Co-administration of ezetimibe and a statin in management of dyslipidemias: a meta-analysis of clinical trials

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Abstract

Introduction: Patients, who have above-target low-density lipoprotein cholesterol (LDL-C) levels, are at increased risk for developing coronary heart disease and cardiovascular disease. Statin monotherapy, which decreases the production of exogenous cholesterol, might not be enough to decrease LDL-C levels. Coadministration of a cholesterol absorption inhibitor with a statin may be more effective at decreasing serum LDL-C levels and improving overall lipid profiles. To assess the effectiveness of ezetimibe 10 mg/day coadministered with a statin in reducing serum LDL-C levels.

Material and methods: A literature search on PubMed and MEDLINE identified 757 potentially eligible publications of which fifteen reports of clinical trials were qualified to be included in the current review.

Results: A total of 5,489 patients included in the studies reviewed were on statin monotherapy prior to study entry for a minimum of 6 weeks. In these studies, the 3,376 patients that received ezetimibe coadministered with a statin had an overall mean percent LDL-C change from baseline of –27.1% (95% CI –27.9 to –26.4%). For the 2,113 that were treated with statin monotherapy the mean change in LDL-C from baseline was –4.5% (95% CI –5.3 to –3.8%). A total of 6,209 patients were treatment-naïve or washed out from any lipid lowering treatment prior to study entry. Of these, the 3,413 that were treated with a combination of statin and ezetimibe combination regimen had an overall mean percent change in LDL-C of –51.5% (95% CI –51.9 to –51.1%). The 2,796 that were treated with statin monotherapy experienced a mean percent change in LDL-C of –40.4% (95% CI –40.9 to –40.0%).

Conclusions: Ezetimibe coadministered with statins is effective in reducing LDL-C in patients who do not attain target LDL-C levels while on statin monotherapy. Simultaneous administration of a statin plus ezetimibe regimen in patients who are treatment-naïve is also efficient at reducing plasma LDL-C.

Key words: ezetimibe, hypercholesterolemia, low-density lipoprotein cholesterol, statin, meta-analysis.

Introduction

Coronary heart disease (CHD) remains a leading cause of mortality with significant burden of illness in the western world [1, 2]. The direct association between plasma concentrations of low-density lipoprotein cholesterol (LDL-C)

and risk for CHD [3-5] and cardiovascular disease (CVD) [5-8] has been well established. Several studies have demonstrated that cardiovascular mortality risk is reduced with lower LDL-C plasma levels [5, 9, 10]. An estimated 36 million adults in the United States with elevated levels of total cholesterol (TC) and LDL-C will require lipid-lowering drug therapy in order to achieve the recommended target goals established by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [11].

Lifestyle modifications including diet and exercise have been shown to be effective in producing decreases in LDL-C [12], however, for clinically significant and sustained reductions in LDL-C, concurrent medication use is the most important factor in achieving appropriate LDL-C values [13]. Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are used as first-line pharmacological therapy for the treatment of hypercholesterolemia with a predominant focus on the reduction of LDL-C [14]. Statins reduce the endogenous production of cholesterol by blocking the first step in the HMG-CoA reductase pathway. The use of statin monotherapy in several large randomized trials has been shown to significantly reduce plasma LDL-C up to 60% [15]. Despite their well documented efficacy, recent studies have shown that an important percentage of high risk patients on statin therapy remain above LDL-C target levels [14, 16, 17]. Possible explanations for this observation include poor adherence and compliance with treatment as well as low tolerability for high-dose statin use [18-20]. In addition, although statins act to inhibit the biosynthesis of cholesterol, they do not affect the absorption of exogenous cholesterol originating from dietary intake. In recognition of the above, combined pharmacological treatment that inhibits both the hepatic biosynthesis and intestinal absorption of cholesterol may prove more effective than statin monotherapy in reducing cholesterol and achieving recommended LDL-C targets.

Ezetimibe is a compound which selectively inhibits cholesterol absorption by binding to the Niemann-Pick C1-like 1 (NPC1L1) protein [21]. It is located in the small intestine, where it contributes substantially to the intestinal uptake and cellular transport of cholesterol by preventing its passage across the intestinal wall [22].

The mechanism of action of ezetimibe is complementary to that of statins in the prevention of serum cholesterol accumulation. Therefore, the purpose of this study was to synthesize the evidence generated in randomized clinical trials that evaluated the effectiveness of either co-administering ezetimibe 10 mg/day with an existing statin or of simultaneous treatment initiation of ezetimibe with a statin.

Material and methods

Data sources and search strategy

Identification of potentially eligible articles involved a search of the PubMed and MEDLINE databases using the keywords "ezetimibe" and "statin". The search was conducted between June 1, 2006 and December 1, 2006 and was restricted to "human subjects" and articles written in the "English language". It was further limited to "core clinical journals", "randomized controlled trials" and "articles added to PubMed or MEDLINE within the last ten years". The abstracts of the identified articles were retrieved and reviewed for eligibility.

In order to be selected for further review, the publications had to report results from randomized controlled trials that assessed either the efficacy of ezetimibe coadministered with a statin in patients who had been on statin monotherapy, or ezetimibe coadministered with a statin in patients who were treatment-naïve or washed out of any lipid-lowering medication (LLMs) prior to study entry. All trials must have reported plasma LDL-C at baseline and either the mean percent change in LDL-C from baseline or post-treatment plasma LDL-C values. Assessment of eligibility and data extraction for each study were conducted independently by three investigators (J.A., N.K., and J.S.S.). Only full, peer-reviewed publications reporting the results of original clinical trials were reviewed. Abstracts and conference proceedings were not included. Disagreements between the three reviewers were resolved by consensus.

When more than one manuscript reporting results from the same study were identified, they were combined into one record using the most complete and recent data. For each study, the following data were extracted: sample size, mean age of patient population, prevalence of related comorbidity, specifically, diabetes mellitus, coronary artery disease, CVD, and hypertension, statin(s) used, statin dose and duration of statin treatment. Outcome data extracted were baseline lipid parameters and percent change in baseline lipid parameters, specifically, LDL-C, TC, TG, high-density lipoprotein cholesterol (HDL-C), and the TC/HDL-C ratio. Data were abstracted only from the published results of the identified trials. No other data sources were used.

Percent changes in lipid parameters as reported in the publication were confirmed from the raw data where possible. When percent changes were not reported, they were estimated from the data available. Percent changes for the longest duration of treatment were used when multiple observations were available. If patients had their statin dose titrated, the percent changes for sequential

durations of treatment were treated as independent observations. Standard deviations (SD) of the percent change in lipid parameters were used where reported. When not reported, the SD of the change was imputed as the weighted average of the SD from other studies where the SD was reported.

Statistical analysis

The primary outcome measure was the percent change in LDL-C from baseline. In patients who were previously on statin therapy, baseline was defined as the time prior to the addition of ezetimibe to ongoing statin therapy. In patients who were washed out from their previous LLMs or treatment-naïve, baseline was defined as the time prior to initiation of treatment with statin and ezetimibe simultaneously. Secondary outcome measures included the percent change from baseline in TC, TG, HDL-C and TC/HDL-C during the treatment period. TG values were reported as both means and medians. In the event that a manuscript did not specify whether TG values were reported as a mean or a median, they were assumed to be means. When only medians were reported, this value was used to replace the mean in the calculation of the overall effect. The standard deviations of the post-treatment mean LDL-C values were often not reported and therefore, were assumed to be equal to the standard deviation of the baseline means.

