ORIGINAL ARTICLE

Ezetimibe-Statin Combination Therapy

Efficacy and Safety as Compared With Statin Monotherapy—a Systematic Review

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SUMMARY

Introduction: To date, most clinical comparisons of ezetimibe-statin combination therapy versus statin monotherapy have relied entirely on surrogate variables. In this systematic review, we study the efficacy and safety of ezetimibe-statin combination therapy in comparison to statin monotherapy in terms of the prevention of cardiovascular events in hyperlipidemic patients with atherosclerosis and/or diabetes mellitus.

Method: This review is based on a systematic literature search (1995 to July 2015) in PubMed, the Excerpta Medica Database (EMBASE), the Cochrane Library, and the ClinicalTrials.gov registry.

Results: Nine randomized, controlled trials with data from a total of 19 461 patients were included. Ezetimibe-statin combination therapy was associated with a lower risk of cardiovascular events than statin monotherapy: 33% of the patients treated with ezetimibe and a statin, and 35% of those treated with a statin alone, had a cardiovascular event within seven years (number needed to treat [NNT]: 50 over 7 years). Combination therapy was also significantly more effective in preventing a composite endpoint consisting of death due to cardiovascular disease, nonfatal myocardial infarction, unstable angina pectoris, coronary revascularization, and nonfatal stroke (hazard ratio [HR] 0.94, 95% confidence interval [0,89; 0,99]; p = 0.016). Diabetic patients benefited from combination therapy rather than monotherapy with respect to cardiovascular morbidity (HR 0.87 [0.78; 0.94]). On the other hand, the addition of ezetimibe to statin therapy did not lessen either cardiovascular or overall mortality. Serious undesired events occurred in 38% of the patients taking ezetimibe and a statin and in 39% of the patients taking a statin alone (relative risk 1.09 [0.77; 1.55]).

Conclusion: In high-risk patients with an acute coronary syndrome, combination therapy with ezetimibe and a statin lowered the risk of cardiovascular events in comparison to statin monotherapy. The risk of dying or suffering an adverse drug effect was similar in the two treatment groups.

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Coronary heart disease (CHD) and its acute manifestations, such as myocardial infarction, are the leading causes of death in Europe (1). Patients with overt CHD and/or with diabetes mellitus are at an increased risk of cardiovascular events and dying from CHD. Lifestyle interventions, such as regular exercise, a healthy diet, weight loss, and smoking cessation, reduce the risk of adverse cardiovascular events (2–4). Controlling other risk factors, such as diabetes, arterial hypertension and hyperlipidemia, with pharmacotherapy also contributes to risk reduction (5).

Today, statins are the treatment of choice for the prevention of cardiovascular disease in patients with increased cholesterol levels or a generally increased risk of CHD (6); their ability to lower cholesterol and their protective effect against CHD have been demonstrated in numerous studies (7–9). The selective cholesterol absorption inhibitor ezetimibe has been available as a statin alternative for more than a decade. Ezetimibe is approved in combination with a statin when the target cholesterol levels are not attained with statin treatment alone (10). To date, studies comparing the advantages and disadvantages of ezetimibe-statin combination therapy with statin treatment alone have generally focused on surrogate parameters, such as the reduction of low-density lipoprotein (LDL) cholesterol levels (11–16). Numerous studies demonstrated a cholesterol-lowering effect (12, 14, 16). However, based on these data alone the benefits of ezetimibe-statin combination therapy cannot be assessed conclusively since it remains controversial whether there is a causal relationship between the lowering of LDL cholesterol levels and the reduction in cardiovascular events (17).

The aim of this study was to evaluate the efficacy and safety of ezetimibe-statin combination therapy for the prevention of cardiovascular events in patients with hyperlipidemia and overt atherosclerosis and/or diabetes mellitus, in comparison with statin treatment alone. This research question is part of a systematic review registered in the PROSPERO database, an international database of prospectively registered systematic reviews in health and social care (18).

Methods

Literature search and selection

We conducted a systematic literature search of PubMed, Excerpta Medica Database (EMBASE) and the Cochrane Library for the period 1995 to July 2015, using combinations of pertinent keywords and, where possible, medical subject headings (MeSH) *(eTable 1)*. In addition, the ClinicalTrials.gov registry as well as reference lists were searched to identify pertinent studies.

The selection of abstracts and full-text articles was carried out in two consecutive steps, each performed independently by two persons. In case of disagreement, a third person was called in. The selection criteria were defined a priori:

- Population: patients of any age with hyperlipidemia and overt atherosclerosis and/or diabetes mellitus
- Intervention: ezetimibe-statin combination therapy
- Control intervention: statin monotherapy
- Endpoints (date of data collection at least 6 months after randomization): cardiovascular morbidity, cardiovascular mortality, all-cause mortality, quality of life, adverse events
- Study design: randomized controlled trials (RCTs).

Risk of bias and quality of evidence

The Cochrane Collaboration's tool for assessing risk of bias (19) was used to judge the risk of bias in the included RCTs. Two persons independently assessed the risk of selection bias, performance bias, detection bias, attrition bias, and reporting bias. The risk of bias was summarized and assessed as follows *(eTable 2)*:

- High risk of bias: The study had methodological shortcomings, making a distortion of results highly likely.
- Unclear risk of bias: For one or more components, the risk of bias was unclear.
- Low risk of bias: The risk of distortion was judged as low for all components.

Disagreements were resolved by discussion. In addition, the quality of evidence was assessed across endpoints using the approach of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group (30). Where good-quality studies were available, the evidence was considered to be associated with a low risk of bias. Evidence was assessed as being consistent if the effect sizes were similar across the individual studies and pointed in the same direction. Evidence was classed as direct when it demonstrated a direct relationship between the intervention and the health-relevant endpoint and the results of the study were applicable to the target population. It was classed as precise when the results showed a low degree of uncertainty. Finally, the quality of evidence was classed as high, moderate, low, or very low. If the quality is high, the authors are very confident that the true effect is close to the effect estimate. In contrast, if the quality is very low, the authors assume that the true effect is likely to be significantly different from the effect estimate (30).

Synthesis of evidence

We performed meta-analyses of comparable studies with the same endpoint. In all meta-analyses, binary endpoints were evaluated and the risk ratio (RR) as well as the corresponding 95% confidence interval (CI) with random effects was calculated using the Mantel-Haenszel method (31). The extent of statistical heterogeneity was determined by I^2 (32). All meta-analyses were performed using Review Manager 5.3, a Cochrane Collaboration software (tech.cochrane.org/revman/download). Due to the limited number of studies available, no funnel plots could be used to estimate the publication bias. If it was not possible to perform a meta-analysis, a descriptive summary of the results of the single study was produced. The effect estimates reported in the studies were discussed. If no relative effect estimates were provided, we calculated the risk ratio with corresponding 95% CI.

Results

Altogether, our search identified 978 abstracts. Of these, 220 were regarded as potentially relevant, included as full-text articles and reviewed. Nine RCTs (11 publications) met the inclusion criteria (20–29, 33). In the *eFigure*, the flow of the literature selection process is depicted and the reasons for exclusion of a full-text article are listed.

The RCTs included in our systematic review contained data of altogether 19 461 adult patients (20–29, 33). One study was classed as having a low risk of bias (27, 28, 33), five an unclear risk of bias (21–23, 25, 26), and three a high risk of bias (20, 24, 29). Five RCTs had a double-blind design (21–23, 26–28) and two an open-label design (24, 29). In two further studies, no information about blinding was provided (20, 25). Four RCTs were sponsored by a pharmaceutical company (22–24, 27, 28, 33), two (25, 26) were supported by national funding bodies, and three provided no information about funding (20, 21, 29). Study durations ranged from 6 to 84 months. In all studies, ezetimibe was administered in the approved dose of 10 mg/day in combination with a statin and compared with statin monotherapy. Information about the type and dosage of the statins used as well as other study characteristics is provided in the *Table* and, in greater detail, in *eTable 3*.

In the following, we will summarize the results by endpoints. First, we will address cardiovascular morbidity, then mortality, and finally adverse events. The quality of evidence of the individual endpoints and the corresponding effect sizes are described in *eTable 4*.

Cardiovascular morbidity

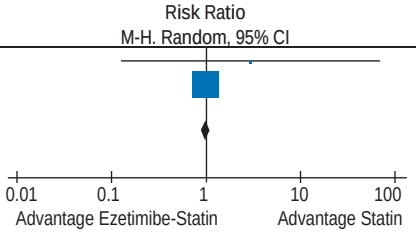
Three RCTs on cardiovascular morbidity evaluated either composite or single endpoints, e.g. myocardial infarction (20, 26–28, 33). It was not possible to perform a meta-analysis because either the endpoint were too different or no results were available in the studies so that the risk ratios could not be calculated.

