: Low-density lipoprotein; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVEF: Left ventricular end systolic volume; MACCE: Major adverse cardiovascular and cerebrovascular events; MACE: Major adverse cardiac events; MI: Myocardial infarction; NODM: New onset diabetes mellitus; NR: Not reported; NS: Not significantly different; PCI: Percutaneous coronary intervention; PON-1: paraoxonase-1; R10: Rosuvastatin 10 mg; R20: Rosuvastatin 20 mg; R40: Rosuvastatin 40 mg; R80: Rosuvastatin 80 mg; RCT: Randomized controlled trial; S40: Simvastatin 40 mg; S80: Simvastatin 80 mg; STEMI: ST-elevation myocardial infarction; TC: Total cholesterol; TG: Triglycerides; URTI: Upper respiratory tract infection; w/out: Without.											

p value presented as difference between the groups.

[†] follow-up in months.

A10: Atorvastatin 10 mg; A20: Atorvastatin 20 mg; A40: Atorvastatin 40 mg; A80: Atorvastatin 80 mg; ACS: Acute coronary syndrome; ADR: Adverse drug reaction; AKI: Acute kidney injury; AMI: Acute myocardial infarction; ASCVD: Atherosclerotic cardiovascular diseases; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CHD: Coronary heart disease; CI: Confidence interval; CPK: Creatinine phosphokinase; CVD: Cardiovascular disease; D/c: Discontinue; DM: Diabetes mellitus; Ez10: Ezetimibe 10 mg; H.choles: Hypercholesterolemia; HDL: High-density lipoprotein; HFH: Heterozygous familial hypercholesterolemia; IVUS: Intravascular ultrasound; LDL: Low-density lipoprotein; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVEF: Left ventricular end systolic volume; MACCE: Major adverse cardiovascular events; MACCE: Major adverse cardiac events; MI: Myocardial infarction; NODM: New onset diabetes mellitus; NR: Not reported; NS: Not significantly different; PCI: Percutaneous coronary intervention; PON-1: paraoxonase-1; R10: Rosuvastatin 10 mg; R20: Rosuvastatin 20 mg; R40: Rosuvastatin 40 mg; R80: Rosuvastatin 80 mg; RCT: Randomized controlled trial; S40: Simvastatin 40 mg; S80: Simvastatin 80 mg; STEMI: ST-elevation myocardial infarction; TC: Total cholesterol; TG: Triglycerides; URTI: Upper respiratory tract infection; w/out: Without.

Table 1. Summary of included studies (cont.).

Study (year), country	F/up [†]	DM (%)	Primary diagnosis	Treatment (n)	Lipid profile			Other outcomes	Reported ADRs	Ref.
					LDL	HDL	TC levels (mmol/l)			
Illingworth et al. (2001) USA	9	NR	H.choles.	S80 (405) A80 (408)	Mean % change from baseline S80: 48.10 A80: 53.60 p < 0.001	Mean % change from baseline S80: 7.50 A80: 3.00 p < 0.001	Mean % change from baseline S80: 23.60 A80: 31.30 p < 0.001	Mean % change of ApoA-I from baseline S80: 2.50 A80: -3.50 p < 0.001	Clinical ADRs, n (%) S80: 46 (11.90); A80: 92 (23.40) D/c due to ADRs S80: 9 (2.30); A80: 11 (2.80) Gastrointestinal symptoms, n (%) S80: 13 (3.00); A80: 41 (10.00) Elevated liver enzymes, n (%) S80: 2 (0.50); A80: 15 (3.80)	[59]
LUNAR (2012) USA	3	13.7	ACS	R20 (277) R40 (270) A80 (278)	Mean % change from baseline R20: -42.00 R40: -46.80 A80: -42.70 R40 vs A80 p < 0.05	Mean % change from baseline R20: 9.70 R40: 11.90 A80: 5.60 p < 0.001	Mean % change from baseline R20: -28.60 R40: -32.20 A80: -30.90 R20 vs A80 p < 0.05	Mean % change from baseline R20: -46.50 R40: -51.50 A80: -44.50 R40 vs A80 p < 0.001	Any serious ADRs, n (%) R20: 28 (10.50); R40: 23 (8.70); A80: 35 (14.10) Serious cardiovascular events, n (%) R20: 9 (3.40); R40: 5 (1.90); A80: 6 (2.20) d/c due to ADRs, n (%) R20: 10 (3.70); R40: 16 (6.10); A80: 25 (9.30) Myalgia, n (%) R20: 27 (10.10); R40: 24 (9.10); A80: 27 (10.00) Angina pectoris, n (%) R20: 27 (10.10); R40: 23 (8.70); A80: 18 (6.70) Noncardiac chest pain, n (%) R20: 13 (4.90); R40: 22 (8.40); A80: 18 (6.70) Fatigue, n (%) R20: 19 (7.10); R40: 9 (3.40); A80: 12 (4.50) Dizziness, n (%) R20: 6 (2.20); R40: 13 (4.90); A80: 15 (5.60) Headache, n (%) R20: 7 (2.60); R40: 9 (3.40); A80: 16 (5.90) Hypertension, n (%) R20: 15 (5.60); R40: 8 (3.40); A80: 6 (2.20) Increased liver enzymes, n (%) R20: 1 (0.40); R40: 0; A80: 1 (0.40) Elevated creatine kinase, n (%) R20: 0; R40: 1 (0.40); A80: 0	[60]

p value presented as difference between the groups.

[†] follow-up in months.

A10: Atorvastatin 10 mg; A20: Atorvastatin 20 mg; A40: Atorvastatin 40 mg; A80: Atorvastatin 80 mg; ACS: Acute coronary syndrome; ADR: Adverse drug reaction; AKI: Acute kidney injury; AMI: Acute myocardial infarction; ASCVD: Atherosclerotic cardiovascular diseases; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CHD: Coronary heart disease; CI: Confidence interval; CPK: Creatinine phosphokinase; CVD: Cardiovascular disease; D/c: Discontinue; DM: Diabetes mellitus; Ez10: Ezetimibe 10 mg; H.choles: Hypercholesterolemia; HDL: High-density lipoprotein; HFH: Heterozygous familial hypercholesterolemia; IVUS: Intravascular ultrasound; LDL: Low-density lipoprotein; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end systolic volume; MACCE: Major adverse cardiovascular events; MACE: Major adverse cardiac events; MI: Myocardial infarction; NODM: New onset diabetes mellitus; NR: Not reported; NS: Not significantly different; PCI: Percutaneous coronary intervention; PON-1: paraoxonase-1; R10: Rosuvastatin 10 mg; R20: Rosuvastatin 20 mg; R40: Rosuvastatin 40 mg; R80: Rosuvastatin 80 mg; RCT: Randomized controlled trial; S40: Simvastatin 40 mg; S80: Simvastatin 80 mg; STEMI: ST-elevation myocardial infarction; TC: Total cholesterol; TG: Triglycerides; URTI: Upper respiratory tract infection; w/out: Without.