In estimating the overall effect across studies, the weight for each study was calculated as the inverse of the variance of the mean change in the lipid parameters assessed. The overall variance across studies was calculated as the inverse of the sum of weights and the standard error (SE) was the square root of the variance. A fixed-effect analysis was performed. The overall effect size was estimated as the weighted mean percent change across all studies. Ninety-five percent confidence intervals (95% CI) of the overall effect size were estimated assuming a normal distribution. All analyses were conducted using the software A Comprehensive Meta-Analysis 2.0. Weighted means were used to describe the age of subjects and the duration of treatment across all studies. Comorbidities were aggregated as weighted mean proportions across all studies where individual comorbidities were reported.

Results

Selection of studies for review

Of the 757 potentially eligible publications identified from the initial search, 739 were excluded because they did not fulfill the initial screening criteria. There were eighteen reports of clinical trials selected for final review. Of these, two were excluded because LDL-apheresis was used [23, 24] and one because it reported results of a subgroup-analysis from a randomized controlled clinical trial that was already reported elsewhere [25]. The remaining fifteen clinical trials were included in this review (Figure 1) [26-40].

Of the fifteen included trials, six [30, 31, 33, 35, 38, 40] reported results for patients who were

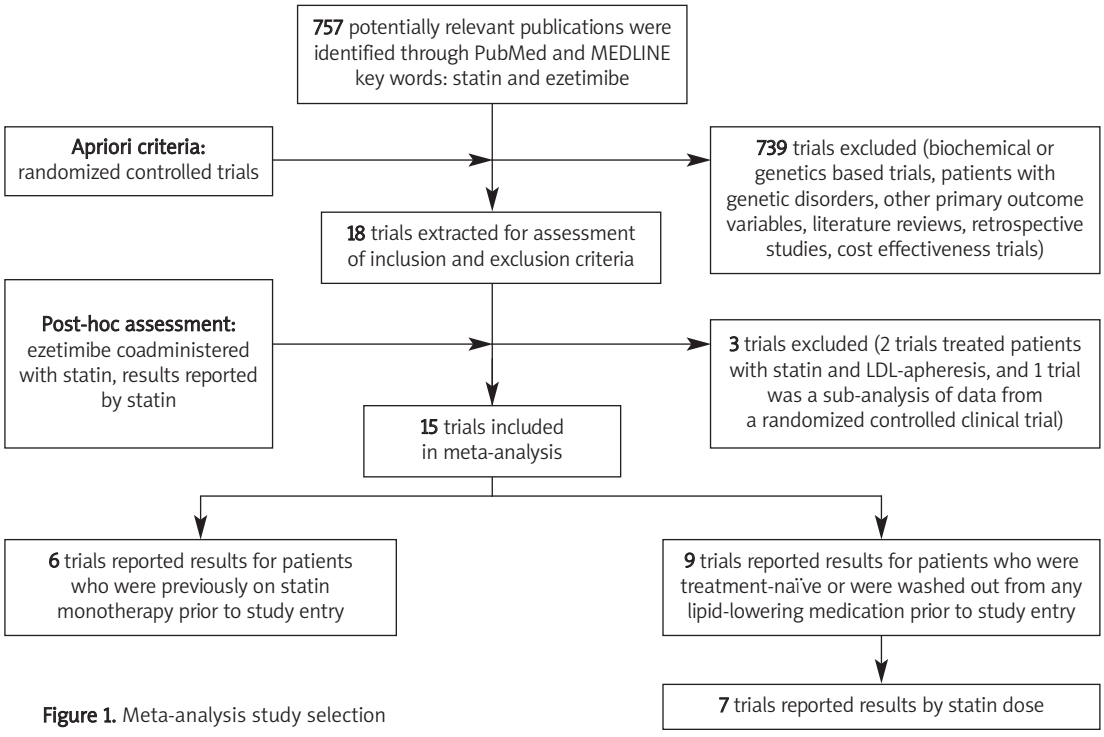

Figure 1. Meta-analysis study selection

previously on a statin monotherapy prior to study entry and nine [26-29, 32, 34, 36, 37, 39] reported results for patients who were treatment-naïve or washed out from any previous LLMs prior to study entry. In total, six different statins were coadministered with ezetimibe in the studies reviewed, specifically, atorvastatin, simvastatin, pravastatin, lovastatin, cerivastatin and fluvastatin. Three trials reported results exclusively for atorvastatin [26, 27, 31], eight for simvastatin [28-30, 32-35, 37, 38], one for pravastatin [39] and one for lovastatin [37]. Two trials reported results for more than one statin [35, 40]. There were no studies exclusively assessing cerivastatin or fluvastatin. The studies were classified into the following three groups according to the statin used: atorvastatin, simvastatin and combination/other. The combination/other group included trials that reported pooled results for more than one statin and those that reported results for lovastatin [37] and pravastatin [39].

The description of the trials included in the analysis is summarized in Table I. All trials were double-blind, with the exception of one in which only patients were blinded to the treatment [34].

Study population and treatment groups

A total of 5,489 patients included in the studies reviewed were on statin monotherapy prior to study entry for a minimum of 6 weeks. Their mean (SD) duration of statin treatment was 6.9 (2.1) weeks and ranged from 6 to 12 weeks. In these studies, 3,376 patients received ezetimibe coadministered with a statin and 2,113 were treated with statin monotherapy. A total of 6,209 patients were treatment-naïve or washed out from any LLMs prior to study entry. Of these, 3,413 were treated with a statin plus ezetimibe combination regimen and 2,796 were treated with statin monotherapy. The mean (SD) duration of treatment was 13.6 (12.1) weeks with a range between 5 to 52 weeks (Table I).

For the patients treated with statin monotherapy prior to study entry, the mean age and reported comorbidities were similar for those receiving a statin and ezetimibe coadministration