FIGURE

a) Risk Ratio: Cardiovascular Mortality

Study	Ezetimibe-Statin Events	Total	Statin Events	Total	G	Risk Ratio M-H, Random, 95% CI
Arimura 2012 (20)	1	25	0	25	0.1%	3.00 [0.13; 70.30]
IMPROVE-IT 2015 (27, 28)	537	9067	538	9077	99.9%	1.00 [0.89; 1.12]
Total (95% CI)		9092		9102	100 %	1.00 [0.89; 1.12]
Total events	538		538			

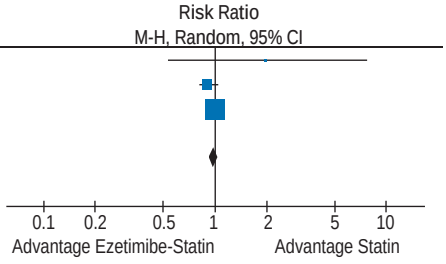
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.47; df = 1 (P = 0.49); I^2 = 0%
Test for overall effect: Z = 0.01 (P = 0.99)



b) Risk ratio: Number of Adverse Events

Study	Ezetimibe-Statin Events	Total	Statin Events	Total	G	Risk Ratio M-H, Random, 95% CI
Dagli et al. 2007 (21)	6	50	3	50	0.4%	2.00 [0.53; 7.56]
Feldmann et al. 2004 (22)	277	457	168	253	31.9%	0.91 [0.81; 1.02]
IMPROVE-IT 2015 (27, 28)	537	9067	5472	9077	67.6%	1.00 [0.98; 1.03]
Total (95% CI)		9574		9038	100%	0.98 [0.89; 1.07]
Total events	5769		5643			

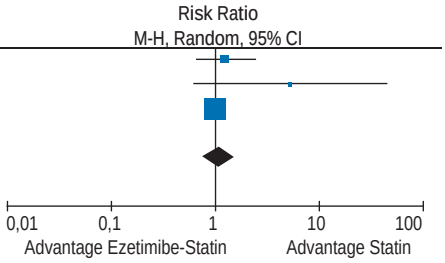
Heterogeneity: Tau^2 = 0.00; Chi^2 = 3.57; df = 2 (P = 0.17); I^2 = 44%
Test for overall effect: Z = 0.53 (P = 0.59)



c) Risk ratio: Number of Serious Adverse Events

Study	Ezetimibe-Statin Events	Total	Statin Events	Total	G	Risk Ratio M-H, Random, 95% CI
Feldmann et al. 2004 (22)	27	457	12	253	20.4%	1.25 [0.64; 2.42]
Gaudiani et al. 2005 (23)	5	104	1	110	2.6%	5.29 [0.63; 44.51]
IMPROVE-IT 2015 (27, 28)	3640	9067	3649	9077	77.0%	1.00 [0.96; 1.03]
Total (95% CI)		9628		9044	100%	1.09 [0.77; 1.55]
Total events)	3672		3662			

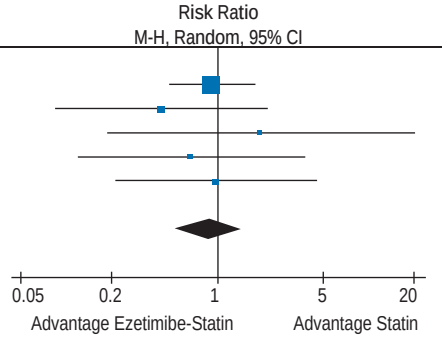
Heterogeneity: Tau^2 = 0.04; Chi^2 = 2.78; df = 2 (P = 0.25); I^2 = 28%
Test for overall effect: Z = 0.49 (P = 0.63)



d) Risk Ratio: Number of Discontinuations due to Adverse Events

Study	Ezetimibe-Statin Events	Total	Statin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dagli et al. 2007 (21)	0	50	0	50		inestimable
Feldmann et al. 2004 (22)	23	457	14	253	64,2%	0,91 [0,48; 1,74]
Gaudiani et al. 2005 (23)	2	104	5	110	10.2%	0.42 [0.08; 2.13]
Masuda et al. 2015 (29)	2	26	1	25	4.9%	1.92 [0.19; 19.90]
Meany et al. 2009 (24)	2	30	3	30	9.1%	0.67 [0.12; 3.71]
Nakamura et al. 2012 (25)	3	32	3	31	11.6%	0.97 [0.21, 4.44]
Total (95% CI)		699		499	100%	0.85 [0.51; 1.43]
Total events	32		26			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.33; df = 4 (P = 0.86); I^2 = 0 %
Test for overall effect: Z = 0.60 (P = 0.55)



Meta-analyses
CI, confidence interval; M-H, Mantel-Haenszel; Random, random effects model

TABLE

Duration, dosage and results of the included studies

Author / study (year), study duration	Intervention (n) vs. control intervention (n); run-in / wash-out phase	Relevant Endpoints	Results
Arimura et al. (2012) (20) 6–8 months	1. Ezetimibe 10 mg/day + Atorvastatin 10 mg/day (25) 2. Atorvastatin 10 mg/day (25)	*Cardiovascular morbidity* a) non-fatal myocardial infarction b) target lesion revascularization c) target vein revascularization d) non-target vein revascularization e) stent thrombosis	a) E + A: 0/25 (0%)*[1]; A: 0/25 (0%)*[1] b) E + A: 2/25 (8%)*[1]; A: 2/25 (8%)*[1] c) E + A: 2/25 (8%)*[1]; A: 3/25 (12%)*[1] d) E + A: 1/25 (4%)*[1]; A: 0/25 (0%)*[1] e) E + A: 0/25 (0%)*[1]; A: 0/25 (0%)*[1]
		Cardiovascular morality	E+A: 1/25 (4%)*[1]; A: 0/25 (0%)*[1]; RR: 3.12; 95% CI: [0.12; 80.39]*[2]
Dagli et al. (2007) (21) 6 months	1. Ezetimibe 10 mg/day + Pravastatin 10 mg/day (50) 2. Pravastatin 40 mg/day (50)	Adverse events	E + P: P: p value
		Number of AEs	6/50 (12%): 3/50 (6%): >0.05
		Discontinuation due to AE	0/50 (0%): 0/50 (0%): not reported
Feldman et al. (2004) (22) 6 months (23 weeks)	1. Ezetimibe 10 mg + Simvastatin 10 mg/day (251) 2. Ezetimibe 10 mg + Simvastatin 20 mg/day (109) 3. Ezetimibe 10 mg + Simvastatin 40 mg/day (97) 4. Simvastatin 20 mg/day (253)	Adverse events	E + S 10/10 mg: E + S 10/20 mg: E + S 10/40 mg: S 20 mg
		Number of AEs	140/251 (56%): 74/109 (68%): 63/97 (65%): 168/253 (66%)
		Number of SAEs	20/251 (8%): 3/109 (3%): 4/97 (4%): 12/253 (5%)
		Discontinuation due to AE	11/251 (4%): 7/109 (6%): 5/97 (5%): 14/253 (6%)
		Rhabdomyolysis	0/251 (0%): 0/109 (0%): 0/97 (0%): 0/253 (0%)
		Hepatitis, hepatotoxicity	0/251 (0%): 0/109 (0%): 0/97 (0%): 0/253 (0%)
Gaudiani et al. (2005) (23) 6 months	1. Ezetimibe 10 mg/day + Simvastatin 20 mg/day open-label (104) 2. Simvastatin 40 mg/day (20 mg of it open-label) (110)	All-cause mortality	E + S: 0/104 (0%); S: 0/110 (0%)
		Adverse events	E + S: S
		Number of SAEs	5/104 (5%): 1/110 (10%)
		Discontinuation due to AE	2/104 (2%): 5/110 (5%)
		Anemia	1/104 (1%): 4/110 (4%)
		Edema	5/104 (5%): 5/110 (5%)
		Weight gain	1/104 (1%): 0/110 (0%)
		Myopathy	0/104 (0%): 0/110 (0%)
IMPROVE-IT study (2014) (27, 28) 84 months	1. Ezetimibe 10 mg/day + Simvastatin 40 mg/day (6% increased dose of simvastatin to 80 mg/day, because LDL >79) (9067) 2. Simvastatin 40 mg/day (27% increased dose of simvastatin to 80 mg/day, because LDL >79) (9077)	*Cardiovascular morbidity* a) Composite endpoint (cardiovascular death, non-fatal MI, unstable AP with hospitalization, coronary revascularization, non-fatal stroke) b) MI c) coronary revascularization ≥ 30 days d) Hospitalization for unstable AP	a) E + S: 2572/9067 (33%); S: 2 742/9077 (35%); HR after 7 years: 0.94; [0.89; 0.99]; p = 0.016; NNT: 50 after 7 years b) E + S: 977/9067 (13%); S: 1 118/9077 (15%); HR after 7 years: 0.87 [0.80; 0.95]; p = 0.002 c) E + S: 1871/9067 (24%); S: 1 962/9077 (26%); HR after 7 years: 0.96; [0.85; 1.33]; p = 0.18 d) E + S: 156/9067 (2%); S: 148/9077 (2%); HR after 7 years: 1.06 [0.85; 1.33]; p = 0.6
		Cardiovascular mortality	E + S: 537/9067 (7%); S: 538/9077 (7%); HR after 7 years: 1 [0.89; 1.13]; p = 1
		All-cause mortality	E + S: 1215/9067 (15%); S: 1 231/9077 (15%); HR after 7 years: 0.99 [0.91; 1.07]; p = 0.78