Table 1. Summary of included studies (cont.).

Table 1. Summary of included studies (cont.).											
Study (year), country	F/up [†]	DM (%)	Primary diagnosis	Treatment (n)	Lipid profile			Other outcomes		Reported ADRs	Ref.
					LDL	HDL	TC levels (mmol/l)	TG levels (mmol/l)			
Karalis <i>et al.</i> (2002) USA	1.5	0.0	H.choles, with or w/out CHD	A10 (629) S20 (641) A80 (207) S80 (207)	Mean % change from baseline A80: -53.00 S80: -47.00 p < 0.001	Mean % change from baseline A80: 2.00 S80: 6.00 p < 0.001	Mean % change from baseline A80: -28.00 S80: -23.00 p < 0.025	Mean % change from baseline A80: -40.00 S80: -38.00 p < 0.001	Mean % change of Apo-B from baseline A80: -44.00 S80: -38.00 p < 0.001	Overall ADRs, % A80: 46.00; S80: 39.00 d/c due to ADRs, % A80: 8.00; S80: 5.00 Increased liver enzymes, n (%) A80: 2 (1.00); S80: 2 (1.00) Increased creatine kinase, n (%) A80: 0; S80: 2 (1.00%)	[61]
Jacobs <i>et al.</i> (2019) USA	11	NR	Atorvastatin- naïve veterans	A80 (103) A40 (102)	Mean % change from baseline A80: -19.90 A40: -13.60 p = 0.24	Mean % change from baseline A80: -1.40 A40: -2.60 p = 0.5	Mean % change from baseline A80: -26.20 A40: -16.10 p = 0.100	Mean % change from baseline A80: -25.80 A40: -2.20 p = 0.14	Mean % change from baseline A80: -26.61 p = 0.349 Mean % change of Chemerin from baseline A80: -42.79 R40: -56.08 p = 0.65 Mean % change of galectin-3 from baseline A80: 0.88 R40: -16.23 p = 0.071	Myalgia, n (%) A80: 11 (11.00); A40: 7 (7.00) Weakness, n (%) A80: 12 (12.00); A40: 9 (9.00) Myopathy, n (%) A80: 0; A40: 1 (1.00) d/c due to ADRs, n (%) A80: 5 (26.00); A40: 2 (15.00)	[62]
Tunçtez <i>et al.</i> (2019) Turkey	1	17.7	AMI	A80 (33) R40 (30)	Mean % change from baseline A80: -39.00 R40: -47.00 p = 0.091	Mean % change from baseline A80: 2.30 R40: 5.30 p = 0.470	Mean % change from baseline A80: -22.00 R40: -30.00 p = 0.101	Mean % change from baseline A80: 1.81 R40: -15.05 p = 0.335	Mean % change of Endocan from baseline A80: -7.96 R40: -26.61 p = 0.349 Mean % change of Chemerin from baseline A80: -42.79 R40: -56.08 p = 0.65 Mean % change of galectin-3 from baseline A80: 0.88 R40: -16.23 p = 0.071		[63]
ECLIPSE (2008) Canada and Europe	6	35.7	H.choles, and a history of CHD or high risk of CHD	A80 (514) R40 (522)	Mean % change from baseline R40: -57.30 A80: -52.20 p < 0.001	Mean % change from baseline R40: +8.40 A80: 1.80 p < 0.001	Mean % change from baseline R40: -41.30 A80: -39.50 p < 0.05	Mean % change from baseline R40: -24.60 A80: -28.00 NS	Mean % change of ApoB from baseline R40: -46.10 A80: -43.50 p < 0.01 Mean % change of Apo A-I from baseline R40: +4.30 A80: -2.00 p < 0.001	Any ADR, n (%) R40: 282 (53.70); A80: 270 (52.50) Serious ADRs, n (%) R40: 0; A80: 2 (0.40%) Increased liver enzymes, n (%) R40: 2 (0.40); A80: 4 (0.80%)	[64]
p value presented as difference between the groups. † follow-up in months. A10: Atorvastatin 10 mg; A20: Atorvastatin 20 mg; A40: Atorvastatin 40 mg; A80: Atorvastatin 80 mg; ACS: Acute coronary syndrome; ADR: Adverse drug reaction; AKI: Acute kidney injury; AMI: Acute myocardial infarction; ASCVD: Atherosclerotic cardiovascular diseases; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CHD: Coronary heart disease; CI: Confidence interval; CPK: Creatinine phosphokinase; CVD: Cardiovascular disease; D/c: Discontinue; DM: Diabetes mellitus; Ez10: Ezetimibe 10 mg; H.choles: Hypercholesteremia; HDL: High-density lipoprotein; HFH: Heterozygous familial hypercholesteremia; IVUS: Intravascular ultrasound; LDL: Low-density lipoprotein; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end systolic volume; MACCE: Major adverse cardiovascular and cerebrovascular events; MACCE: Major adverse cardiac events; MI: Myocardial infarction; NODM: New onset diabetes mellitus; NR: Not reported; NS: Not significantly different; PCI: Percutaneous coronary intervention; PON-1: paraoxonase-1; R10: Rosuvastatin 10 mg; R20: Rosuvastatin 20 mg; R40: Rosuvastatin 40 mg; R80: Rosuvastatin 80 mg; RCT: Randomized controlled trial; S40: Simvastatin 40 mg; S80: Simvastatin 80 mg; STEMI: ST-elevation myocardial infarction; TC: Total cholesterol; TG: Triglycerides; URTI: Upper respiratory tract infection; w/out: Without.											

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[†] follow-up in months.

A10: Atorvastatin 10 mg; A20: Atorvastatin 20 mg; A40: Atorvastatin 40 mg; A80: Atorvastatin 80 mg; ACS: Acute coronary syndrome; ADR: Adverse drug reaction; AKI: Acute kidney injury; AMI: Acute myocardial infarction; ASCVD: Atherosclerotic cardiovascular diseases; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CHD: Coronary heart disease; CI: Confidence interval; CPK: Creatinine phosphokinase; CVD: Cardiovascular disease; D/c: Discontinue; DM: Diabetes mellitus; Ez10: Ezetimibe 10 mg; H.choles: Hypercholesterolemia; HDL: High-density lipoprotein; HFH: Heterozygous familial hypercholesterolemia; IVUS: Intravascular ultrasound; LDL: Low-density lipoprotein; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end systolic volume; MACCE: Major adverse cardiovascular and cerebrovascular events; MACE: Major adverse cardiac events; MI: Myocardial infarction; NODM: New onset diabetes mellitus; NR: Not reported; NS: Not significantly different; PCI: Percutaneous coronary intervention; PON-1: paraoxonase-1; R10: Rosuvastatin 10 mg; R40: Rosuvastatin 40 mg; R80: Rosuvastatin 80 mg; RCT: Randomized controlled trial; S40: Simvastatin 40 mg; S80: Simvastatin 80 mg; STEMI: ST-elevation myocardial infarction; TC: Total cholesterol; TG: Triglycerides; URTI: Upper respiratory tract infection; w/out: Without.

