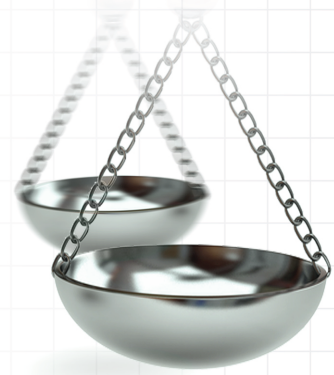
Meta-Analysis



Journal of **Comparative Effectiveness Research**

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 ≥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 slow-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 ≥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 CHESS 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

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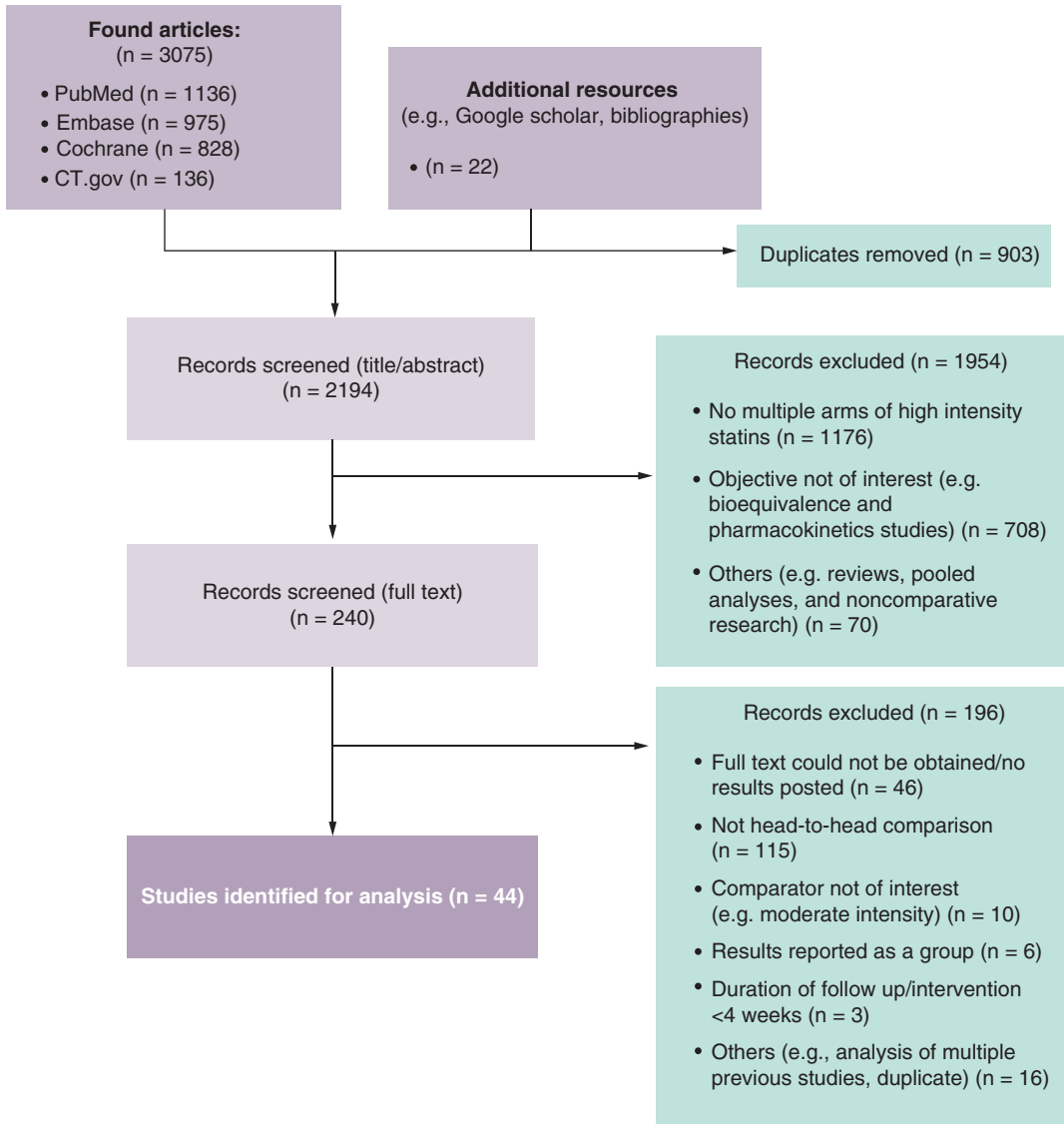

Figure 1. PRISMA flow diagram.

Study or subgroup	A80 Mean (%)	A80 SD (%])	A80 Total	R40 Mean (%)	R40 SD (%)	R40 Total	Weight (%)	Mean difference IV, fixed, 95% CI	Year
Schneck *et al.* (2003)	-53.5	8.42	41	-56.8	7.29	45	15.2	3.30 [-0.04, 6.64]	2003
(RADAR) Jukema *et al.* (2005)	-48.1	18.23	231	-55.3	18.2	230	15.4	7.20 [3.87, 10.53]	2005
(POLARIS) Leiter *et al.* (2007)	-52.5	13.16	439	-57	15.91	432	45.2	4.50 [2.56, 6.44]	2007
(LUNAR) Pitt *et al.* (2012)	-42.7	17.7	278	-46.8	18.2	279	19.1	4.10 [1.12, 7.08]	2012
Bulent *et al.* (2019)	-39.54	19.45	53	-43.82	18.11	53	3.3	4.28 [-2.87, 11.43]	2019
Tunçez *et al.* (2019)	-39	20	33	-47	20	30	1.7	8.00 [-1.89, 17.89]	2019
Total (95% CI)			**1075**			**1069**	**100.0**	**4.71 [3.41, 6.01]**	