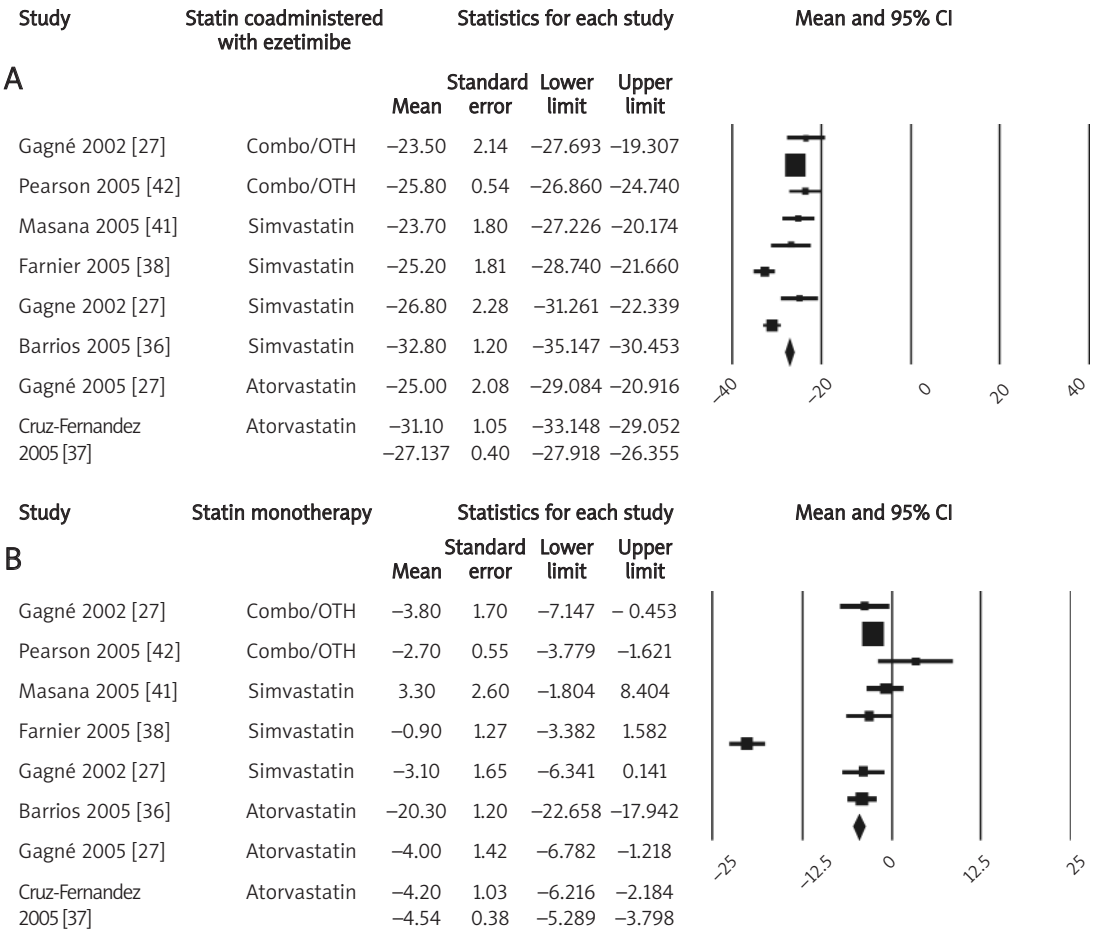

Figure 2. Mean percent reduction in LDL-C for patients on statin monotherapy prior to study entry for (**A**) patients coadministered a statin with ezetimibe and (**B**) patients continuing on their existing statin monotherapy regimen

CI - confidence interval

Table I. Description of included trials

Source	Patient entry criteria	Pre-trial protocol	Monotherapy group (no. of participants)	Active treatment group (no. of participants)	Duration [weeks]
Patients on statin monotherapy prior to entry					
Barrios 2005 [30]	LDL-C ranging from 100 to 160 mg/dl	Stable statin dose for at least 6 weeks and a 1 week diet/stabilization period	Atorvastatin 20 mg (214)	Simvastatin 20 mg + ezetimibe 10 mg (221)	6
Farnier 2005 [33]	LDL-C levels > 100 mg/dl	Stable statin dose (simvastatin 10 mg or 20 mg) for at least 6 weeks	Simvastatin 10-20 mg (191)	Simvastatin 10-20 mg + ezetimibe 10 mg (181)	6
Cruz-Fernandez 2005 [31]	Patients had not achieved LDL-C goal of < 100 mg/dl	Stable statin dose for at least 6 weeks and a 4 week diet run-in	Atorvastatin 10-20 mg (230)	Atorvastatin 10-20 mg + ezetimibe 10 mg (220)	6
Masana 2005 [38]	Patients had not achieved ATP II goals	6 week open label simvastatin run-in	Simvastatin 10-20-40-80 mg (78)	Simvastatin 10-20-40-80 mg + ezetimibe 10 mg (355)	12
Pearson 2005 [40]	Patients exceeding their LDL-C NCEP ATP III goals	Stable statin dose for at least 6 weeks and a cholesterol lowering diet	Atorvastatin 10-20-40-80 mg (386)	Atorvastatin 10-20-40-80 mg + ezetimibe 10 mg (769)	6
			Simvastatin 10-20-40-80 mg (279)	Simvastatin 10-20-40-80 mg + ezetimibe 10 mg (562)	
			Pravastatin 20-40 mg (209)	Pravastatin 20-40 mg + ezetimibe 10 mg (412)	
			Other statin mg (92)	Other statin + ezetimibe 10 mg (192)	
Gagné 2002 [35]	Patients not achieving their LDL-C NCEP ATP goals	Stable statin dose for at least week 6 weeks and a cholesterol lowering diet	Simvastatin 10-20-40-80 mg (112)	Simvastatin 10-20-40-80 mg + ezetimibe 10 mg (114)	8
			Atorvastatin 10-20-40-80 mg (152)	Atorvastatin 10-20-40-80 mg + ezetimibe 10 mg (136)	
			Lovastatin 10-20-40 mg (10)	Lovastatin 10-20-40 mg + ezetimibe 10 mg (7)	
			Pravastatin 10-20-40 mg (51)	Pravastatin 10-20-40 mg + ezetimibe 10 mg (52)	
			Fluvastatin 20-40-80 mg (19)	Fluvastatin 20-40-80 mg + ezetimibe 10 mg (30)	
			Cerivastatin 0.2-0.3-0.4-0.8 mg (25)	Cerivastatin 0.2-0.3-0.4-0.8 mg + ezetimibe 10 mg (17)	

Table I. Description of included trials - cont.

Source	Patient entry criteria	Pre-trial protocol	Monotherapy group (no. of participants)	Active treatment group (no. of participants)	Duration [weeks]
Patients washed out or treatment-naïve prior to entry					
Ballantyne 2003 [26]	Patients with primary hypercholesteremia (LDL-C > 145 mg/dl and < 250 mg/dl)	2-12 week screening/washout period, NCEP step 1 diet throughout trial, and 4 week single blind, placebo lead-in period	Atorvastatin 10 (52), 20 (52), 40 (57), 80 (57) mg	Atorvastatin 10 (61), 20 (55), 40 (57), 80 (50) mg + ezetimibe 10 mg	12
Ballantyne 2004 [27]	Patients with primary hypercholesteremia (LDL-C > 145 mg/dl and < 250 mg/dl)	Patients were enrolled from an extension study where they were washed out for 2-12 weeks and 4 week single blind, placebo lead-in period	Atorvastatin 10 (45) mg	Atorvastatin 10 (201) mg + ezetimibe 10 mg	52
Ballantyne 2005 [29]	LDL-C exceeding NCEP ATP III goals	Discontinued fibrate therapy for 9 weeks and all other lipid lowering therapy for 7 weeks, and 4 week single blind, placebo lead-in period	Atorvastatin 10 (235), 20 (230), 40 (232), 80 (230) mg	Simvastatin 10 (230), 20 (233), 40 (236), 80 (224) mg + ezetimibe 10 mg	6
Ballantyne 2004 [28]	LDL-C above drug treatment threshold established by NCEP ATP III goals (> 130 mg/dl)	Discontinued fibrate therapy for 9 weeks and all other lipid lowering therapy for 7 weeks, and 4 week single blind, placebo lead-in period	Atorvastatin 10 (262) mg	Simvastatin 10 (263), 20 (263) mg + ezetimibe 10 mg	24
Melani 2003 [39]	LDL-C ≥ 145 mg/dl to ≤ 250 mg/dl	2-12 week screening/washout period, NCEP step 1 diet throughout trial, and 4 week single blind, placebo lead-in period	Pravastatin 10-20-40 mg (205)	Pravastatin 10-20-40 mg + ezetimibe 10 mg (204)	12
Kerzner 2003 [37]	LDL-C > 145 mg/dl and < 250 mg/dl	2-12 week screening/washout period, NCEP step 1 diet throughout trial, and 4 week single blind, placebo lead-in period	Lovastatin 10-20-40 mg (220)	Lovastatin 10-20-40 mg + ezetimibe 10 mg (192)	12
Goldberg 2004 [36]	Patients with LDL-C > 145 mg/dl and > 250 mg/dl	Discontinued lipid lowering drugs for 6 weeks (statins) and 8 weeks (fibrates), NCEP step I diet throughout trial, and 4 week single blind, placebo lead-in period	Simvastatin 10 (79), 20 (89), 40 (90), 80 (87) mg	Simvastatin 10 (87), 20 (86), 40 (89), 80 (91) mg + ezetimibe 10 mg	12
Davidson 2002 [32]	Patients with LDL > 145 mg/dl and < 250 mg/dl	2-12 week screening/washout period and 4 week single blind, placebo lead-in period	Simvastatin 10 (70), 20 (61), 40 (65), 80 (67) mg	Simvastatin 10 (67), 20 (69), 40 (73), 80 (65) mg + ezetimibe 10 mg (274)	12
Feldman 2004 [34]	LDL-C > 130 mg/dl	Discontinued all lipid lowering agents for at least 6 weeks and a 4 week placebo diet run-in	Simvastatin 20 (253) mg	Simvastatin 10 (251), 20 (109), 40 (97) mg + ezetimibe 10 mg	5