Table 1. Summary of included studies (cont.).

Study (year), country	F/up [†]	DM (%)	Primary diagnosis	Treatment (n)	Lipid profile				Other outcomes	Reported ADRs	Ref.
					LDL	HDL	TC levels (mmol/l)	TG levels (mmol/l)			
analysis of RADAR study (2007) The Netherlands	4.5	16.2	established CVD and HDL <40 mg/dL	R40 (34) A80 (34)	Absolute change from baseline, mmol/l R40: -2.10 A80: -2.00 p = 0.480	Absolute change from baseline, mmol/l R40: 0.10 A80: 0.10 p = 0.95	Absolute change from baseline, mmol/l R40: -2.70 A80: -2.40 p = 0.450	Absolute change from baseline, mmol/l R40: -0.90 A80: -1.40 p = 0.28	Absolute change of PON-1 activity from baseline, U/L R40: 6.39 A80: 1.84 p = 0.11		[65]
CHESS (2003) NR	6	11.5	H.choles.	S80 (453) A80 (464)	Mean % change from baseline S80: -45.50 A80: -53.50 p < 0.001	Mean % change from baseline S80: 8.30 A80: 4.30 p < 0.001	Mean % change from baseline S80: -25.80 A80: -34.10 p < 0.001	Mean % change from baseline S80: -25.80 A80: -34.10 p < 0.001	Mean % change of ApoA-1 from baseline S80: 3.70 A80: -1.40 p < 0.001	Clinical ADRs, n (%) S80: 67 (14.80); A80: 85 (18.30) d/c due to ADRs, n (%) S80: 12 (2.60); A80: 28 (6.00) Diarrhea, % S80: 1.30; A80: 3.00 Constipation, % S80: 1.30; A80: 1.50 Nausea, % S80: 1.80; A80: 0.90	[66]
Ciucanu <i>et al.</i> (2020) Romania	1	0.0	H.choles.	R5 (16) R10 (16) R20 (16) R40 (16)	Mean % change from baseline R20: -52.20 R40: -56.00 p < 0.01	Mean % change from baseline R20: +8.60 R40: +9.60 p = 0.06	Mean % change from baseline R20: -38.10 R40: -41.80 p = 0.070	Mean % change from baseline R20: -20.40 R40: -22.70 p < 0.05	Mean % change of ApoB from baseline R20: -45.30 R40: -48.90 p < 0.050 Mean % change from baseline of ApoA-1 R20: +5.40 R40: +6.60 p < 0.01 Mean % change from baseline of free fatty acids R20: -21.20 R40: -23.30 p < 0.05 Mean % change from baseline of total fatty acids R20: -30.44 R40: -33.40 p < 0.05		[67]

p value presented as difference between the groups.

† follow-up in months.

A10: Atorvastatin 10 mg; A20: Atorvastatin 20 mg; A40: Atorvastatin 40 mg; A80: Atorvastatin 80 mg; ACS: Acute coronary syndrome; ADR: Adverse drug reaction; AKI: Acute kidney injury; AMI: Acute myocardial infarction; ASCVD: Atherosclerotic cardiovascular diseases; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CHD: Coronary heart disease; CI: Confidence interval; CPK: Creatinine phosphokinase; CVD: Cardiovascular disease; D/c: Discontinue; DM: Diabetes mellitus; Ez10: Ezetimibe 10 mg; H.choles: Hypercholesterolemia; HDL: High-density lipoprotein; HFH: Heterozygous familial hypercholesterolemia; IVUS: Intravascular ultrasound; LDL: Low-density lipoprotein; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end systolic volume; MACCE: Major adverse cardiovascular events; MACE: Major adverse cardiac events; MI: Myocardial infarction; NODM: New onset diabetes mellitus; NR: Not reported; NS: Not significantly different; PCI: Percutaneous coronary intervention; PON-1: paraoxonase-1; R10: Rosuvastatin 10 mg; R20: Rosuvastatin 20 mg; R40: Rosuvastatin 40 mg; R80: Rosuvastatin 80 mg; RCT: Randomized controlled trial; S40: Simvastatin 40 mg; S80: Simvastatin 80 mg; STEMI: ST-elevation myocardial infarction; TC: Total cholesterol; TG: Triglycerides; URTI: Upper respiratory tract infection; w/out: Without.

Table 1. Summary of included studies (cont.).