Heterogeneity: Chi² = 3.48, df = 5 (p = 0.63); I² = 0%
Test for overall effect: Z = 7.08 (p < 0.00001)

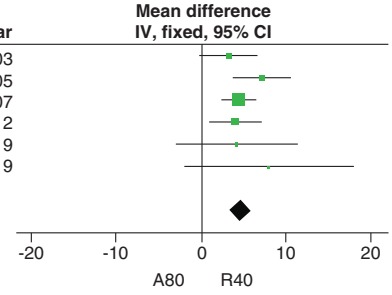

Figure 2. Forest plot.
A80: Atorvastatin 80 mg; CI: Confidence interval; R40: Rosuvastatin 40 mg; SD: Standard deviation.

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)	TG 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: 4.40 (3.60–5.00) S80: 4.4 (3.50–5.50) p = 0.589	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: 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.

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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)			
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.).

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) R20 + Ez10 (214) S40 + Ez 10 (202) S80+ Ez 10 (203)	Mean % change from baseline (SD) R20+Ez10: -63.50 (16.70) S80+Ez10: -57.40 (20.50) p < 0.005	Mean % change from baseline (SD) R20+Ez10: 7.50 (16.40) S80+Ez10: 4.30 (12.60) R20+Ez10 vs S80+ Ez10 p < 0.001	Mean % change from baseline (SD) R20+Ez10: -46.60 (12.80) S80+Ez10:-41.70 (15.20) R20+Ez10 vs S80+Ez10 p < 0.005	Mean % change from baseline (SD) R20+Ez10: -35.00 (24.00) S80+Ez10: -25.80 (26.60) R20+Ez10 vs S80+ Ez10 p < 0.001			[34]
Agrawal *et al.* (2018) India	6	0	History of ASCVD	A40 (120) A80 (120)	Mean % change from baseline (SD) A40: -50.03 (18.06) A80: -52.30 (13.72) p = 0.149	Mean % change from baseline (SD) A40: +11.36 (28.62) A80: +9.02 (27.47) p = 0.269		Mean % change from baseline (SD) A40: 24.11 (16.14) A80: 26.15 (21.30) p = 0.214		increase in HbA1c, % (SD) A40: 0.38 (6.27); A80: 0.74 (6.75); p = 0.340 Increase of CPK, % (SD) A40: 37.56 (57.96); A80: 53.17 (73.15); p = 0.041 Increase of liver enzymes, % (SD) A40: 65.73 (82.77); A80: 86.14 (92.05); p = 0.043 Myalgia, n (%) A40: 2 (1.67); A80: 7 (5.83); p = 0.045	[35]
Aydin *et al.* (2015) Turkey	1	21.5	STEMI	A80 (59) R20 (61)	Mean % change from baseline (SD) A80: -52.00 (15.00) R20: -52.00 (14.00) p = 0.900	Mean % change from baseline (SD) A80: +0.90 (22.00) R20: +7.60 (26.00) p = 0.07	Mean % change from baseline (SD) A80: -36.00 (14.00) R20: -35.00 (12.00) p = 0.590	Mean % change from baseline (SD) A80: -15.00 (57.00) R20: 16.00 (54.00) p = 0.99			[36]
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	Between group differences: NR	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	[37]

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.

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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)			
Kilit *et al.* (2016) Turkey	1	23.6	AMI	A80 (31) R40 (24)	Absolute difference from baseline, mg/dl (SD) A80: -76.00 (36.00) R40: -65.00 (34.00) p = 0.277	Absolute difference from baseline, mg/dl (IQR) A80: -2.00 (-10.00 – 2.00) R40: 1.00 (-4.00 – 5.00) p = 0.012	Absolute difference from baseline, mg/dl (SD) A80: -78.00 (37.00) R40: -67.00 (44.00) p = 0.342	Absolute difference from baseline, mg/dl (IQR) A80: 22.00 (-45.00 – 59.00) R40: 2.00 (-52.00 – 48.00 p = 0.374	Total oxidant status Absolute difference, μmol 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 *et al.* (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 *et al.* (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]

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.

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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)			
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 S80 vs R20 p < 0.001 S80 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.

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.

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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)			
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 ARDs, % 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 creatinine 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]

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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)			
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 *et al.* (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 form 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 Said *et al.* (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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					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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					LDL	HDL	TC levels (mmol/l)	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					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	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		[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]

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					LDL	HDL	TC levels (mmol/l)	TG 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 $p < 0.001$	Mean % change of ApoB from baseline R20: -34.20 R40: -37.90 A80: -36.30 NS Mean % change of ApoA-I from baseline R20: 10.30 R40: 10.10 A80: 4.20 R20 vs 80 $p < 0.01$ 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: 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.).

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 *et al.* (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: -34.00 $p < 0.001$	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 *et al.* (2019) USA	11	NR	Atorvastatin-naive 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		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]
Tunçez *et al.* (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; 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)	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 of ApoA-I 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 *et al.* (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: 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.).

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: +2.40 R40: +9.90 p < 0.001	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: 110.00 (87.00–150.00) R40: 120.00 (91.00–159.00) p = 0.020	% 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: 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.

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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 ± 36, -65 ± 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 ≥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 ≥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.

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