Author / study (year), study duration	Intervention (n) vs. control intervention (n); run-in / wash-out phase	Relevant Endpoints	Results		
		Adverse events	E + S	S	p-value not adj.
		Number of AEs	5486/9067 (61%)	5472/9077 (60%)	p-value not reported
		Number of SAEs	3640/9067 (40%)	3649/9077 (40%)	p-value not reported
		Cancer	748/9067 (10%)	732/9077 (10%)	p = 0.57
		Cholecystectomy	133/9067 (2%)	134/9077 (2%)	p = 0.96
		Gallbladder-related AEs	281/9067 (3%)	321/9077 (4%)	p = 0.10
		Rhabdomyolysis	13/9067 (0.1%)	18/9077 (0.2%)	p = 0.37
		Myopathy	15/9067 (0.2%)	10/9077 (0.1%)	p = 0.32
Masuda et al. (2015) (29) 6 months	1. Ezetimibe 10 mg/day + Rosuvastatin 5 mg/day (26) 2. Rosuvastatin 5 mg/day (25)	Cardiovascular morbidity a) MI b) coronary revascularization	c) E + R: 0/26 (0%); R: 0/25 (0%) d) E + R: 1/26 (4%); R: 1/25 (4%)		
		All-cause mortality	E + R: 0/26 (0%); R: 0/25 (0%)		
		Adverse events	E + R		R
		Discontinuation due to AE	2/26 (8%)		1/25 (4%)
		Rhabdomyolysis	0/26 (0%)		0/25 (0%)
		Myalgia	0/26 (0%)		1/25 (4%)
		Skin rash	1/26 (4%)		0/25 (0%)
Meaney et al. (2009) (24) 12 months	1. Ezetimibe + Simvastatin (10/20 mg/day): Starting month 2, the dose was increased to 10/40 mg/day, if the therapeutic goal had not been reached (30). 2. Pravastatin 40 mg/day; starting month 2, 10 mg ezetimibe, if the therapeutic goal had not been reached (30). 3. Simvastatin 40 mg /day: Starting month 2, the dose was increased to 80 mg, if the therapeutic goal had not been reached (30).	Adverse events	E + S	P + possibly E	S
		Discontinuation due to rash	1/30 (3%)	0/30 (0%)	0/30 (0%)
		Discontinuation due to myalgia	1/30 (3%)	0/30 (0%)	0/30 (0%)
		Discontinuation due to CPK increase	0/30 (0%)	0/30 (0%)	3/30 (10%)
Nakamura et al. (2012) (25) 6 months	1. Ezetimibe 10 mg/day + statin (individual dose) (32) 2. Statin (doubling of previous dose) (31)	Adverse events	E + St		St
		Discontinuation due to AE	3/32 (9%)		3/31 (10%)
		Stroke	1/32 (3%)		0/31 (0%)
		Rash	1/32 (3%)		0/31 (0%)
West et al. (2011) (26) 24 months	1. Ezetimibe 10 mg/day + Simvastatin 40 mg/day (22) 2. Simvastatin 40 mg/day (22)	Cardiovascular morbidity MACE (= CV death, MI, stroke, transient ischemic attack)	E + S: 4/22 (18%); S: 2/22 (10%); RR: 2.22 [0.36; 13.62]*[2]		
		Adverse events	E + S		S
		Myalgia	0/22 (0%)		1/22 (5%)

A, atorvastatin; adj., adjusted; AE, adverse event; AP, angina pectoris; CPK, creatine phosphokinase; E, ezetimibe; HR, Hazard Ratio; CI, confidence interval; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event; MI, myocardial infarction; n, number of subjects; NNT, number needed to treat; p, p-value; P, pravastatin; R, rosuvastatin; RR, Risk Ratio; SAE, serious adverse event; S, Simvastatin; St, statin

*[1] self-calculated for intention-to-treat (ITT) analysis; in the article, a per-protocol analysis was performed.

*[2] Risk Ratio (self-calculated)

Composite endpoint

The IMPROVE-IT study included 18 144 patients presenting with acute coronary syndrome (myocardial infarction, unstable angina pectoris [AP]). The primary composite endpoint comprised cardiovascular death, non-fatal myocardial infarction, unstable AP requiring hospitalization, coronary revascularization, and non-fatal stroke (27, 28, 33). The risk of experiencing one of these cardiovascular events during the 7-year study period was significantly lower in the ezetimibe-statin group compared with the statin group (33% versus 35%; Hazard Radio (HR) 0.94; 95% CI [0.89; 0.99]; p = 0.016). Consequently, 50 patients have to be treated with ezetimibe-statin combination therapy to prevent one recurrence of a cardiovascular event compared with patients treated with statin alone (number needed to treat: 50 in seven years). The primary endpoint difference between the groups was due to differences in coronary revascularization, myocardial infarction and stroke event rates, but not due to mortality (all-cause mortality). Looking selectively at the patients with diabetes mellitus in the IMPROVE-IT study (n = 4899), 40% of these patients in the ezetimibe-statin combination therapy group and 46% in the statin monotherapy group experienced a cardiovascular event (HR 0.87 [0.78; 0.94]). Subjects without diabetes mellitus (n = 13 202) showed a comparable risk for cardiovascular events in both treatment groups (HR 0.98 [0.92; 1.04]) (27, 28, 33).

In the study by West et al. (n = 44), 18% of patients on ezetimibe-statin combination therapy and 10% on statin monotherapy experienced the composite endpoint (death, myocardial infarction, stroke, and transient ischemic attack; RR 2.22 [0.36; 13.62]) after 24 months (26).

Myocardial infarction

The IMPROVE-IT study demonstrated a lower risk of myocardial infarction for patients on ezetimibe-statin combination therapy. Of the 9067 patients treated with ezetimibe-statin therapy, 13% experienced a myocardial infarction, compared with 15% in the statin monotherapy group (HR 0.87 [0.80–0.95]) (27, 28, 33).

In the studies by Arimura et al. (20) and Masuda et al. (29), none of the 50 and 51 subjects, respectively, experienced a myocardial infarction within 6 to 8 months.

Other endpoints of cardiovascular morbidity

For other single endpoints, such as coronary revascularization (20, 27, 28, 33), unstable angina pectoris (AP) (27, 28, 33) and stent thrombosis (20), no relevant differences were found between the treatment groups *(Table).*

Cardiovascular mortality

Two of the included studies with altogether 18 194 patients reported cardiovascular mortality (20, 27, 28, 33) and were combined in a meta-analysis. The risk of cardiovascular death was 6% in both treatment groups (RR 1 [0.89; 1.12]) *(Figure a).*

All-cause mortality

All three studies showed comparable mortality rates in the treatment groups (23, 27–29, 33). In the IMPROVE-IT study, 15% of patients died in each of the two treatment arms (HR 0.99 [0.91; 1.07]). Thus, ezetimibe as an adjunct to statin treatment did not reduce all-cause mortality (27, 28, 33). In the studies by Gaudiani et al. (23) and Masuda et al. (29), none of the 224 and 51 patients, respectively, died within 6 to 8 months. With no events in either of the two studies, the results could not be aggregated in a meta-analysis.

Adverse events

Adverse drug reactions (ADRs) were operationalized by the following endpoints: number of adverse events (AEs), number of serious adverse events (SAEs) and discontinuation due to adverse events. Evidence synthesis in the form of meta-analyses was possible. For the 3 meta-analyses, between-study heterogeneity was within an acceptable range (I^2: 0–44%). Altogether, 7 RCTs reported data on AEs (21–25, 27–29, 33). In addition, the most common actual AEs were identified.