Study (year), country	F/up [†]	DM (%)	Primary diagnosis	Treatment (n)	Lipid profile				Other outcomes	Reported ADRs	Ref.	
					LDL	HDL	TC levels (mmol/l)	TG levels (mmol/l)				
Altunkeser et al. (2019) Turkey	1	24.6	ACS	A80 (53) R40 (53)	Mean % change from baseline A80: 39.54 R40: 43.82 p = 0.245	Mean % change from baseline A80: +6.48 R40: +10.21 p = 0.283	Mean % change from baseline A80: 27.49 R40: 30.02 p = 0.371	Mean % change from baseline A80: 13.06 R40: 12.75 p = 0.961			[68]	
Thongtang et al. (2011) USA	1.5	7.5	H.choles.	A80 (135) R40 (137)	Mean % change from baseline A80: -50.00 R40: -52.00 p = 0.013	Mean % change from baseline A80: -39.00 R40: -41.00 p = 0.137	Mean % change from baseline A80: -29.00 R40: -28.00 p = 0.774				[69]	
SATURN (2011) International	26	15.3	Patients undergoing coronary angiography	A80 (519) R40 (520)	levels mg/dl (SD) at baseline A80: 119.90 (28.90) R40: 120.00 (27.30) levels mg/dl (SD) after treatment A80: 70.20 (1.00) R40: 62.60 (1.00) p < 0.001	levels mg/dl (SD) at baseline A80: 44.70 (10.70) R40: 45.30 (11.80) levels mg/dl (SD) after treatment A80: 48.60 (0.50) R40: 50.40 (0.50) p = 0.01	levels mg/dl (SD) at baseline A80: 193.50 (34.20) R40: 193.90 (34.10) levels mg/dl (SD) after treatment A80: 144.10 (1.20) R40: 139.40 (1.20) p < 0.006	levels mg/dl median (IQR) at baseline A80: 130.00 (97.00–177.00) R40: 128.00 (91.00–181.00) levels mg/dl (SD) after treatment A80: 75.10 (0.90) R40: 72.50 (0.90) p = 0.03	% atheroma volume after treatment A80: 34.90 R40: 35.40 p = 0.64 levels of ApoB after treatment, mg/dl (SD) A80: 75.10 (0.90) R40: 72.50 (0.90) p = 0.03 Levels of ApoA-I after treatment, mg/dl (SD) A80: 137.70 (1.00) R40: 146.80 (1.00) p < 0.001	Death from cardiovascular event, n (%) A80: 2 (0.30); R40: 2 (0.30) Nonfatal MI, n (%) A80: 11 (1.60); R40: 11 (1.60) Nonfatal stroke, n (%) A80: 2 (0.30); R40: 3 (0.40) Hospitalization for unstable angina, n (%) A80: 13 (1.90); R40: 16 (2.30) Arterial revascularization, n (%) A80: 41 (6.00); R40: 42 (6.10) First major adverse cardiovascular event, n (%) A80: 49 (7.10); R40: 52 (7.50) d/c due to ADR, n (%) A80: 48 (7.00); R40: 45 (6.50)		[70]
NASDAC (2004) USA	2	16.3	H.choles.	A10 (229) A20 (228) A40 (231) A80 (231)	Mean % change from baseline A80: -52.20 A40: -48.60 p < 0.01	Mean % change from baseline A80: 2.30 A40: 4.20 P: NR	Mean % change from baseline A80: -36.20 A40: -28.80 P: NR	Mean % change of ApoB from baseline A80: -44.60 A40: -40.70 P: NR	Any ADR, n (%) A80: 38 (16.50); A40: 26 (11.30) d/c due to ADR, n (%) A80: 7 (3.00); A40: 5 (2.20) Elevated liver enzymes, n (%) A80: 2 (0.90); A40: 2 (0.90)		[71]	
p value presented as difference between the groups. [†] follow-up in months.												
A10: Atorvastatin 10 mg; A20: Atorvastatin 20 mg; A40: Atorvastatin 40 mg; A80: Rosuvastatin 80 mg; ACS: Acute coronary syndrome; ADR: Adverse drug reaction; AKI: Acute kidney injury; AMI: Acute myocardial infarction; ASCVD: Atherosclerotic cardiovascular diseases; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CHD: Coronary heart disease; CI: Confidence interval; CPK: Creatinine phosphokinase; CVD: Cardiovascular disease; D/c: Discontinue; DM: Diabetes mellitus; Ez10: Ezetimibe 10 mg; H.choles: Hypercholesterolemia; HDL: High-density lipoprotein; HFH: Heartzorgous familial hypercholesterolemia; IVUS: Intravascular ultrasound; LDL: Low-density lipoprotein; LVEDV: Left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end systolic volume; MACCE: Major adverse cardiovascular and cerebrovascular events; MACE: Major adverse cardiac events; MI: Myocardial infarction; NODM: New onset diabetes mellitus; NR: Not reported; NS: Not significantly different; PCI: Percutaneous coronary intervention; PON-1: paraoxonase-1; R10: Rosuvastatin 10 mg; R20: Rosuvastatin 20 mg; R40: Rosuvastatin 40 mg; R80: Rosuvastatin 80 mg; RCT: Randomized controlled trial; S40: Simvastatin 40 mg; S80: Simvastatin 80 mg; STEMI: STElevation myocardial infarction; TC: Total cholesterol; TG: Triglycerides; URTI: Upper respiratory tract infection; w/out: without.												

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the other studies, showing significance, were RCTs and used a larger sample size. The GRAVITY study compared S80+Ez10 to R20+Ez10 in patients with ASCVD risk >20% and reported a significant reduction in LDL, TG, and TC and a significant HDL increase in the rosuvastatin group compared with simvastatin after three months of follow-up [34]. The results were consistent when R20 and R40 were each compared with S80 monotherapy as presented by the STELLAR study [43,45].

Upon comparing different high-intensity doses of the same agent, Rahal *et al.* [28] compared different dosing of high-intensity atorvastatin, i.e., A80 versus A40, but found no significant difference in the proportion of patients who achieved the LDL target of <70 mg/dl over one year. However, this non-significance could be due to having a significantly higher LDL baseline in the A80 group. Nonetheless, the number of patients who achieved >50% reduction in LDL levels was lower in the A40 group compared with A80 (15.2% vs 21.2%, $p = 0.022$). Hoogerbrugge *et al.* [51], the NASDAC [71] and the CURE-ACS [48] studies, compared the same doses of atorvastatin in patients with hypercholesteremia and found a significant effect on LDL and TC, with A80 compared with A40, indicating a dose-dependent response. On the contrary, Agrawal *et al.* [35] showed no significant percentage change from baseline of LDL, HDL, and TG, with A80 compared with A40, which could be due to having higher baseline LDL levels compared with the other studies. This non-significance can also be due to patients taking other medications as this was not highlighted in the baseline characteristics of the included patients.

Upon looking at the variabilities with rosuvastatin dosing, Betto *et al.* [29] compared the different dosing of rosuvastatin, i.e., R10, R20, and R40, through an observational cohort study. Considering the high-intensity dosing in this review, over six weeks, the study showed no significance in the number of patients who achieved the LDL level targeted by the physicians at the beginning of the study. However, this indicated a difference in the mean percent change among the different dosing groups, with the highest change observed in the R40, followed by R20 and R10, i.e., -47.4%, -36.8%, -31.4%, respectively, $p = 0.39$. When the same comparison was investigated in an RCT; a statistically significant difference was observed indicating a dose-dependent response in all lipid parameters (LDL, TG, TC, HDL) [67].

When comparing atorvastatin to rosuvastatin, Schneck *et al.* [32] compared these statins with matched dosing among 374 patients with hypercholesteremia over 6 weeks. Overall, the study found consistently higher effectiveness with rosuvastatin in improving lipid profile readings compared with atorvastatin of the corresponding dosing. While the tolerability was similar between the two statins. The POLARIS study [33] which focused on high-risk patients found a higher percentage decrease in LDL and TG among the patients who received R40 compared with those who received A80. Additionally, HDL change was significantly higher in the R40 group after 6.5 months of follow-up. Within one month of follow-up Aydin *et al.* [36] and Kilit *et al.* [38] found no difference between A80 versus R20, and A80 versus R40, among patients with STEMI and AMI, respectively; but both groups showed a significant decrease of LDL >50% from baseline [(52% vs 52% $p = 0.90$), $(-76 \pm 36, -65 \pm 34, p = 0.277)$, respectively]. Hong *et al.* [57] showed R20 to be more effective than A40 in lowering LDL and TC after 11 months of follow-up. However, when the follow-up was one month no difference was found between these two doses [58]. These findings suggest that a longer observation time is needed to prove the benefit of one dose over the other. The studies that compared R40 to A80 and presented the LDL % change from baseline, with standard deviation, were pooled into a meta-analysis [Figure 2](#), which demonstrated an overall greater effect of R40 on LDL levels compared with A80 [mean difference (confidence interval) 4.71 (3.14 – 6.01), overall effect $Z = 7.08, p < 0.001$]. Although the studies included in the meta-analysis are different in the follow-up period and population, the overall benefit of rosuvastatin did not change upon performing the sensitivity analysis. All studies included in the meta analysis had different population groups, except for two studies that focused on ACS. Hence a subgroup analysis was conducted for the ACS group, which are presented in [Supplementary File 3](#). The subgroup analysis reflect similar outcome where R40 is favored over A80 in patients with ACS.