Note: In Ballantyne 2003 [26] the number of patients included by statin dose corresponded to the number of patients whose hs-CRP levels were measured at the end of the trial.
In Ballantyne 2005 [29] and Pearson 2005 [40] the number of patients included in each statin dose category were the number patients who completed the trial.
In Ballantyne 2004 [27] patients who did not attain their NCEP ATP II LDL-C targets were titrated to the next highest statin dose at intervals of 6 weeks. However, only a small percentage of patients were titrated and results of their titration were not reported. In Feldman 2004 [34] only results after 5 weeks of treatment were used in the analysis because patients were titrated at subsequent durations and insufficient data for analysis was reported at these durations.

Table IIa. Demographics of patients on statin monotherapy prior to study entry

Source	Statin	Population size (*n*)	Mean age (years ± SD)	DM [%]	MS [%]	CHD [%]	CVD [%]	HTN [%]
Patients treated with statin/ezetimibe								
Barrios 2005 [30]	Simvastatin	221	63.5 ±9.6	26.7	N/A	100	N/A	63.8
Farnier 2005 [33]	Simvastatin	181	61.2 ±11.0	12.2	N/A	100	N/A	N/A
Cruz-Fernandez 2005 [31]	Atorvastatin	220	63.0 ±9.3	17.0	N/A	100	N/A	58.0
Masana 2005 [38]	Simvastatin	355	59.0	N/A	N/A	N/A	N/A	N/A
Gagné 2002 [35]	Atorvastatin/ simvastatin/ combo/other	379	60.0	64.6	N/A	N/A	N/A	N/A
Pearson 2005 [40]	Combo/other	2020	62.2 ±11.2	38.0	60.2	76.8	N/A	N/A
Total weighted average			**61.7 ±10.9**	**37.4**	**60.2**	**82.3**	**N/A**	**60.9**
Total		**3376**						
Patients treated with statin monotherapy								
Barrios 2005 [30]	Atorvastatin	214	63.4 ±10.2	24.8	N/A	100	N/A	54.2
Farnier 2005 [33]	Simvastatin	191	60.8 ±9.9	19.4	N/A	100	N/A	N/A
Cruz-Fernandez 2005 [31]	Atorvastatin	230	63.0 ±9.3	18.0	N/A	100	N/A	54.0
Masana 2005 [38]	Simvastatin	78	59.0	N/A	N/A	N/A	N/A	N/A
Gagné 2002 [35]	Simvastatin/ atorvastatin/ combo/other	390	60.0	70.8	N/A	N/A	N/A	N/A
Pearson 2005 [40]	Atorvastatin/ simvastatin/ combo/other	1010	61.6 ±11.5	39.1	59.0	N/A	N/A	N/A
Total weighted average			**61.5 ±10.8**	**39.4**	**59.0**	**100**	**N/A**	**54.1**
Total		**2113**						

Table IIb. Demographics of patients who were washed out or treatment-naïve prior to entry

Source	Statin	Population size (*n*)	Mean age (years ± SD)	DM [%]	MS [%]	CHD [%]	CVD [%]	HTN [%]
Patients treated with statin/ezetimibe								
Ballantyne 2004 [27]	Atorvastatin	201	57.6	7.0	N/A	11.4	3.5	33.8
Feldman 2004 [34]	Simvastatin	457	62.1 ±10	50.1	N/A	65.9	N/A	N/A
Ballantyne 2003 [26]	Atorvastatin	255	58.7 ±11.4	6.7	N/A	9.0	N/A	33.3
Melani 2003 [39]	Pravastatin	204	56.9	5.0	N/A	8.0	2.0	32.0
Kerzner 2003 [37]	Lovastatin	192	57.0 ±11.0	6.0	N/A	7.0	N/A	28.0
Goldberg 2004 [36]	Simvastatin	89	≥ 65	6.8	N/A	7.1	N/A	33.7
		264	< 65					
Ballantyne 2005 [29]	Simvastatin	951	59.0 ±10.6	N/A	N/A	46.4	N/A	N/A
Ballantyne 2004 [28]	Simvastatin	526	59.7 ±10.7	N/A	N/A	N/A	N/A	N/A
Davidson 2002 [32]	Simvastatin	274	57.6	3.3	N/A	8.4	N/A	30.0
Total weighted average			**59.1 ±10.6**	**16.3**	**N/A**	**30.0**	**2.7**	**32.0**
Total		**3413**						
Patients treated with statin monotherapy								
Ballantyne 2004 [27]	Atorvastatin	45	58.5	2.2	N/A	13.3	2.2	42.2
Feldman 2004 [34]	Simvastatin	253	62.1 ±9.7	45.0	N/A	66.0	N/A	N/A
Ballantyne 2003 [26]	Atorvastatin	248	57.8 ±11.7	4.4	N/A	9.3	N/A	32.3
Melani 2003 [39]	Pravastatin	205	55.1	7.0	N/A	8.0	0.98	31.0
Kerzner 2003 [37]	Lovastatin	220	56.0 ±12.0	9.0	N/A	10.0	N/A	29.0
Goldberg 2004 [36]	Simvastatin	80	≥ 65	4.3	N/A	6.6	N/A	28.7
		269	< 65					
Ballantyne 2005 [29]	Atorvastatin	951	58.5 ±10.2	N/A	N/A	46.1	N/A	N/A
Ballantyne 2004 [28]	Atorvastatin	262	60.8 ±10.0	N/A	N/A	N/A	N/A	N/A
Davidson 2002 [32]	Simvastatin	263	56.4	2.7	N/A	6.0	N/A	28.9
Total weighted average			**58.3 ±10.5**	**11.5**	**N/A**	**28.1**	**1.2**	**30.3**
Total		**2796**						