Number of adverse events

Adverse events comprise all types of ADRs. In 3 RCTs, the number of all AEs which occurred during the study among the altogether 19 954 patients were documented (21, 22, 27, 28, 33). The meta-analysis revealed that in both the ezetimibe-statin combination therapy group and the statin monotherapy group 60% of patients experienced AEs (RR 0.98 [0.89; 1.07]) *(Figure b).*

Serious adverse events

Serious adverse events (SAEs) comprise death, life-threatening events and events resulting in hospitalization, congenital anomaly or disability or permanent damage (35). Three RCTs (22, 23, 27, 28, 33) with altogether 18 068 patients reported SAEs which occurred during the studies; these were combined in a meta-analysis. Under ezetimibe-statin combination therapy, 38% of the 9628 patients experienced serious adverse events compared with 39% of the 9440 patients treated with statin monotherapy (RR 1.09 [0.77; 1.55]) *(Figure c).*

Study discontinuation due to adverse events

Six RCTs with altogether 1198 patients reported on discontinuation due to AEs during periods ranging from 6 to 12 months (21–25, 29) and were aggregated in a meta-analysis. In both the ezetimibe-statin combination therapy group and the statin monotherapy group, 5% of patients discontinued the study due to AEs (RR 0.85 [0.51; 1.43]) *(Figure d).*

Actual adverse events

Ezetimibe-simvastatin combination therapy and simvastatin monotherapy had comparable incidence rates of cancer (each 10% within 7 year), cholecystectomies (2%) and gallbladder-related AEs (3–4%) (33). In 2 six-month studies evaluating rosuvastatin and simvastatin,

respectively, none of the patients experienced rhabdomyolysis (22, 29). However, in the 84-month study, rhabdomyolysis occurred in 0.1% and 0.2% of the patients treated with ezetimibe-simvastatin combination therapy and simvastatin monotherapy, respectively (33). Myopathies were observed in none of the 224 patients of a six-month study (23) and in 0.2% and 0.1% of the patients with ezetimibe-simvastatin and simvastatin, respectively, in the 84-month study (33). Further information on adverse events, type and dosages of the statins is provided in the *Table*.

Discussion

Patient-relevant endpoints for the evaluation of the efficacy of ezetimibe-statin combination therapy were reported in 5 of the 9 identified RCTs. From 4 RCTs, only information about adverse drug reactions was obtained.

The evidence showed that patients treated with ezetimibe-statin combination therapy had a lower risk of cardiovascular events compared with those treated with statin monotherapy. However, the absolute difference between the two groups was small (2 percentage points) and due to differences in revascularization, myocardial infarction and stroke. Nevertheless, due to the high relevance of these events for patients, even minor effects are considered to be clinically relevant. Especially patients with diabetes mellitus appear to benefit from ezetimibe-statin combination therapy with respect to cardiovascular morbidity. Even though these conclusions were drawn from an a priori planned and methodologically sound subgroup analysis, they should be interpreted with caution because of the absence of the effects of randomization.

Ezetimibe as an adjunct to statin therapy did not lower cardiovascular mortality and all-cause mortality.

No relevant differences between the groups were found for the rates of adverse events and discontinuation due to adverse events.

Even though 9 RCTs were identified, the results were dominated by the IMPROVE-IT study due to its substantial size (n = 18 144). Here it should be noted that the subjects of the IMPROVE-IT study had low mean lipid levels and experienced an acute coronary syndrome (ACS) event not long before the start of the study. Thus, the results of this review can be applied to post-ACS patients, but not generally to all affected patients with atherosclerosis and/or diabetes mellitus as their risk profile is different. Since the 8 smaller studies were not designed to evaluate cardiovascular endpoints or adverse drug reactions as primary endpoints, data from these studies did not allow to draw reliable conclusions on patients with atherosclerosis and/or diabetes in general. Consequently, this sample was not statistically analyzed to test for significant differences in these endpoints, especially since the event rates were too low to allow the exclusion of random effects.

When interpreting these results, it is important to keep in mind that our meta-analyses were based on pooled data from studies which varied in duration and statin doses used. Furthermore, the baseline plasma cholesterol levels of the included studies were not identical. However, this does not limit the validity of the results obtained, since our focus was on the differences between treatment groups within one study and the groups within a study were comparable in this respect. Other systematic reviews conducted so far have typically been focused on surrogate parameters rather than patient-relevant endpoints. Furthermore, most studies included in these reviews were short, lasting only a few weeks (11–16, 36–38). The authors of a comparable review (17), also focusing on patient-relevant endpoints, arrived at the conclusion that, based on the available evidence, no additional or fewer benefits and no greater or lesser harm can be attributed to ezetimibe-statin combination therapy. However, data from the IMPROVE-IT study, which demonstrated a significant cardiovascular morbidity advantage for ezetimibe-statin combination therapy, were not yet included in their review.

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Conflict of interest statement
The authors declare that no conflict of interest exists.

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KEY MESSAGES

- Cardiovascular mortality and all-cause mortality were not reduced by the use of ezetimibe as an adjunct to statin therapy.
- Ezetimibe-statin combination therapy reduced the risk of cardiovascular events compared with statin monotherapy.
- Especially patients with additional diabetes mellitus should benefit from an ezetimibe-statin combination therapy.
- The rates of adverse events were not significantly different between ezetimibe-statin combination therapy and statin monotherapy.
- The evidence did not indicate that adding ezetimibe to statin therapy reduces or increases the risk of actual adverse events.

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Supplementary material
eTables, eFigure:
www.aerzteblatt-international.de/16m0445

Supplementary material to:

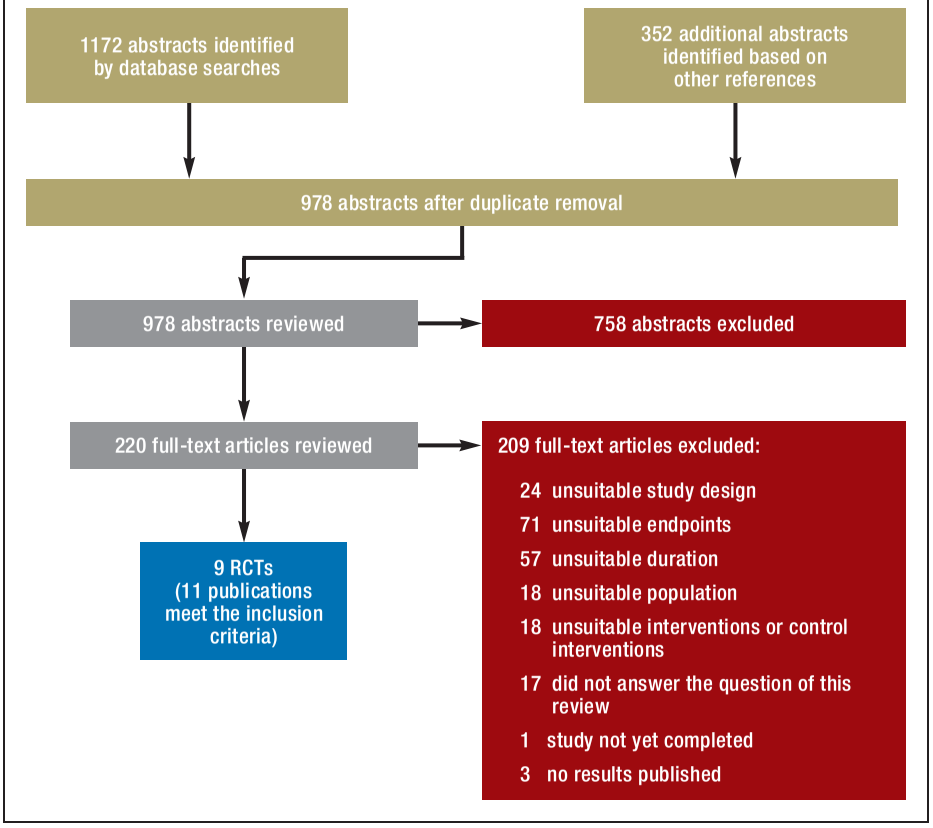
Ezetimibe-Statin Combination Therapy

Efficacy and Safety as Compared With Statin Monotherapy—a Systematic Review

by Barbara Nußbaumer, Anna Glechner, Angela Kaminski-Hartenthaler, Peter Mahlknecht, and Gerald Gartlehner

Dtsch Arztebl Int 2016; 113: 445–53. DOI: 10.3238/arztebl.2016.0445

eFIGURE



Process of literature selection

RCT, randomized controlled trial

eTABLE 1

a) PubMed search strategy (9 September 2014)

Search	Terms	Hits
#1	ezetimib*[tw] OR ezetrol[tw] OR inegy[tw] OR vytorin[tw] OR zetia[tw]	1943
#2	163222–33–1[rn]	1249
#3	SCH 58235[tw] OR SCH58235[tw]	20
#4	(#1 OR #2 OR #3)	1944
#5	„atherosclerosis“[MeSH] OR atherosclero*[tiab]	116 899
#6	„diabetes mellitus“[MeSH] OR diabetes[tiab]	445 031
#7	„hypercholesterolemia“[MeSH] OR hypercholesterol*[tiab]	37 936
#8	sitosterol*[tw]	4326
#9	phytosterol*[tw]	3184
#10	„cholesterol“[MeSH] OR cholesterol[tiab] OR ldl[tiab]	241 224
#11	low[tiab] AND lipoprotein*[tiab]	64 098
#12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	748 618
#13	(#4 AND #12)	1644
#14	systematic[sb]	222 746
#15	„randomized controlled trial“[publication type] OR randomized controlled trial[tiab] OR randomised controlled trial[tiab] OR „single blind method“[MeSH] OR „double blind method“[MeSH] OR „random allocation“ [MeSH]	477 053
#16	(#13 AND (#14 OR #15))	366
#17	„animals“[MeSH] NOT „humans“[MeSH]	3 924 347
#18	(#16 NOT #17)	362
#19	(#18 AND 1995:2014[dp])	362

b) Cochrane Library search strategy (4 September 2014)