Surprisingly few studies used a much higher dose of rosuvastatin R80 as a comparator, which is a dose not commonly recommended by guidelines. Two studies concluded a better effect of R80 in improving LDL, HDL, and TC after 4.5 and 6 months of follow-up compared with A80 [42,56]. However, another study showed no significance in any of the lipid readings after one and a half months of follow-up; nonetheless, the rate of adverse effects was higher in R80 in all studies [42,49,56].

The STELLAR study compared multiple statin doses to rosuvastatin and showed significance with R40, when compared with A40 and A80, in the percentage reduction of LDL (-55.0 vs -47.8 and vs -51.1, $p < 0.002$ and $p < 0.001$ respectively) [43,45]. This effect was consistent even when a subgroup analysis was done among women [53].

Other outcomes

Cardiovascular-associated death, non-fatal ACS, and non-fatal stroke were compared between A40 and A80 in patients with ACS and were insignificant at one month follow-up and remained insignificant after one year [28]. Similarly, when major adverse cardiovascular events (MACE) were investigated, high-intensity R20 and A40–80 showed no significant difference after three years of follow-up among patients with MI [30]. On the other hand, Li *et al.* [40] compared MACE between A40 and A80 groups after emergency PCI at one month, six months, and 12 months, postoperatively. They found significance at six and 12 months with A80 being more protective than A40. Most studies did not compare the adverse events statistically but only presented the number of patients who experienced a specific event. Nonetheless, most adverse events were higher in the higher doses of statins indicating an expected dose-related effect.

Quality assessment

The overall average was 81% with a range of 60–93%. A total of 18 studies scored 85% or more indicating good quality. Because of the limited number of included studies, all articles were included in the systematic review if they satisfy the inclusion criteria regardless of their quality. Detailed scoring for the quality assessment of individual articles are included in [Supplementary File 4](#).

Discussion

Understanding which high-intensity statin can provide better protection against ASCVD can help clinicians in decision making, especially in patients who are at high risk of ASCVD. Thus, this systematic review was conducted to compare the effectiveness of high-intensity statins particularly in lowering LDL-C levels. The pooled analysis showed a significant advantage of rosuvastatin 40 mg over atorvastatin 80 mg, based on the six RCTs included in the meta-analysis. The results of this review are consistent with previous reviews that compared rosuvastatin to atorvastatin and proved, through pooled analysis, the advantage of rosuvastatin over atorvastatin even at lower doses than those typically used as moderate intensity dosing [20,72–74]. In line with the VOYAGER review, rosuvastatin can achieve higher LDL reduction even at lower doses to that of atorvastatin, which is an observation that was also confirmed in this review. This further confirms that high intensity statins are not equipotent even at similar dosing categorization (i.e., high intensity). In addition to its advantage in reducing LDL levels, Kumar *et al.* concluded that rosuvastatin is more effective in lowering the percentage of atheroma volume and total atheroma volume, which can be considered as indicators of atherosclerotic diseases, as compared with atorvastatin [72]. Also, Ma *et al.* favored rosuvastatin over atorvastatin in reducing C-reactive protein, which is considered a major biomarker for predicting cardiovascular events [73]. Additionally, the safety profile of the high-intensity statins was similar and, as expected, the rate of adverse effects correlated with the dosing where higher rates of adverse events were observed when higher doses are used. Few studies included S80 as a comparator, where its effect in reducing LDL was not as strong as with other high-intensity statins, and the rate of side effects was higher in the S80 group, further supporting the AHA/ACC guidelines in not to include the S80 in the high-intensity group [13,75].

Although a statistically significant effect was favoring rosuvastatin in this review, the question about whether this difference is of clinical significance remains, since all high-intensity statins reduce the LDL levels by $\geq 50\%$, which is the recommended decrease for primary and secondary prevention of ASCVD [75]. Nonetheless, a follow-up review, which used the VOYAGER data, showed the superiority of rosuvastatin over atorvastatin in reducing the risk of major vascular events among patients with known ASCVD [76]. Therefore, a study that looks at the cardiovascular outcomes as end points when comparing high-intensity statins can further guide the clinicians' decisions, especially toward ASCVD primary prevention. This is especially important since the LDL concentration is only considered a surrogate end point for evaluating the effect of the medication and cardiovascular diseases. In this review, only three studies included cardiovascular outcomes as primary observations [28,30,40]. Two of these studies compared A40 and A80, while one study compared atorvastatin to rosuvastatin. Therefore, more studies are needed with longer follow-up duration to prove the clinical significance of rosuvastatin over atorvastatin.

To note, RCTs reported a statistical difference between the included groups, while no difference was detected in the observational studies. RCTs are always considered higher in the research hierarchy of evidence than observational studies [77], yet observation studies can provide real-world data. Many factors can be contributing to this observation, such as having confounding factors influencing the outcome, including taking other medications or having other comorbidities. Therefore, a large observational study with a large sample size covering a variety of patient characteristics can add further confirmation to the detected difference between the high-intensity dosing [78].

Limitations

Several limitations in this review need to be acknowledged. Although the study had a robust methodology, there remains the possibility that additional relevant studies were missed, especially since we only included studies published in English. While we believe that the use of MeSH terms, multiple databases and grey literature would capture the targeted literature, it is always possible that relevant references may have been missed. The calculated percentage difference and its standard deviation are underestimated due to the small number of papers that were included in the meta-analysis. Additionally, it was difficult to statistically estimate how statins affected different populations because results of primary studies were not reported in a systematic approach. This highlights the need for a standardized reporting in these effectiveness studies to be able to compare and generalize findings. Additionally, the interpretation of the results is limited by the short-term duration of the included studies. Longer follow-up studies are needed to see if the medication effect is maintained over extended durations. Finally, the analysis mainly focused on LDL levels and not cardiovascular-related outcomes. Nonetheless, LDL is considered a valid and reliable surrogate marker, and many literature studies, as well as guidelines, report the strong relationship between LDL and cardiovascular-related events [13,19,75,79].

Conclusion

In summary, this systematic review further confirms that the high-intensity statins atorvastatin and rosuvastatin can reduce LDL by $\geq 50\%$, relative to baseline. The results of the meta-analysis confirm the favorable effectiveness of high-intensity rosuvastatin over high-intensity atorvastatin in lowering LDL, even at lower doses, and with a similar rate of adverse events. Additional data are needed to confirm the clinical significance of cardiovascular outcomes using real-world studies.