Note: Goldberg 2004 [36] was excluded from the calculation of mean age. Gagné 2002 [35] did not report patient comorbidities by statin type. Ballantyne 2004 [28] did not report any comorbidities.
DM – diabetes mellitus, MS – metabolic syndrome, CHD – coronary heart disease, CVD – cardiovascular disease, HTN – hypertension

Table IIIa. Baseline and post-treatment lipid profile of patients on statin monotherapy prior to study entry

Study	Statin	Baseline LDL	Post LDL	% Change LDL	Baseline TC	Post TC	% Change TC	Baseline TG	Post TG	% Change TG	Baseline HDL	Post HDL	% Change HDL	Baseline TC/HDL	Post TC/HDL	% Change TC/HDL
Patients treated with statin/ezetimibe combination therapy																
Barrios 2005 [30]	Simvastatin	123.4 (17.4)	82.9	–32.8 (17.8)	205.3 (23.2)	163.6	–20.3 (11.9)	131.0 (60.2)	120.0	–8.4 (37.2)	53.4 (12.0)	54.4	1.8 (11.9)	4.0 (0.8)	3.2	–20.9 (14.9)
Farnier 2005 [33]	Simvastatin	121.4 (14.7)	90.8	–25.2 (N/A)	201.9 (19.3)	168.6	–16.5 (N/A)	131.9 (56.6)	115.4	–12.5 (N/A)	51.4 (11.2)	52.4	2.0 (N/A)	3.9 (N/A)	3.2	–17.9 (N/A)
Masana 2005 [38]	Simvastatin	136.6 (47.3)	104.2	–23.7 (33.9)	216.0 (49.0)	181.7	–15.9 (22.6)	131.0 (4.1)	120.3	–8.2 (32.0)	50.1 (11.9)	51.1	2.0 (20.7)	4.5 (1.4)	3.8	–16.6 (28.3)
Cruz-Fernandez 2005 [31]	Atorvastatin	123.0 (16.6)	84.7	–31.1 (15.5)	204.6 (22.4)	163.5	–20.1 (11.0)	136.3 (69.0)	115.3	–15.4 (29.0)	51.4 (11.6)	52.9	2.9 (12.8)	4.1 (0.85)	3.2	–21.6 (12.5)
Pearson 2005 [40]	Combo/other	129.0 (N/A)	95.0	–25.8 (N/A)	N/A	N/A	N/A	151.0 (N/A)	131.0	–12.8 (N/A)	48.0 (N/A)	49.0	1.3 (N/A)	N/A	N/A	N/A
Gagné 2002 [35]	Combo/other atorvastatin simvastatin	138.0 (42.8)	103.5	–26.8 (N/A) –25 (N/A) –23.5 (N/A)	218.0 (44.8)	181.0	–17.0 (11.7)	136.0 (79.8)	117.0	–14.0 (27.3)	49.0 (11.7)	50.3	2.7 (9.7)	4.6 (1.9)	3.7	–19.0 (11.7)
Weighted average		**129.6 (31.8)**	**95.2**	**–27.1 (23.4)**	**211.1 (35.3)**	**173.9**	**–18.3 (13.9)**	**143.9 (51.9)**	**125.7**	**–12.5 (30.7)**	**49.1 (11.7)**	**50.2**	**1.8 (13.4)**	**4.3 (1.3)**	**3.5**	**–19.6 (15.7)**

Table IIIa. Baseline and post-treatment lipid profile of patients on statin monotherapy prior to study entry - cont.

Study	Statin	Baseline LDL	Post LDL	% Change LDL	Baseline TC	Post TC	% Change TC	Baseline TG	Post TG	% Change TG	Baseline HDL	Post HDL	% Change HDL	Baseline TC/HDL	Post TC/HDL	% Change TC/HDL
Patients treated with statin monotherapy																
Barrios 2005 [30]	Atorvastatin	125.3 (18.9)	99.9	–20.3 (17.6)	208.4 (24.7)	181.3	–13.0 (13.2)	121.2 (64.6)	113.0	–6.5 (36.6)	55.7 (13.5)	55.5	–0.4 (11.7)	3.9 (0.86)	3.5	–11.7 (14.6)
Farnier 2005 [33]	Simvastatin	123.4 (14.7)	122.3	–0.9 (N/A)	203.8 (19.7)	204.6	0.4 (N/A)	132.8 (69.9)	140.4	5.7 (N/A)	50.7 (13.1)	51.4	1.3 (N/A)	4.0 (N/A)	3.9	–1.0 (N/A)
Masana 2005 [38]	Simvastatin	131.4 (45.6)	135.7	3.3 (23.0)	211.3 (48.6)	216.6	2.5 (15.9)	128.0 (8.4)	134.9	5.4 (30.0)	51.0 (13.4)	50.7	–0.6 (14.1)	4.3 (1.1)	4.5	3.7 (18.5)
Cruz-Fernandez 2005 [31]	Atorvastatin	121.0 (15.5)	115.9	–4.2 (15.6)	202.6 (22.4)	197.5	–2.5 (10.8)	132.8 (69.0)	131.7	–0.8 (34.9)	51.8 (12.4)	51.9	0.1 (12.3)	4.1 (1.0)	4.0	–1.7 (13.4)
Pearson 2005 [40]	Combo/other	129.0 (N/A)	125.0	–2.7 (N/A)	N/A	N/A	N/A	151.9 (N/A)	151.0	–1.6 (N/A)	49.0 (N/A)	49.0	–0.8 (N/A)	N/A	N/A	N/A
Gagné 2002 [35]	Combo/other atorvastatin simvastatin	139.0 (39.5)	133.9	–3.8 (N/A) –4.0 (N/A) –3.1 (N/A)	219.0 (41.5)	214.0	–2.3 (19.9)	137.0 (64.7)	133.0	–2.9 (29.6)	50.0 (11.8)	50.5	1.0 (9.9)	4.6 (2.0)	4.5	–2.8 (11.8)
Weighted average		**129.2 (26.6)**	**123.3**	**–4.5 (17.4)**	**210.3 (31.0)**	**202.8**	**–3.2 (15.4)**	**141.4 (62.5)**	**140.2**	**–1.2 (32.4)**	**50.4 (12.6)**	**50.5**	**–0.1 (11.2)**	**4.2 (1.4)**	**4.1**	**–3.4 (18.2)**

Note: Baseline and % changes are expressed as the mean (SD). If baseline and/or post-treatment lipid values were reported in mmol/l, they were converted to mg/dl using a conversion factor of 38.67 for LDL-C, TC, HDL-C and 88.5 for TG. If trials did not report post-treatment values, they were calculated. The overall % change (SD) for lipid parameters were taken from Figure 2
Gagné 2002 [35] reported % changes by statin type for LDL-C only

regimen and those receiving statin monotherapy (Table IIa). The mean age and comorbidities reported in patients who were treatment-naïve or washed out from previous LLMs were also similar between treatment groups (Table IIb). However, patients treated with statin monotherapy prior to study entry were slightly older and presented more comorbidities than patients who were treatment-naïve or washed out from previous LLMs prior to study entry (Tables IIa, IIb).