Search	Terms	Hits
#1	ezetimib* or ezetrol or inegy or „SCH 58235“ or SCH58235 or vytorin or zetia in other reviews, trials, methods studies, technology assessments and economic evaluations	516
#2	(ezetimib* or ezetrol or inegy or „SCH 58235“ or SCH58235 or vytorin or zetia):ti,ab in Cochrane Reviews (reviews and protocols)	3
#3	#1 or #2	519
#4	[mh atherosclerosis] or atherosclero*:ti,ab,kw	5308
#5	[mh „diabetes mellitus“] or diabetes:ti,ab,kw	27 208
#6	[mh hypercholesterolemia] or hypercholesterol*em*:ti,ab,kw	4583
#7	sitosterol*em*:ti,ab,kw	7
#8	phytosterol*em*:ti,ab,kw	2
#9	[mh cholesterol] or (cholesterol or ldl):ti,ab,kw or (low near/3 lipoprotein*):ti,ab,kw	19 763
#10	{or #4–#9}	46 874
#11	#3 and #10 [or #4–#9]	449
#12	#11 publication year from 1995 to 2014	449
#13	[mh animals] not [mh humans]	5673
#14	#12 not #13	446

c) EMBASE search strategy (9 September 2014)

Search	Terms	Hits
#1	'ezetimibe'/exp OR ezetimib*:ab,ti	6185

#2	ezetrol:ab,ti OR inegy:ab,ti OR vytorin:ab,ti OR zetia:ab,ti	155
#3	'163222 33 1':rn	5238
#4	'sch 58235':ab,ti OR sch58235:ab,ti	19
#5	#1 OR #2 OR #3 OR #4	6202
#6	'atherosclerosis'/exp OR atherosclero*:ab,ti	204 392
#7	'diabetes mellitus'/exp OR diabetes:ab,ti	698 376
#8	'hypercholesterolemia'/exp OR hypercholesterol*:ab,ti	62 397
#9	sitosterol*em*	339
#10	phytosterol*em*	92
#11	'cholesterol'/exp OR cholesterol:ab,ti OR ldl:ab,ti	317 237
#12	(low NEAR/6 lipoprotein*):ab,ti	65 326
#13	#6 OR #7 OR #8 OR #9OR #10 OR #11 OR #12	1 103 174
#14	#5 AND #13	5151
#15	'systematic review'/exp OR 'meta analysis'/exp OR 'systematic review':ab,ti OR (meta NEXT/1 analy*):ab,ti OR metaanaly*:ab,ti OR (review:it AND systematic:ab,ti) OR (systematic:ab,ti AND (bibliographic:ab,ti OR literature:ab,ti OR review:ab,ti OR reviewed:ab,ti OR reviews:ab,ti)) OR 'research synthesis':ab,ti OR 'research integration':ab,ti OR 'evidence synthesis':ab,ti OR (comprehensive*:ab,ti AND (bibliographic:ab,ti OR literature:ab,ti))	224 209
#16	'randomized controlled trial'/exp OR (randomi?ed NEXT/1 'controlled trial'):ab,ti OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'triple blind procedure'/exp OR 'randomization'/exp OR (allocat* NEAR/2 random*):ab,ti	461 090
#17	#15 OR #16	664 729
#18	#14 AND #17	736
#19	'animal'/exp NOT 'human'/exp	4 362 176
#20	#18 NOT #19	735
#21	#20 AND [1995–2014]/py	735
#22	#21 AND [embase]/lim NOT [medline]/lim	197

d) ClinicalTrials.gov search strategy (9 September 2014)

Search	Terms	Hits
#1	interventional studies | ezetimib* OR ezetrol OR inegy OR vytorin OR zetia	219

e) PubMed search strategy – Update search (6 July 2015)

Search	Terms	Hits
#1	ezetimib*[tw] OR ezetrol[tw] OR inegy[tw] OR vytorin[tw] OR zetia[tw]	2146
#2	163222–33–1[rn]	1331
#3	SCH 58235[tw] OR SCH58235[tw]	20
#4	(#1 OR #2 OR #3)	2147
#5	„atherosclerosis"[MeSH] OR atherosclero*[tiab]	123 052
#6	„diabetes mellitus"[MeSH] OR diabetes[tiab]	470 624
#7	„hypercholesterolemia"[MeSH] OR hypercholesterol*[tiab]	39 111
#8	sitosterol*[tw]	4546
#9	phytosterol*[tw]	3383
#10	„cholesterol"[MeSH] OR cholesterol[tiab] OR ldl[tiab]	250 229
#11	low[tiab] AND lipoprotein*[tiab]	67 123
#12	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)	786 117
#13	(#4 AND #12)	1798
#14	systematic[sb]	254 021

#15	„randomized controlled trial“[publication type] OR randomized controlled trial[tiab] OR randomised controlled trial[tiab] OR „single blind method“[MeSH] OR „double blind method“[MeSH] OR „random allocation“[MeSH]	500 987
#16	(#13 AND (#14 OR #15))	402
#17	„animals“[MeSH] NOT „humans“[MeSH]	4 017 863
#18	(#16 NOT #17)	398
#19	(#18 AND 2014:2015[dp])	46

f) Cochrane Library search strategy – Update search (6 July 2015)

Search	Terms	Hits
#1	ezetimib* or ezetrol or inegy or „SCH 58235“ or SCH58235 or vytorin or zetia in other reviews, trials, methods studies, technology assessments and economic evaluations	644
#2	(ezetimib* or ezetrol or inegy or „SCH 58235“ or SCH58235 or vytorin or zetia):ti,ab in Cochrane Reviews (reviews and protocols)	3
#3	#1 or #2	647
#4	[mh atherosclerosis] or atherosclero*:ti,ab,kw	6005
#5	[mh „diabetes mellitus“] or diabetes:ti,ab,kw	32 921
#6	[mh hypercholesterolemia] or hypercholesterol*em*:ti,ab,kw	5003
#7	sitosterol*em*:ti,ab,kw	7
#8	phytosterol*em*:ti,ab,kw	4
#9	[mh cholesterol] or (cholesterol or ldl):ti,ab,kw or (low near/3 lipoprotein*):ti,ab,kw	22 266
#10	{or #4–#9}	54 638
#11	#3 and #10	569
#12	#11 publication year from 2014 to 2015	70

g) EMBASE search strategy – Update search (6 July 2015)

Search	Terms	Hits
#1	'ezetimibe'/exp OR ezetimib*:ab,ti	6185
#2	ezetrol:ab,ti OR inegy:ab,ti OR vytorin:ab,ti OR zetia:ab,ti	155
#3	'163222 33 1':rn	5238
#4	'SCH 58235':ab,ti OR SCH58235:ab,ti	19
#5	#1 OR #2 OR #3 OR #4	6202
#6	'atherosclerosis'/exp OR atherosclero*:ab,ti	204 392
#7	'diabetes mellitus'/exp OR diabetes:ab,ti	698 376
#8	'hypercholesterolemia'/exp OR hypercholesterol*:ab,ti	62 397
#9	sitosterol*em*	339
#10	phytosterol*em*	92
#11	'cholesterol'/exp OR cholesterol:ab,ti OR ldl:ab,ti	317 237
#12	(low NEAR/6 lipoprotein*):ab,ti	65 326
#13	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	1 103 174
#14	#5 AND #13	5151
#15	'systematic review'/exp OR 'meta analysis'/exp OR 'systematic review':ab,ti OR (meta NEXT/1 analy*):ab,ti OR metaanaly*:ab,ti OR (review:it AND systematic:ab,ti) OR (systematic:ab,ti AND (bibliographic:ab,ti OR literature:ab,ti OR review:ab,ti OR reviewed:ab,ti OR reviews:ab,ti)) OR 'research synthesis':ab,ti OR 'research integration':ab,ti OR 'evidence synthesis':ab,ti OR (comprehensive*:ab,ti AND (bibliographic:ab,ti OR literature:ab,ti))	224 209
#16	'randomized controlled trial'/exp OR (randomi?ed NEXT/1 'controlled trial'):ab,ti OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'triple blind procedure'/exp OR 'randomization'/exp OR (allocat* NEAR/2 random*):ab,ti	461 090

#17	#15 OR #16	664 729
#18	#14 AND #17	736
#19	'animal'/exp NOT 'human'/exp	4 362 176
#20	#18 NOT #19	803
#21	#20 AND [2014–2015]/py	92
#22	#21 NOT [medline]/lim	51

h) ClinicalTrials.gov search strategy – Update search (6 July 2015)

Search	Terms	Hits
#1	ezetimib* OR ezetrol OR inegy OR vytorin OR zetia | interventional studies | updated on or after 09/01/2014	133