Summary points

- This Systematic Review was conducted to summarize the effectiveness of high-intensity statins.
- Statins classified as high intensity are not equipotent at similar dosing, yet they all reduce lipoprotein cholesterol from baseline by $\geq 50\%$.
- Based on six randomized controlled trial pooled analysis showed a significant advantage of rosuvastatin 40 mg over atorvastatin 80 mg in improving lipid profile.
- Similar adverse effects were observed across the high intensity statins.
- Adverse effects rates were higher when higher dosing is used.
- Studies should standardize their outcome reporting. Only six studies were pooled into quantitative analysis due to the differences in outcome reporting of studies which did not allow for more studies to be included in the meta analysis. Therefore, studies should standardize their outcome reporting.
- Statistical difference was observed in randomized clinical trials but not observational studies, highlighting the need for larger real world observational studies to confirm clinical significance.
- Future studies should investigate cardiovascular outcomes as end points when comparing high-intensity statins.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/cer-2022-0163>

Author contributions

All authors had substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial & competing interests disclosure

The study received a research fund from Qatar University, grant no. QUST-1-CPH-2021-8. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

1. World Health Organization. Cardiovascular diseases (2021). Available from: www.who.int/health-topics/cardiovascular-diseases#tab=tab.1 (Accessed: 1 September 2022).
2. Abushanab D, Al-Badriyeh D, Marquina C *et al.* A systematic review of cost-effectiveness of non-statin lipid-lowering drugs for primary and secondary prevention of cardiovascular disease in patients with type 2 diabetes mellitus. *Curr. Probl. Cardiol.* doi: 10.1016/j.cpcardiol.2022.101211 (2022).
3. Talic S, Marquina C, Zomer E *et al.* Attainment of low-density lipoprotein cholesterol goals in statin treated patients: Real-world evidence from Australia. *Curr. Probl. Cardiol.* 47(7), 101068 (2022).
4. Pedersen TR, Kjekshus J, Berg K *et al.* Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 344(8934), 1383–1389 (1994).
5. Long-Term Intervention with Pravastatin in Ischaemic Disease (Lipid) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N. Engl. J. Med.* 339(19), 1349–1357 (1998).
6. Amarenco P, Bogousslavsky J, Callahan A 3rd *et al.* High-dose atorvastatin after stroke or transient ischemic attack. *N. Engl. J. Med.* 355(6), 549–559 (2006).
7. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J. Am. Coll. Cardiol.* 48(3), 438–445 (2006).
8. Fulcher J, O'connell R, Voysey M *et al.* Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 385(9976), 1397–1405 (2015).
9. Grundy SM, Stone NJ, Bailey AL *et al.* 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* 73(24), 3168–3209 (2019).
10. Mills EJ, O'regan C, Eyawo O *et al.* Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients. *Eur. Heart J.* 32(11), 1409–1415 (2011).
11. Cannon CP, Braunwald E, McCabe CH *et al.* Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N. Engl. J. Med.* 350(15), 1495–1504 (2004).
12. Larosa JC, Grundy SM, Waters DD *et al.* Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N. Engl. J. Med.* 352(14), 1425–1435 (2005).
13. Stone NJ, Robinson JG, Lichtenstein AH *et al.* 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J. Am. Coll. Cardiol.* 63(25 Pt B), 2889–2934 (2014).
14. Rodriguez F, Lin S, Maron DJ, Knowles JW, Virani SS, Heidenreich PA. Use of high-intensity statins for patients with atherosclerotic cardiovascular disease in the Veterans Affairs Health System: practice impact of the new cholesterol guidelines. *Am. Heart J.* 182, 97–102 (2016).
15. Pokharel Y, Tang F, Jones PG *et al.* Adoption of the 2013 American College of Cardiology/American Heart Association Cholesterol Management Guideline in Cardiology Practices Nationwide. *JAMA Cardiol.* 2(4), 361–369 (2017).
16. Tran JN, Kao TC, Caglar T *et al.* Impact of the 2013 Cholesterol Guideline on Patterns of Lipid-Lowering Treatment in Patients with Atherosclerotic Cardiovascular Disease or Diabetes After 1 Year. *J. Manag. Care Spec. Pharm.* 22(8), 901–908 (2016).
17. Giustino G, Colantonio LD, Brown TM *et al.* Titration to high-intensity statin therapy following acute myocardial infarction in patients with and without diabetes mellitus. *Cardiovasc. Drugs Ther.* 32(5), 453–461 (2018).
18. National Institute for Health and Care Excellence. Lipid modifying drugs. Available from: www.nice.org.uk/guidance/ktt3 (2015 [updated 2019]).
19. Meek CL, Reston JD, Ramsbottom T, Pathmanathan H, Viljoen A. Use of high-intensity statin therapy with simvastatin 80 mg and atorvastatin 80 mg in primary care. *Int. J. Clin. Pract.* 65(2), 120–126 (2011).
20. Karlson BW, Wiklund O, Palmer MK, Nicholls SJ, Lundman P, Barter PJ. Variability of low-density lipoprotein cholesterol response with different doses of atorvastatin, rosuvastatin, and simvastatin: results from VOYAGER. *Eur. Heart J. Cardiovasc. Pharmacother.* 2(4), 212–217 (2016).
- Summarizes the extent of the variability in LDL-C reduction in response to treatment across the recommended doses of different statins regardless of intensity.
21. Moorman JM, Boyle J, Bruno L *et al.* Utilization of high-intensity statins in patients at risk for cardiovascular events: a national cross-sectional study. *Am. J. Ther.* 29(1), e1–e17 (2020).
22. Page MJ, McKenzie JE, Bossuyt PM *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372, n71 (2021).