Change in LDL-C

Overall effect

For the 3,376 patients who were treated with a statin plus ezetimibe coadministration regimen in the studies where ezetimibe was added to ongoing statin monotherapy, the weighted mean (SD) baseline serum LDL-C was 129.6 (31.8) mg/dl (95% CI 128.5 to 130.7 mg/dl) and the mean (SD) post-treatment LDL-C was 95.2 (31.8) mg/dl (95% CI 94.1 to 96.3 mg/dl) (Table IIIa). This is equivalent to an overall mean percent LDL-C change from baseline of –27.1% (95% CI –27.9 to –26.4%) (Table IIIa and Figure 2a). For the 2,113 patients in these studies treated with statin monotherapy, the weighted mean (SD) baseline plasma LDL-C was 129.2 (26.6) mg/dl (95% CI 127.4 to 131.0 mg/dl) and the mean (SD) post-treatment serum LDL-C was 123.3 (26.6) mg/dl (95% CI 121.3 to 125.1 mg/dl) (Table IIIa). This is equivalent to a change in LDL-C from baseline of –4.5% (95% CI –5.3 to -3.8%) (Table IIIa, Figure 2b).

In the studies that required patients to be treatment-naïve or to be washed out from LLMs prior to study entry, a total of 3,413 patients were treated with a statin plus ezetimibe coadministration therapy. For these patients, the mean (SD) baseline serum LDL-C level was 176.5 (31.2) mg/dl (95% CI 175.5 to 177.5 mg/dl) and the post-treatment mean (SD) LDL-C level was 86.5 (31.2) mg/dl (95% CI 85.5 to 87.5 mg/dl) (Table IIIb). A total of 2,796 patients in these studies were treated with statin monotherapy. These patients had a mean (SD) baseline serum LDL-C of 178.1 (31.5) mg/dl (95% CI 176.9 to 179.3 mg/dl) and a mean post treatment LDL-C level of 107.8 (31.5) mg/dl (95% CI 106.6 to 109.0 mg/dl). These changes represent an overall mean percent change in LDL-C of –51.5% (95% CI –51.9 to –51.1%) for the statin plus ezetimibe coadministration regimen and of –40.4% (95% CI –40.9 to –40.0%) for statin monotherapy (Table IIIb, Figures 3a, 3b, respectively).

Change in HDL-C

Overall effect

For the 3,376 patients who were treated with a statin plus ezetimibe coadministration regimen in the studies where ezetimibe was added to ongoing statin monotherapy, the weighted mean (SD) baseline serum HDL-C was 49.1 (11.7) mg/dl and the mean (SD) post-treatment HDL-C was 50.2 (11.7) mg/dl (Table IIIa). This is equivalent to an overall mean percent HDL-C change from baseline of 1.8% (Table IIIa). For the 2,113 patients in these studies treated with statin monotherapy, the weighted mean (SD) baseline plasma HDL-C was 50.4 (12.6) mg/dl and the mean (SD) post-treatment serum HDL-C was 50.5 (12.6) mg/dl (Table IIIa). This is equivalent to a change in HDL-C from baseline of –0.1% (Table IIIa).

For the 3,413 patients in the treatment-naïve category were treated with a statin plus ezetimibe coadministration therapy, the mean (SD) baseline serum HDL-C level was 49.0 (12.3) mg/dl and the post-treatment mean (SD) HDL-C level was 52.8 (12.3) mg/dl (Table IIIb). A total of 2,796 patients in these studies were treated with statin monotherapy. These patients had a mean (SD) baseline serum HDL-C of 49.4 (12.0) mg/dl and a mean post treatment HDL-C level of 52.1 (12.0) mg/dl. These changes represent an overall mean percent change in LDL-C of 8.7% for the statin plus ezetimibe coadministration regimen and of 5.6% for statin monotherapy (Table IIIb).

Tables IIIa and IIIb also summarize the mean percent changes in TC, TG, and TC/HDL-C observed in the studies reviewed. Across all patient populations, ezetimibe coadministered with statin produced higher reductions in TC, TG and TC/HDL-C when compared to statin monotherapy.

Discussion

Epidemiological studies and clinical trials have confirmed the association between elevated levels of LDL-C and increased risk for CHD. More recently, attention has been given to the potential beneficial effects of higher levels of HDL-C in the prevention of CHD. Therefore, optimal preventive interventions would reduce LDL-C and increase HDL-C [3-5].

Through the complementary action offered by statin and ezetimibe coadministration, the likelihood of achieving LDL-C goals in hypercholesterolemic patients is increased significantly when compared to statin monotherapy [26, 32]. In the EASE trial, 71% of patients reached their NCEP ATP III LDL-C goal when ezetimibe was added to their statin therapy, compared with only 21% of patients who reached their goal when a placebo was added to their statin regimen [40]. As a result, itis expected that a higher proportion of patients will achieve their recommended target LDL-C goals if treated with combination therapy. In patients who fail to reach their lipid goal while on statin monotherapy, combination therapy with ezetimibe provides an alternative to titrating the statin dose, which has been associated with an increased incidence of adverse events [26, 32, 35, 41].

Table IIIb. Baseline and post-treatment lipid profile of patients who were treatment-naïve or washed out prior to study entry

Study	Statin	Baseline LDL	Post LDL	% Change LDL	Baseline TC	Post TC	% Change TC	Baseline TG	Post TG	% Change TG	Baseline HDL	Post HDL	% Change HDL	Baseline TC/HDL	Post TC/HDL	% Change TC/HDL
Statin/ezetimibe combination therapy																
Goldberg 2004 [36]	Simvastatin	175.0	81.9	–53.2	260.0	162.0	–37.7	169.0	121.7	–28.0	51.0	55.2	8.2	5.4	3.1	–41.7
		(27.0)		(17.2)	(30.0)		(13.3)	(93.0)		(28.0)	(13.0)		(13.1)	(1.0)		(14.3)
Davidson 2002 [32]	Simvastatin	176.3	88.0	–49.9	264.0	167.0	–36.6	178.8	133.0	–24.1	50.4	54.5	9.3	5.5	3.2	–41.2
		(19.9)		(14.9)	(N/A)		(11.6)	(65.1)		(23.2)	(12.2)		(13.2)	(N/A)		(13.2)
Feldman 2004 [34]	Simvastatin	166.8	81.7	–51.0	248.9	159.0	–36.1	177.6	137.1	–22.8	45.1	48.2	6.9	5.5	3.3	–39.9
		(35.3)		(12.7)	(39.2)		(9.6)	(95.2)		(25.2)	(10.5)		(10.9)	(N/A)		(10.9)
Ballantyne 2005 [29]	Simvastatin	177.7	82.8	–53.4	264.2	191.8	–27.4	171.0	124.1	–27.4	49.1	53.0	7.9	5.4	3.6	–33.3
		(37.9)		(N/A)	(42.0)		(N/A)	(94.9)		(N/A)	(12.6)		(N/A)	(N/A)		(N/A)
Ballantyne 2004 [28]	Simvastatin	179.6	83.2	–53.7	264.8	161.5	–39.0	175.3	122.2	–30.3	46.7	51.7	10.7	5.7	3.1	–45.6
		(41.5)		(13.4)	(44.8)		(10.2)	(101.2)		(27.4)	(11.5)			(N/A)		(N/A)
Ballantyne 2004 [27]	Atorvastatin	181.7	92.8	–48.4	266.8	174.0	–35.4	159.3	115.1	–29.6	54.1	54.1	6.3	4.9	3.2	–34.7
		(23.2)		(18.8)	(27.1)		(14.0)	(N/A)		(N/A)	(15.5)		(13.4)	(N/A)		(N/A)
Ballantyne 2003 [26]	Atorvastatin	179.8	81.8	–54.5	267.2	157.4	–41.1	168.2	113.0	–32.8	50.7	54.4	7.3	5.3	2.9	–44.5
		(24.7)		(15.0)	(24.7)		(11.8)	(N/A)		(N/A)	(12.4)		(11.7)	(N/A)		(13.9)
Kerzner 2003 [37]	Lovastatin	176.0	107.4	–39.0	262.0	186.0	–29.0	172.0	134.2	–22.0	50.0	54.5	9.0	5.0	3.3	–34.0
		(13.9)		(13.9)	(27.7)		(13.9)	(55.4)		(27.7)	(13.9)		(13.9)	(1.4)		(13.9)
Melani 2003 [39]	Pravastatin	177.9	108.3	–37.7	263.0	193.4	–27.1	177.0	141.6	–17.6	50.3	54.1	8.1	5.4	3.6	–32.0
		(19.3)		(12.9)	(N/A)		(8.6)	(62.0)		(30.0)	(11.6)		(11.4)	(N/A)		(11.4)
Weighted average		**176.5**	**86.5**	**–51.5**	**262.0**	**173.8**	**–35.2**	**172.5**	**126.3**	**–27.8**	**49.0**	**52.8**	**8.7**	**5.4**	**3.3**	**–35.2**
		(31.2)		**(13.9)**	**(37.2)**		**(10.7)**	**(88.2)**		**(27.1)**	**(12.3)**		**(13.2)**	**(1.1)**		**(12.8)**