The database searches were performed between 4 and 9 September 2014. The detailed search strategies are shown in the *eTables 1a-d*. The PubMed search identified 362 articles, the Cochrane Library search 446, the EMBASE search 197, and the clinicaltrials.gov search 219. The results of these update searches conducted in July 2015 are shown in the *eTables 1e-h*.

eTABLE 2

Authors' judgement of risk of bias for the included studies

Author (year)	Adequate method of randomization	Concealment of treatment sequence ensured	Treatment groups comparable after randomization	Blinding of participants	Blinding of endpoint assessors	Identical treatment except for intervention under investigation	Endpoint determined at the same point in time	Drop-out rate <20%	Differential-drop-out rate between study groups <15%	ITT analysis	Determined endpoint actually reported	Risk of bias
Arimura et al. (2012) (20)	unclear	unclear	yes	unclear	unclear	yes	no	yes	yes	no	yes	high
Dagli et al. (2007) (21)	unclear	unclear	yes	yes	yes	yes	yes	unclear	unclear	yes	unclear	unclear
Feldman et al. (2004) (22)	unclear	unclear	yes	yes	unclear	yes	yes	yes	yes	yes	unclear	unclear
Gaudiani et al. (2005) (23)	unclear	unclear	yes	yes	unclear	yes	yes	yes	yes	yes	unclear	unclear
IMPROVE-IT Studie (2014) (27, 28)	yes	yes	yes	yes	yes*[1]	yes	no	no*[2]	yes	yes	yes	low
Masuda et al. (2015) (29)	yes	yes	unclear*[3]	no	no	yes	yes	no*[4]	yes	yes*[5]	yes	high
Meaney et al. (2009 (24)	unclear	unclear	unclear	no	yes	yes	yes	no*[6]	no	unclear	yes	high
Nakamura et al. (2012) (25)	yes	yes	yes	unclear	yes	unclear*[7]	yes	yes	yes	no	yes	unclear
West et al. (2011) (26)	yes	unclear	yes	yes	yes	unclear	yes	no	yes	no	yes	unclear

ITT, Intention to Treat

*[1] Endpoints were determined by an independent Clinical Events Committee, except for revascularization.

*[2] Of the 18 144 randomized subjects, 42% discontinued the intake of the medication early.

*[3] Study participants in the statin monotherapy group were older than those in the ezetimibe-statin combination therapy group. The ezetimibe-statin combination therapy group included more smokers and patients with diabetes mellitus.

*[4] Of the 51 subjects, 11 discontinued the study.

*[5] ITT analysis, at least for the analysis of the adverse events

*[6] Of the 90 study participants, 26 discontinued the study early (drop-out rate: 29%).

*[7] Individual treatment for coronary heart disease (CHD)

eTABLE 3

Characteristics and results of the included studies

Author / study (year), study design, pharmaceutical sponsor, country, duration	Population (n), age (SD / MinMax), gender, baseline cholesterol levels, other characteristics	Intervention (n) vs. control intervention (n), run-in / wash-out phase	Relevant endpoints	Results	Risk of bias
Arimura et al. (2012), RCT (monocentric, unclear whether blinded), sponsor: not specified, Japan[20] 6–8 months medication; starting on the day of stent placement; follow-up: 6–8 months (253 ±77 days)	Adult patients with stable angina pectoris and dyslipidemia (defined as: LDL-C≥140mg/dL, triglycerides ≥150mg/dL, or HDL-C <40mg/dL), with a stent (metal or drug-eluting), without familial hypercholesterolemia (50) 6 patients dropped out of the study (3 each group); the following information is based on the 44 remaining patients: Age: E + A: 69 J (± 9), A: 69 J (± 8) Sex distribution: E + A: 68% m, 32% f A: 73% m, 27% f Baseline cholesterol: not specified Proportion of patients with diabetes: not specified	1. Ezetimibe 10 mg/day + Atorvastatin 10 mg/day (25) 2. Atorvastatin 10 mg/day (25) Run-in/wash-out phase: not specified	Cardiovascular morbidity a) non-fatal myocardial infarction b) target lesion revascularization c) target vein revascularization d) non-target vein revascularization e) stent thrombosis	 a) E + A: 0/25 (0%)*[1] A: 0/25 (0%)*[1] b) E + A: 2/25 (8%)*[1] A: 2/25 (8%)*[1] c) E + A: 2/25 (8%)*[1] A: 3/25 (12%)*[1] d) E + A: 1/25 (4%)*[1] A: 0/25 (0%)*[1] e) E + A: 0/25 (0%)*[1] A: 0/25 (0%)*[1]	high
			Cardiovascular mortality	E + A: 1/25 (4%)*[1] A: 0/25 (0%)*[1] RR: 3,12; 95% CI: [0.12; 80.39]*[2]	
			All-cause mortality	not specified	
			Quality of life	not specified	
			Adverse events	not specified	
Dagli et al. (2007), RCT (single-center, double-blind), sponsor: not specified, Tukey (21) 6 months	Adult patients with primary hyperlipidemia and CHD or known CHD risk or 10-year CHD risk <20%, LDL 210–370mg/dL after 10-week wash-out phase; patients unstable AP or MI were excluded (100) Age: E + P: 53 yrs (± 12); P: 57 yrs (± 11) Sex distribution: E + P: 46% m, 54% f P: 52% m, 48% f Baseline cholesterol (mg/dL): E + P (total): 250.9 ± 51.8; LDL: 158,1 ± 47,5 P (total): 231.1 ± 83,5; LDL: 165,7 ± 29,7 Proportion of patients with diabetes: 0%	1. Ezetimibe 10 mg/day + Pravastatin 10 mg/day (50) 2. Pravastatin 40 mg/day (50) Wash-out phase: 4–12 weeks before randomization	Cardiovascular morbidity	not specified	unclear
			Cardiovascular mortality	not specified	
			All-cause mortality	not specified	
			Quality of life	not specified	
			Adverse events	E + P	P	p-value
			Number of AEs	6/50 (12%)	3/50 (6%)	p >0.05
			Number of SAEs	not specified		
			Discontinuation due to AE	0/50 (0%)	0/50 (0%)	not reported

Author / study (year), study design, pharmaceutical sponsor, country, duration	Population (n), age (SD / MinMax), gender, baseline cholesterol levels, other characteristics	Intervention (n) vs. control intervention (n), run-in / wash-out phase	Relevant endpoints	Results	Risk of bias
Feldman et al. (2004), RCT (multicenter, double-blind), Merck/Schering Plough Pharmaceuticals, USA (22) 6 months (23 weeks)	Adult patients with CHD or CHD risk equivalent according to the NCEP ATP III guideline*[3] and LDL cholesterol ≥130 mg/dL and TG ≤ 350 mg/dL (710) Age: E + S 10/10 mg: 61 yrs (± 10) E + S 10/20 mg: 64 yrs (± 10) E + S 10/40 mg: 62 yrs (± 10) S 20 mg: 62 yrs (± 10) Sex distribution: E + S 10/10 mg: 69% m, 31% f E + S 10/20 mg: 54% m, 46% f E + S 10/40 mg: 62% m, 38% f S 20 mg: 62% m, 38% f Baseline cholesterol (mg/dL): E + S 10/10 mg (total): 247.6 ± 38.0; LDL: 165.1 ± 34.3 E + S 10/20 mg (total): 248.8 ± 37.9; LDL: 167.3 ± 33.0 E + S 10/40 mg (total): 252.3 ± 43.7; LDL: 170.5 ± 40.6 S 20 mg (total): 256.7 ± 46.8; LDL: 173.8 ± 44.7 Proportion of patients with diabetes: E + S 10/10 mg: 51% E + S 10/20 mg: 55% E + S 10/40 mg: 42% S 20 mg: 45%	1.Ezetimibe 10 mg + Simvastatin 10 mg/day (251) 2. Ezetimibe 10 mg + Simvastatin 20 mg/day (109) 3. Ezetimibe 10 mg + Simvastatin 40 mg/day (97) 4. Simvastatin 20 mg/day (253) Every 6 weeks after randomization, the simvastatin dose was increased to max. 80mg/day, as long as an LDL level of 100 mg/dL was not attained. Simvastatin was open-label, blinding was only performed for ezetimibe Run-in phase: 4 weeks placebo	Cardiovascular morbidity	not specified	unclear
			Cardiovascular mortality	not specified	
			All-cause mortality	not specified	
			Quality of life	not specified	

Adverse events	E + S 10/10 mg	E + S 10/20 mg	E + S 10/40 mg	S 20 mg
Number of AEs	140/251 (56%)	74/109 (68%)	63/97 (65%)	168/253 (66%)
Number of SAEs	20/251 (8%)	3/109 (3%)	4/97 (4%)	12/253 (5%)
Discontinuation due to AE	11/251 (4%)	7/109 (6%)	5/97 (5%)	14/253 (6%)
Rhabdomyolysis	0/251 (0%)	0/109 (0%)	0/97 (0%)	0/253 (0%)
Hepatitis, hepatotoxicity	0/251 (0%)	0/109 (0%)	0/97 (0%)	0/253 (0%)