23. Higgins JPT, Thomas J, Chandler J *et al.* (Eds). *Cochrane Handbook for Systematic Reviews of Interventions. Version 6.2.* Cochrane (2021). Available from: www.training.cochrane.org/handbook
24. Crowe M, Sheppard L. A general critical appraisal tool: an evaluation of construct validity. *Int. J. Nurs. Stud.* 48(12), 1505–1516 (2011).
25. Crowe M, Sheppard L, Campbell A. Reliability analysis for a proposed critical appraisal tool demonstrated value for diverse research designs. *J. Clin. Epidemiol.* 65(4), 375–383 (2012).
26. Crowe M, Sheppard L, Campbell A. Comparison of the effects of using the Crowe Critical Appraisal Tool versus informal appraisal in assessing health research: a randomised trial. *Int. J. Evid. Based Healthc.* 9(4), 444–449 (2011).
27. Review Manager (RevMan)[Computer program]. Version 5.4. The Cochrane Collaboration (2020). <https://training.cochrane.org/online-learning/core-software/revman>
28. Rahhal A, Khir F, Aljundi AH *et al.* Clinical outcomes of high-intensity doses of atorvastatin in patients with acute coronary syndrome: a retrospective cohort study using real-world data. *Br. J. Clin. Pharmacol.* 87(4), 2043–2052 (2021).
29. Betto M, Fares J, Saliba N, Ballout H. Efficacy and safety of a generic rosuvastatin in a real-world setting: prospective, observational clinical study in Lebanese patients. *Ann. Saudi Med.* 37(5), 366–374 (2017).
30. Choi JY, Choi CU, Choi BG *et al.* New onset diabetes mellitus and cardiovascular events in Korean patients with acute myocardial infarction receiving high-intensity statins. *BMC Pharmacol. Toxicol.* 22(1), 11 (2021).
31. Roy D, Mahapatra T, Manna K *et al.* Comparing effectiveness of high-dose Atorvastatin and Rosuvastatin among patients undergone Percutaneous Coronary Interventions: a non-concurrent cohort study in India. *PLoS One* 15(5), e0233230–e0233230 (2020).
32. Schneck DW, Knopp RH, Ballantyne CM, McPherson R, Chitra RR, Simonson SG. Comparative effects of rosuvastatin and atorvastatin across their dose ranges in patients with hypercholesterolemia and without active arterial disease. *Am. J. Cardiol.* 91(1), 33–41 (2003).
33. Leiter LA, Rosenson RS, Stein E *et al.* Efficacy and safety of rosuvastatin 40 mg versus atorvastatin 80 mg in high-risk patients with hypercholesterolemia: results of the POLARIS study. *Atherosclerosis* 194(2), e154–e164 (2007).
34. Ballantyne CM, Hoogeveen RC, Raya JL, Cain VA, Palmer MK, Karlson BW. Efficacy, safety and effect on biomarkers related to cholesterol and lipoprotein metabolism of rosuvastatin 10 or 20 mg plus ezetimibe 10 mg vs. simvastatin 40 or 80 mg plus ezetimibe 10 mg in high-risk patients: results of the GRAVITY randomized study. *Atherosclerosis* 232(1), 86–93 (2014).
35. Agrawal D, Manchanda SC, Sawhney JPS *et al.* To study the effect of high dose Atorvastatin 40 mg versus 80 mg in patients with dyslipidemia. *Indian Heart J.* 70(Suppl. 3), S8–S12 (2018).
36. Aydin MU, Aygul N, Altunkeser BB, Unlu A, Taner A. Comparative effects of high-dose atorvastatin versus moderate-dose rosuvastatin on lipid parameters, oxidized-LDL and inflammatory markers in ST elevation myocardial infarction. *Atherosclerosis* 239(2), 439–443 (2015).
37. De Zeeuw D, Anzalone DA, Cain VA *et al.* Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial. *Lancet Diabetes Endocrinol.* 3(3), 181–190 (2015).
38. Kilit C, Koçak FE, Paşalı Kilit T. Comparison of the effects of high-dose atorvastatin and high-dose rosuvastatin on oxidative stress in patients with acute myocardial infarction: a pilot study. *Türk. Kardiyol. Dern. Ars.* 45(3), 235–243 (2017).
39. Jukema JW, Liem AH, Dunselman PH, Van Der Sloot JA, Lok DJ, Zwinderman AH. LDL-C/HDL-C ratio in subjects with cardiovascular disease and a low HDL-C: results of the RADAR (Rosuvastatin and Atorvastatin in different Dosages And Reverse cholesterol transport) study. *Curr. Med. Res. Opin.* 21(11), 1865–1874 (2005).
40. Li Q, Zhao YG, Wang Z, Jiang HP, Liu WB, Cao BF. Effects of First High-Dose Atorvastatin Loading in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Percutaneous Coronary Intervention. *Am. J. Ther.* 25(3), e291–e298 (2018).
41. Crouse JR 3rd, Frohlich J, Ose L, Mercuri M, Tobert JA. Effects of high doses of simvastatin and atorvastatin on high-density lipoprotein cholesterol and apolipoprotein A-I. *Am. J. Cardiol.* 83(10), 1476–1477a1477 (1999).
42. Stein EA, Strutt K, Southworth H, Diggle PJ, Miller E. Comparison of rosuvastatin versus atorvastatin in patients with heterozygous familial hypercholesterolemia. *Am. J. Cardiol.* 92(11), 1287–1293 (2003).
43. Mckenney JM, Jones PH, Adamczyk MA, Cain VA, Bryzinski BS, Blasetto JW. Comparison of the efficacy of rosuvastatin versus atorvastatin, simvastatin, and pravastatin in achieving lipid goals: results from the STELLAR trial. *Curr. Med. Res. Opin.* 19(8), 689–698 (2003).
44. Jones PH, Davidson MH, Stein EA *et al.* Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am. J. Cardiol.* 92(2), 152–160 (2003).
45. Wolffenbuttel BH, Franken AA, Vincent HH. Cholesterol-lowering effects of rosuvastatin compared with atorvastatin in patients with type 2 diabetes – CORALL study. *J. Intern. Med.* 257(6), 531–539 (2005).
46. Stein B, Ward T, Hale G, Lyver E. Safety of High-Intensity Statins in the Veteran Population: atorvastatin 40 to 80 mg Compared With Rosuvastatin 20 to 40 mg. *Ann. Pharmacother.* 54(5), 405–413 (2020).
47. Lablanche JM, Leone A, Merkely B *et al.* Comparison of the efficacy of rosuvastatin versus atorvastatin in reducing apolipoprotein B/apolipoprotein A-I ratio in patients with acute coronary syndrome: results of the CENTAURUS study. *Arch. Cardiovasc. Dis.* 103(3), 160–169 (2010).