Table IIIb. Baseline and post-treatment lipid profile of patients who were treatment-na?ve or washed out prior to study entry – cont.

Study	Statin	Baseline LDL	Post LDL	% Change LDL	Baseline TC	Post TC	% Change TC	Baseline TG	Post TG	% Change TG	Baseline HDL	Post HDL	% Change HDL	Baseline TC/HDL	Post TC/HDL	% Change TC/HDL
Statin monotherapy																
Goldberg 2004 [36]	Simvastatin	175.0	107.6	–38.5	259.0	190.6	–26.4	167.0	141.6	–15.2	49.0	52.7	7.6	5.5	3.8	–30.8
		(25.0)		(14.2)	(30.0)		(11.3)	(89.0)		(34.1)	(12.0)		(11.9)	(1.0)		(13.0)
Davidson 2002 [32]	Simvastatin	178.5	114.0	–36.1	265.0	196.0	–25.8	168.7	137.0	–16.6	51.0	54.4	6.9	5.4	3.8	–30.0
		(20.0)		(14.6)	(N/A)		(11.4)	(59.8)		(22.7)	(10.9)		(13.0)	(N/A)		(13.0)
Feldman 2004 [34]	Simvastatin	173.8	107.8	–38.0	256.7	187.4	–27.0	169.5	137.3	–19.0	46.1	48.5	5.1	5.7	3.9	–30.0
		(44.7)		(12.7)	(46.8)		(11.1)	(88.8)		(30.2)	(11.2)		(11.1)	(N/A)		(11.1)
Ballantyne 2005 [29]	Atorvastatin	178.9	97.9	–45.3	264.5	197.0	–25.5	167.0	124.4	–29.9	48.8	50.9	4.3	5.4	3.9	28.3
		(37.9)		(N/A)	(42.0)		(N/A)	(94.0)		(N/A)	(11.9)		(N/A)	(N/A)		(N/A)
Ballantyne 2004 [28]	Atorvastatin	180.6	99.3	–45.0	266.8	175.0	–34.4	171.5	121.8	–29.0	46.9	50.0	6.5	5.7	3.5	38.4
		(45.6)		(14.0)	(49.8)		(10.1)	(94.0)		(25.9)	(11.4)		(14.3)	(N/A)		(N/A)
Ballantyne 2004 [27]	Atorvastatin	185.6	112.1	–38.6	270.7	193.4	–27.5	159.3	132.8	–16.9	50.3	54.1	5.4	5.4	3.6	–33.3
		(23.2)		(12.4)	(23.2)		(10.4)	(N/A)		(N/A)	(11.6)		(3.13)	(N/A)		(N/A)
Ballantyne 2003 [26]	Atorvastatin	179.8	102.0	42.4	268.8	182.5	–32.1	150.5	113.1	–24.5	53.8	56.1	4.3	5.0	3.3	–44.5
		(23.6)		(15.0)	(24.4)		(11.8)	(N/A)		(N/A)	(12.6)		(11.7)	(N/A)		(13.9)
Kerzner 2003 [37]	Lovastatin	178	133.5	–25.0	265.0	217.3	–18.0	178.0	158.4	–11.0	51.0	53.0	4.0	6.0	4.7	–21.0
		(14.8)		(14.8)	(29.7)		(14.8)	(59.3)		(29.7)	(14.8)		(14.8)	(1.5)		(14.8)
Melani 2003 [39]	Pravastatin	177.9	135.3	–24.3	263.0	216.6	–17.2	177.0	159.3	–7.6	50.3	54.1	6.7	5.5	4.3	–21.7
		(23.2)		(12.9)	(N/A)		(8.6)	(62.0)		(30.1)	(11.6)		(11.5)	(N/A)		(11.5)
Weighted average		**178.1**	**107.8**	**-40.4**	**263.8**	**194.9**	**–27.8**	**167.8**	**133.0**	**–23.3**	**49.4**	**52.1**	**5.6**	**5.5**	**3.9**	**–34.4**
		(31.5)		**(13.9)**	**(38.2)**		**(10.8)**	**(83.5)**		**(27.3)**	**(12.0)**		**(11.7)**	**(1.2)**		**(12.8)**

Note: Baseline and % changes are expressed as the mean (SD). If baseline and/or post-treatment lipid values were reported in mmol/l, they were converted to mg/dl using a conversion factor of 38.67 for LDL-C, TC, HDL-C and 88.5 for TG. If trials did not report post-treatment values, they were calculated. The overall % change (SD) for lipid parameters were taken from Figure 2.
In Ballantyne 2004 [28], baseline values were taken as an average of all patients at study entry and the post-treatment values were obtained by a weighted average of the mean percent changes in lipid parameters over the different durations of treatment

Beyond LDL-C, evidence has shown that high HDL-C protects against CHD, and that low blood levels of HDL-C indicate high risk of a coronary event [42]. Low HDL-C is widely prevalent in the United States [42]. In recognition of its anti-atherogenic effects, recent guidelines have increased the threshold for defining low levels of HDL-C for both men and women [42]. Gordon *et al.* showed that an increase in HDL-C of 1 mg/dl equates with a 2% relative risk reduction in the incidence of coronary events in men and 3% in women [41]. These observations suggest that, in order to properly reduce morbidity and mortality due to CHD, pharmacological increases in HDL-C should, also be targeted in the prevention of CHD.

In the studies reviewed, two possible approaches to the management of hypercholesterolemia were assessed. One involves the addition of ezetimibe to existing statin monotherapy in patients who fail to reach their treatment goals, while the other involves the simultaneous administration of a statin plus ezetimibe regimen in treatment-naïve patients.