Author / study (year), study design, pharmaceutical sponsor, country, duration	Population (n), age (SD / MinMax), gender, baseline cholesterol levels, other characteristics	Intervention (n) vs. control intervention (n), run-in / wash-out phase	Relevant endpoints	Results		Risk of bias
Gaudiani et al. (2005), RCT (multicenter, double-blind), Merck/Schering-Plough Pharmaceuticals, USA (23) 6 months	Adult patients with hypercholesterolemia and type-2 diabetes mellitus (for 3 months with stable thiazolidinedione treatment) (excluded, if MI within last 3 months or familial hypercholesterolemia) (214) Age: E + S: 58 yrs (35–80) S: 58 yrs (37–78) Sex distribution: E + S: 60% m, 40% f S: 56% m, 44% f Baseline cholesterol levels (mg/dL)*[4]: E + S (total): 173.3 ± 40.5; LDL: 94.6 ± 28.8 S (total): 169 ± 29.6; LDL: 92.3 ± 24.5 Proportion of patients with atherosclerosis: not specified	1. Ezetimibe 10 mg/day + Simvastatin 20 mg/day „open-label“ (104) 2. Simvastatin 40 mg/day (20 mg of this open-label) (110) Run-in phase: 6-week open-label Simvastatin 20 mg/day	Cardiovascular morbidity	not specified		unclear
			Cardiovascular mortality	not specified		
			All-cause mortality	E + S: 0/104 (0%); S: 0/110 (0%)		
			Quality of life	not specified		
			Adverse events	E + S	S	
			Number of AEs	not specified		
			Number of SAEs	5/104 (5%)	1/110 (10%)	
			Discontinuation due to AE	2/104 (2%)	5/110 (5%)	
			Anemia	1/104 (1%)	4/110 (4%)	
			Edema	5/104 (5%)	5/110 (5%)	
			Weight gain	1/104 (1%)	0/110 (0%)	
			Myopathy	0/104 (0%)	0/110 (0%)	

Author / study (year), study design, pharmaceutical sponsor, country, duration	Population (n), age (SD / MinMax), gender, baseline cholesterol levels, other characteristics	Intervention (n) vs. control intervention (n), run-in / wash-out phase	Relevant endpoints	Results	Risk of bias
IMPROVE-IT study (2014), RCT (multicenter, double-blind) Merck Sharp & Dohme, USA, Europe, Australia, New Zealand, South America, Israel, Asia, South Africa (27, 28) 84 months	Adults hospitalized <10 days for acute coronary syndrome (18 144): MI (75%) or unstable AP (25%) Age: E + S: 64 yrs (SD: not specified) S: 64 yrs (SD: not specified) Sex distribution: E + S: 75% m, 25% f S: 76% m, 24% f Baseline cholesterol (mg/dL): E + S (total): not specified; LDL: 95 (79, 110) S (total): not specified; LDL: 95 (79, 220) Proportion of patients with diabetes: E + S: 27% S: 27%	1. Ezetimibe 10 mg/day + Simvastatin 40 mg/day (6% increased simvastatin to 80 mg/day, because LDL >79) (9067) 2. Simvastatin 40mg/day (27% eincreased to 80 mg/day, because LDL >79) (9077) Run-in / wash-out phase: not specified	Cardiovascular morbidity a) Composite endpoint (cardiovascular death, MI, unstable AP requiring hospitalization, coronary revascularization, stroke) b) MI c) Coronary revascularization ≥ 30 daye d) Hospitalization for unstable AP	a) E + S: 2572/9067 (33%) S: 2742/9077 (35%) HR after 7 years: 0.94 [0.89; 0.99]; p = 0.016; NNT: 50 Patients with diabetes mellitus had a greater advantage due to ezetimibe than those without diabetes mellitus: Diabetes melltius: HR: 0.86 [0.78; 0.94] kein Diabetes melltius: HR: 0.98 [0.92; 1.04]; Interaktion p = 0.023 b) E + S: 977/9067 (13%); S: 1118/9077 (15%); HR after 7 years: 0.87 [0.80; 0.95]; p = 0.002 c) E + S: 1871/9067 (24%); S: 1962/9077 (26%); HR after 7 years: 0.96 [0.85; 1.33]; p = 0.18 d) E + S: 156/9067 (2%); S: 148/9077 (2%); HR after 7 years: 1.06 [0.85; 1.33]; p = 0.62	unclear
			Cardiovascular mortality	E + S: 537/9067 (7%); S: 538/9077 (7%); HR after 7 years: 1 [0.89; 1.13]; p = 1	
			All-cause mortality	E + S: 1215/9067 (15%); S: 1231/9077 (15%); HR after 7 years: 0.99 [0.91; 1.07]; p = 0.78	
			Quality of life	not specified	

Adverse events	E + S	S	p-value not adj.
Number of AEs	5486/9067 (61%)	5472/9077 (60%)	p not reported
Number of SAEs	3640/9067 (40%)	3649/9077 (40%)	p not reported
Cancer	748/9067 (10%)	732/9077 (10%)	p = 0.57
Cholecystectomy	133/9067 (2%)	134/9077 (2%)	p = 0.96
Gallbladder-related AEs	281/9067 (3%)	321/9077 (4%)	p = 0.10
Rhabdomyolysis	13/9067 (0.1%)	18/9077 (0.2%)	p = 0.37
Myopathy	15/9067 (0.2%)	10/9077 (0.1%)	p = 0.32

Author / study (year), study design, pharmaceutical sponsor, country, duration	Population (n), age (SD / MinMax), gender, baseline cholesterol levels, other characteristics	Intervention (n) vs. control intervention (n), run-in / wash-out phase	Relevant endpoints	Results		Risk of bias
Masuda et al. (2015), (RCT single-center, open-label), sponsor: not specified, Japan (29) 6 months	Adult patients with clinically stable AP, prior to elective percutaneous coronary intervention, with LDL-C levels of at least 100mg/dl at baseline (51) The following information is based solely on the 44 subjects who underwent intravascular ultrasonography. Age: E + R: 64 yrs (± 8) R: 70 yrs (± 8) Sex distribution: E + R: 91% m, 9% f R: 84% m, 16% f Baseline cholesterol (mg/dL): not specified Proportion of patients with diabetes: E + R: 52% R: 42%	1. Ezetimibe 10 mg/day + Rosuvastatin 5 mg/day (26) 2. Rosuvastatin 5 mg/day (25) Run-in / wash-out phase: not specified	Cardiovascular morbidity a) MI b) Coronary revascularization	c) E + R: 0/26 (0%); R: 0/25 (0%) d) E + R: 1/26 (4%); R: 1/25 (4%)		high
			Cardiovascular mortality	not specified		
			All-cause mortality	E + R: 0/26 (0%); R: 0/25 (0%)		
			Quality of life	not specified		
			Adverse events	E + R	R	
			Discontinuation due to AE	2/26 (8%)	1/25 (4%)	
			Rhabdomyolysis	0/26 (0%)	0/25 (0%)	
			Myalgia	0/26 (0%)	1/25 (4%)	
			Drug eruption	1/26 (4%)	0/25 (0%)	
			Number of AEs, SAEs	not specified		

Author / study (year), study design, pharmaceutical sponsor, country, duration	Population (n), age (SD / MinMax), gender, baseline cholesterol levels, other characteristics	Intervention (n) vs. control intervention (n), run-in / wash-out phase	Relevant endpoints	Results			Risk of bias
Meaney et al. (2009), RCT (single-center, open-label), Merck Sharp & Dohme, Mexiko (24) 12 months	Adult patients with 10-year risk of cardiovascular mortality ≥ 20 according to ATP III recommendations. Age: S + E: 58 yrs (± 9); P + (possibly E): 59 yrs (± 7); S: 57 yrs (± 8) Sex distribution (conflicting information): S + E: 19 m, 21 f; P + (possibly E): 13 m, 17 f; S: 12 m, 19 f Baseline cholesterol (mg/dL): S + E (total): 216 ± 40; LDL: 131 ± 39 P+ (possibly E) (total): 207 ± 31; LDL: 128 ± 30 S (total): 215 ± 38; LDL: 130 ± 33 Proportion of patients with diabetes: S + E: 14/30 (47%); P + (possibly E): 16/30 (53%); S: 15/30 (50%)	1. Ezetimibe + Simvastatin (10/20 mg/day): Starting month 2, the dose was increased to 10/40 mg/day, if the therapeutic goal was not attained (30). 2. Pravastatin 40 mg/day: Starting month 2, additional 10 mg ezetimibe, if the therapeutic goal was not attained (30). 3. Simvastatin 40 mg /day: Starting month 2, the dose was increased to 80 mg , if the therapeutic goal was not attained (30). Run-in / wash-out phase: not specified	Cardiovascular morbidity	not specified			high
			Cardiovascular mortality	not specified			
			All-cause mortality	not specified			
			Quality of life	not specified			
			Adverse events	E + S	P + evtl. E	S	
			Discontinuation due to skin rash	1/30 (3%)	0/30 (0%)	0/30 (0%)	
			Discontinuation due to myalgia	1/30 (3%)	0/30 (0%)	0/30 (0%)	
			Discontinuation due to CPK increase	0/30 (0%)	0/30 (0%)	3/30 (10%)	
			Number of AEs, SAE	not specified			