48. Kaul U, Varma J, Kahali D *et al.* Post-marketing study of clinical experience of atorvastatin 80 mg vs 40 mg in Indian patients with acute coronary syndrome- a randomized, multi-centre study (CURE-ACS). *J. Assoc. Physicians India* 61(2), 97–101 (2013).
49. Marais AD, Raal FJ, Stein EA *et al.* A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia. *Atherosclerosis* 197(1), 400–406 (2008).
50. El Said NO, El Wakeel LM, Khorshid H, Darweesh EaG, Ahmed MA. Impact of lipophilic vs hydrophilic statins on the clinical outcome and biomarkers of remodelling in heart failure patients: a prospective comparative randomized study. *Br. J. Clin. Pharmacol.* 87(7), 2855–2866 (2021).
51. Hoogerbrugge N, Jansen H. Atorvastatin increases low-density lipoprotein size and enhances high-density lipoprotein cholesterol concentration in male, but not in female patients with familial hypercholesterolemia. *Atherosclerosis* 146(1), 167–174 (1999).
52. Toso A, Leoncini M, Maioli M, Tropeano F, Villani S, Bellandi F. A prospective, randomized, open-label trial of atorvastatin versus rosuvastatin in the prevention of contrast-induced acute kidney injury, worsened renal function at 30 days, and clinical events after acute coronary angiography: the PRATO-ACS-2 Study. *Cardiorenal Med.* 10(5), 288–301 (2020).
53. Welty FK, Lewis SJ, Friday KE, Cain VA, Anzalone DA. A comparison of statin therapies in hypercholesterolemia in women: a subgroup analysis of the STELLAR Study. *J. Womens Health (Larchmt)* 25(1), 50–56 (2016).
54. Pierri MD, Crescenzi G, Zingaro C *et al.* Prevention of atrial fibrillation and inflammatory response after on-pump coronary artery bypass using different statin dosages: a randomized, controlled trial. *Gen. Thorac Cardiovasc. Surg.* 64(7), 395–402 (2016).
55. Sardella G, Lucisano L, Mancone M *et al.* Comparison of high reloading ROsuvastatin and Atorvastatin pretreatment in patients undergoing elective PCI to reduce the incidence of Myocardial periprocedural necrosis. The ROMA II trial. *Int. J. Cardiol.* 168(4), 3715–3720 (2013).
56. Schwartz GG, Bolognese MA, Tremblay BP *et al.* Efficacy and safety of rosuvastatin and atorvastatin in patients with hypercholesterolemia and a high risk of coronary heart disease: a randomized, controlled trial. *Am. Heart J.* 148(1), e4 (2004).
57. Hong YJ, Jeong MH, Hachinohe D *et al.* Comparison of effects of rosuvastatin and atorvastatin on plaque regression in Korean patients with untreated intermediate coronary stenosis. *Circ. J.* 75(2), 398–406 (2011).
58. Khurana S, Gupta S, Bhalla H, Nandwani S, Gupta V. Comparison of anti-inflammatory effect of atorvastatin with rosuvastatin in patients of acute coronary syndrome. *J. Pharmacol. Pharmacother.* 6(3), 130–135 (2015).
59. Illingworth DR, Crouse JR 3rd, Hunninghake DB *et al.* A comparison of simvastatin and atorvastatin up to maximal recommended doses in a large multicenter randomized clinical trial. *Curr. Med. Res. Opin.* 17(1), 43–50 (2001).
60. Pitt B, Loscalzo J, Monyak J, Miller E, Raichlen J. Comparison of lipid-modifying efficacy of rosuvastatin versus atorvastatin in patients with acute coronary syndrome (from the LUNAR study). *Am. J. Cardiol.* 109(9), 1239–1246 (2012).
61. Karalis DG, Ross AM, Vacari RM, Zarren H, Scott R. Comparison of efficacy and safety of atorvastatin and simvastatin in patients with dyslipidemia with and without coronary heart disease. *Am. J. Cardiol.* 89(6), 667–671 (2002).
62. Jacobs D, Wassell K, Guidry TJ, Sullivan J. Safety outcomes of atorvastatin 80 mg versus atorvastatin 40 mg in a veteran population. *Ann. Pharmacother.* 54(2), 151–156 (2020).
63. Tunçez A, Altunkeser BB, Öztürk B *et al.* Comparative effects of atorvastatin 80 mg and rosuvastatin 40 mg on the levels of serum endocan, chemerin, and galectin-3 in patients with acute myocardial infarction. *Anatol. J. Cardiol.* 22(5), 240–249 (2019).
64. Faergeman O, Hill L, Windler E *et al.* Efficacy and tolerability of rosuvastatin and atorvastatin when force-titrated in patients with primary hypercholesterolemia: results from the ECLIPSE study. *Cardiology* 111(4), 219–228 (2008).
65. Bergehean SC, Van Tol A, Dallinga-Thie GM *et al.* Effect of rosuvastatin versus atorvastatin treatment on paraoxonase-1 activity in men with established cardiovascular disease and a low HDL-cholesterol. *Curr. Med. Res. Opin.* 23(9), 2235–2240 (2007).
66. Ballantyne CM, Blazing MA, Hunninghake DB *et al.* Effect on high-density lipoprotein cholesterol of maximum dose simvastatin and atorvastatin in patients with hypercholesterolemia: results of the Comparative HDL Efficacy and Safety Study (CHESS). *Am. Heart J.* 146(5), 862–869 (2003).
67. Ciucanu CI, Olariu S, Vlad DC, Dumitraşcu V. Influence of rosuvastatin dose on total fatty acids and free fatty acids in plasma: correlations with lipids involved in cholesterol homeostasis. *Medicine (Baltimore)* 99(48), e23356 (2020).
68. Altunkeser BB, Tunceze A, Ozturk B *et al.* Comparative effects of high-dose atorvastatin versus rosuvastatin on lipid parameters, oxidized low-density lipoprotein, and proprotein convertase subtilisin kexin 9 in acute coronary syndrome. *Coron. Artery Dis.* 30(4), 285–290 (2019).
69. Thongtang N, Ai M, Otokozawa S *et al.* Effects of maximal atorvastatin and rosuvastatin treatment on markers of glucose homeostasis and inflammation. *Am. J. Cardiol.* 107(3), 387–392 (2011).
70. Nicholls SJ, Ballantyne CM, Barter PJ *et al.* Effect of two intensive statin regimens on progression of coronary disease. *N. Engl. J. Med.* 365(22), 2078–2087 (2011).
71. Jones PH, McKenney JM, Karalis DG, Downey J. Comparison of the efficacy and safety of atorvastatin initiated at different starting doses in patients with dyslipidemia. *Am. Heart J.* 149(1), e1 (2005).

72. Kumar A, Shariff M, Doshi R. Impact of rosuvastatin versus atorvastatin on coronary atherosclerotic plaque volume - a systematic review and meta-analysis with trial sequential analysis of randomized control trials. *Eur. J. Prev. Cardiol.* 27(19), 2138–2141 (2020).
73. Ma Q, Zhou Y, Zhai G *et al.* Meta-analysis comparing rosuvastatin and atorvastatin in reducing concentration of c-reactive protein in patients with hyperlipidemia. *Angiology* 67(6), 526–535 (2016).
- **Article summarize the evidence of rosuvastatin vs atorvastatin showing better reducing of CRP with rosuvastatin**
74. Zhang L, Zhang S, Yu Y, Jiang H, Ge J. Efficacy and safety of rosuvastatin vs. atorvastatin in lowering LDL cholesterol: a meta-analysis of trials with East Asian populations. *Herz* 45(6), 594–602 (2020).
75. Arnett DK, Blumenthal RS, Albert MA *et al.* 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 140(11), e596–e646 (2019).
76. Karlson BW, Nicholls SJ, Lundman P, Barter PJ, Palmer MK. Modeling statin-induced reductions of cardiovascular events in primary prevention: A VOYAGER Meta-Analysis. *Cardiology* 140(1), 30–34 (2018).
- **Summarizes the extent of the variability in LDL-C reduction in response to treatment across the recommended doses of different statins regardless of intensity.**
77. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N. Engl. J. Med.* 342(25), 1887–1892 (2000).
78. Boyko EJ. Observational research—opportunities and limitations. *J. Diabetes Comp.* 27(6), 642–648 (2013).
79. Yetley EA, Demets DL, Harlan WR Jr. Surrogate disease markers as substitutes for chronic disease outcomes in studies of diet and chronic disease relations. *Am. J. Clin. Nutrition* 106(5), 1175–1189 (2017).