Author / study (year), study design, pharmaceutical sponsor, country, duration	Population (n), age (SD / MinMax), gender, baseline cholesterol levels, other characteristics	Intervention (n) vs. control intervention (n), run-in / wash-out phase	Relevant endpoints	Results		Risk of bias
Nakamura et al. (2012), RCT (single-center, blinding unclear), no pharmaceutical sponsor, Japan (25) 6 months	Adult patients with hypercholesterolemia (increased chylomicron remnants ≥ 5.0mg and LDL ≥ 100mg/dL + at least 1 organic stenosis of an important coronary artery demonstrated by angiography); all patients had stable CHD (no AP) at rest, no increase in AP attacks during the last year, no acute coronary syndrome within the last 4 weeks) (63) Age: E + St: 61 yrs (± 10); St: 64 yrs (± 9) Sex distribution: E + St: 76% m, 24% f; St: 82% m, 18% f Baseline cholesterol (mg/dL): E + St (total): 193 (182, 221); LDL: 120 (105, 139) St (total): 200 (187, 221); LDL: 121 (107, 141) Proportion of patients with diabetes: E + St: 35%; St: 37%	1. Ezetimibe 10 mg/day + Statin (individual dose) (32) 2. Statin (doubling of the previous dose) (31) E + statin (statin and average dose) Atorvastatin: 7%, 10 mg Pravastatin: 59%, 12.7 mg Rosuvastatin: 24%, 5.8 mg Pitavastatin: 10%, 1.5 mg Statin: (Statin and average baseline dose) Atorvastatin: 21%, 11.7 mg Pravastatin: 43%, 11.7 mg Rosuvastatin: 32%, 6,1 mg Pitavastatin: 4%, 2 mg Run-in / wash-out phase: not specified	Cardiovascular morbidity	not specified		unclear
			Cardiovascular mortality	not specified		
			All-cause mortality	not specified		
			Quality of life	not specified		
			Adverse events	E + St	St	
			Discontinuation due to AE	3/32 (9%)	3/31 (10%)	
			Stroke	1/32 (3%)	0/31 (0%)	
			Skin rash	1/32 (3%)	0/31 (0%)	
			Number of AEs, SAE	not specified		
West et al. (2011), RCT (single-center, double-blind), no pharmaceutical sponsor, USA (26) 24 months	Statin-naive adults with peripheral arterial occlusive disease (PAOD) (44) (n = 34 remaining in the study) Age: E + S: 62 yrs (± 8); S: 59 yrs (± 10) Sex distribution: S + E: 56% m, 44% f; S: 69% m, 31% f Baseline cholesterol (mg/dL): E + S (total): 189 ± 10; LDL: 118 ± 9 S (total): 194 ± 11; LDL: 118 ± 10 Proportion of patients with diabetes: E + S: 28%; S: 31%	1. Ezetimibe 10 mg/day + Simvastatin 40 mg/day (22) 2. Simvastatin 40 mg/day (22) 3. Study arm was part of a parallel observational study and thus not reported here	Cardiovascular morbidity MACE (= death, myocardial infarction, stroke, transient ischemic attack)	E + S: 4/22 (18%); S: 2/22 (10%); RR 2,22; [0.36; 13,62]*[1]		unclear
			Cardiovascular mortality	not specified		
			All-cause mortality	not specified		
			Quality of life	not specified		
			Adverse events	E + S	S	
			Myalgia	0/22 (0%)	1/22 (5%)	
			Number of AEs, SAE, Discontinuation due to AE	not specified		

A, Atorvastatin; adj., adjusted; AE, adverse event; AP, angina pectoris; CHD, coronary heart disease; CI, confidence interval; CPK, creatine phosphokinase; E, ezetimibe; f, female; HDL, high-density lipoprotein; HR, Hazard Ratio; LDL, low-density lipoprotein; m, male; MACE, major adverse cardiovascular event; MinMax, minimum and maximum value; MI, myocardial infarction; n, number of study participants; NCEP ATP, National Cholesterol Education Program Adult Treatment Panel; NNT, number needed to treat; p, p-value; P, Pravastatin; PAOD, peripheral arterial occlusive disease; R, rosuvastatin; RCT, randomized controlled trial; RR, risk ratio; S, simvastatin; SAE, serious adverse event; SD, standard deviation; St, statin; TG, triglyceride; yrs, years

*[1] self-calculated for ITT analysis; analysis in the article per protocol

*[2] Risk Ratio self-calculated

*[3] NCEP ATP III guideline: Patients with CHD or CHD risk equivalent have a target LDL cholesterol levels <100. For patients with 2 or more risk factors, the target LDL cholesterol levels <130. In persons with no risk factors, target LDL cholesterol levels are <160 (34).

*[4] units converted from mmol/l to mg/dl using an online calculator: www.tellmed.ch/tellmed/tools/diagnostische_scores_berechnungen/umrechnung_von_mg_dl.php

eTABLE 4

Quality of evidence based on the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) and results for each endpoint

Quality assessment						Number of events and number of patients		Effect	Quality of evidence
No. of studies	Study design	Risk of bias	Inconsistency	Indirect-ness	Imprecision	Ezetimibe 10 mg/day + statin 10–80 mg/day	Statin 10–80 mg/day	Risk ratio (95% CI)	
Cardiovascular morbidity in high-risk patients after acute coronary syndrome (follow-up: 84 months)									
1*[1]	RCT	not high	not high	not high	not high	2572/9067 (33%)	2742/9077 (35%)	HR: 0.94 [0.89; 0.99]	⊕⊕⊕⊕ high
Cardiovascular morbidity in hyperlipidemic patients with atherosclerosis without acute coronary syndrome (follow-up: 6–24 months)									
3*[2]	RCT	high*[3]	not high	not high	very high*[4]	4/22 (18%)	2/22 (10%)	RR: 2.22 [0.36; 13.62]	◯⊖◯◯ very low
Cardiovascular mortality (follow-up: 6–84 months))									
2	RCT	high*[3]	not high	not high	not high	538/9092 (6%)	538/9102 (6%)	HR: 1.00 [0.89; 1.12]	⊖⊖⊖◯moderate
All-cause mortality in high-risk patients after acute coronary syndrome (follow-up: 84 months)									
1	RCT	not high	not high	not high	not high	1215/9067 (15%)	1231/9077 (15%)	HR: 0.99 [0.91; 1.07]	⊕⊕⊕⊕ high
All-cause mortality in hyperlipidemic patients with atherosclerosis without acute coronary syndrome									
1	RCT	high*[3]	not high	not high	very high*[4]	0/104 (0%)	0/110 (0%)	RR not calculable	◯⊖◯◯ very low
Quality of life – no evidence identified									
Number of adverse events (follow-up: 6 months)									
3	RCT	not high	not high	not high	high*[5]	5769/9574 (60%)	5643/9380 (60%)	RR: 0.98 [0.89; 1.07]	⊖⊖⊖◯moderate
Number of serious adverse events (follow-up: 6 months)									
3	RCT	not high	not high	not high	very high*[4]	3672/9628 (38%)	3662/9440 (39%)	RR: 1.09 [0.77; 1.55]	◯⊖⊖◯ low
Study discontinuation due to adverse events (follow-up: 6–12 months)									
6	RCT	high*[6]	not high	not high	high*[5]	32/699 (5%)	26/499 (5%)	RR: 0.85 [0.51; 1.43]	◯⊖⊖◯ low

GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, Hazard Ratio; CI, confidence interval; RCT, randomized controlled trial; RR, risk ratio

*[1] This study reports both a composite endpoint and individual endpoints (myocardial infarction, revascularization, unstable angina pectoris). Since the composite endpoint was the study's primary endpoint, it was reported here.

*[2] Cardiovascular morbidity was reported in three RCTs (in one study as a composite endpoint, in the other studies as single endpoints [myocardial infarction, revascularization, stent thrombosis]). Since the data were not combined in a meta-analysis, the results of the study which evaluated a composite endpoint (death, myocardial infarction, stroke, and transient ischemic attack), are reported here. In the two other studies, the incidence of cardiovascular events was comparably low in both treatment groups.

*[3] Randomization, concealed assignment, blinding at times unclear

*[4] The confidence interval contains effect estimates that can indicate both an advantage and a disadvantage for ezetimibe-statin therapy. The number of subjects is very small; thus, the results may be due to random effects and lack of power. Result rates very low.

*[5] The confidence interval contains effect estimates that can indicate both an advantage and a disadvantage for ezetimibe-statin therapy.

*[6] Randomization was unclear and no blinding was carried out.