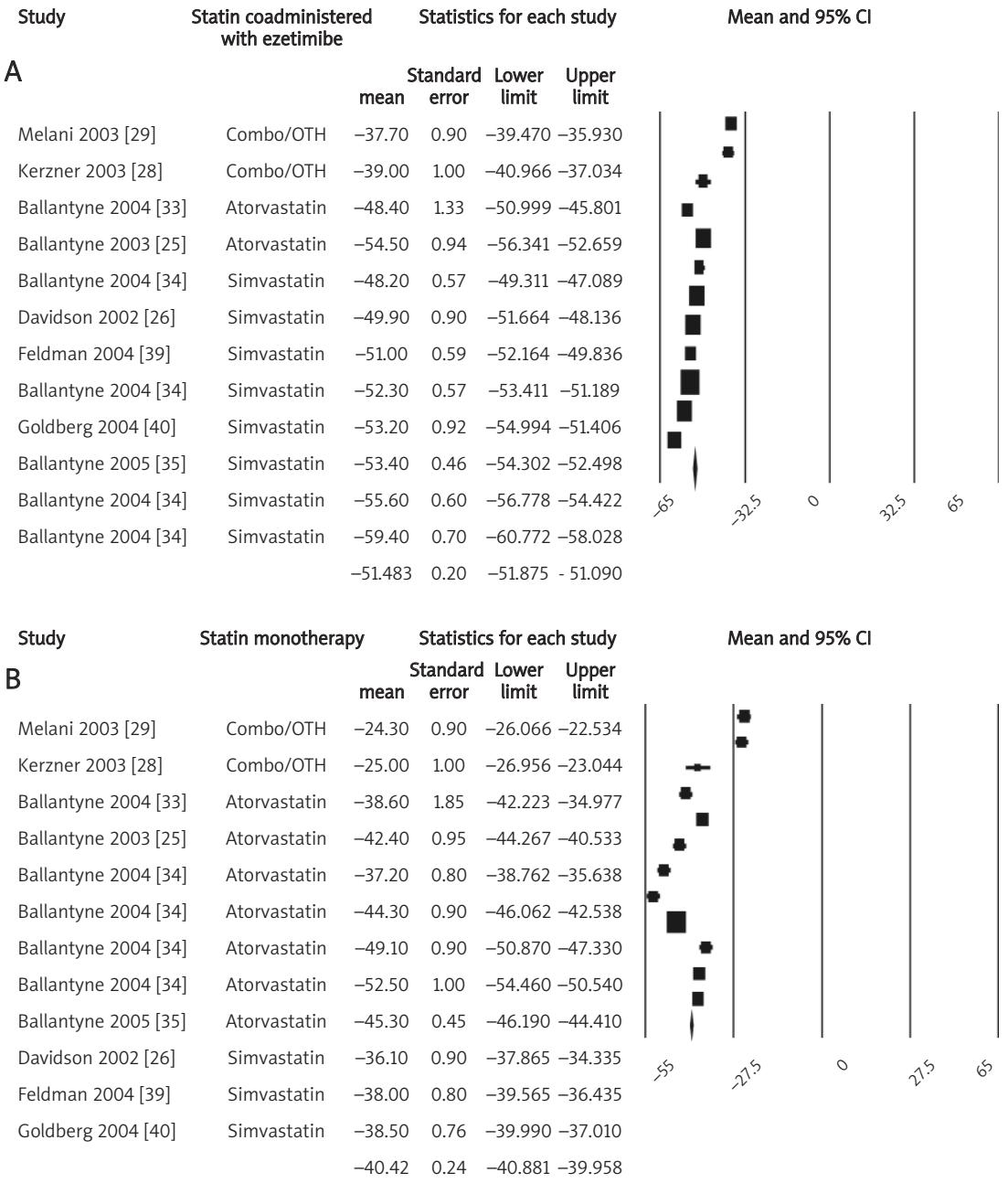

Figure 3. Mean percent reduction in LDL-C for patients who were treatment-naïve or washed out prior to study entry for (**A**) patients coadministered a statin with ezetimibe and (**B**) patients continuing on their existing statin monotherapy regimen

CI – confidence interval

The addition of ezetimibe to patients previously on a statin therapy produced less of a reduction in serum LDL-C when compared to the simultaneous administration of both these agents in patients washed out from previous LLMs. The difference in baseline LDL-C values would explain the higher mean percent change observed in treatment-naïve patients or washed out patients from their previous LLMs. This difference is explained by the effect of prior statin monotherapy in lowering LDL-C. Once patients have been washed out, lipid profiles return to pre-treatment levels. Therefore, a greater baseline change was observed in this population as their baseline LDL-C levels were higher. Patients who were on statin monotherapy and had ezetimibe added-on, have baseline LDL-C levels reflective of the effect of their statin therapy. However, both groups attained similar post-treatment LDL-C levels of < 100 mg/dl.

When compared to statin monotherapy, statin coadministered with ezetimibe was found to produce greater reductions in plasma LDL-C. While both treatment groups had similar baseline values, they differed in their post-treatment LDL-C values as the combination therapy group was reduced to 83.0 mg/dl and the monotherapy group, to 103.0 mg/dl. These results indicate that the post-treatment LDL-C values in patients treated with statin plus ezetimibe combination therapy were, on average, significantly lower than the recommended 100 mg/dl LDL-C target set by current treatment guidelines. Evans *et al*. suggested that, for every 38.6 mg/dl decrease in LDL-C values in patients treated with statins, regardless of baseline LDL-C values, an estimated 25% reduction in cardiovascular risk can be expected [44]. Applying this model to the results of this meta-analysis, the 20 mg/dl difference observed between the combination therapy and monotherapy groups would result in an estimated 13% additional cardiovascular risk reduction. Recently, two studies have been released regarding the effects of ezetimibe on cardiovascular outcomes. The ENHANCE [21, 45] and SEAS [46] studies set out to assess the effect of ezetimibe on the rate of atherosclerosis progression and aortic valve stenosis respectively. Although these studies failed to show ezetimibe having any effect on these cardiovascular outcomes, the SEAS study showed a reduction in the risk of ischemic cardiovascular events in patients taking combination therapy. Also, the validity of the results in the ENHANCE trial have been questioned for numerous reasons. Firstly, change in carotid intima-media thickness (IMT) in the study population was probably not an effective surrogate for the rate of cardiovascular clinical events. Also, most individuals in the study had been under previous treatment with a statin making it more difficult to improve their baseline IMT [47]. Ezetimibe related cardiovascular outcomes are currently the subject of ongoing outcomes trials. Also, the effect this drug has on mortality in this population remains to be fully evaluated by the IMROVE-IT trial which should be available in 2011 [47].

Limitations

A potential limitation of the current meta analysis is that for a small number of studies, certain assumptions were made for the estimation of variance and standard deviations. This could lead to biased estimates of effect. This manuscript relates to short term data, with a mean duration of treatment of 13.6 weeks in patients who were treatment naïve or washed out of any LLMs and a mean duration of treatment of 6.9 weeks in patients that were on statin monotherapy prior to study entry. Due to the well-documented differences in medication adherence in short and long term studies, data regarding long term efficacy of treatment with ezetimibe and statin are needed.

In conclusion, the aim of this study was to look at the effect of ezetimibe/statin coadministration with a focus on biomarkers traditionally used for the approval of lipid lowering medications. The results indicate that adding ezetimibe to ongoing statin therapy is efficient in reducing serum LDL-C in patients who may not attain target levels on statin therapy alone. They also indicate that the simultaneous administration of a statin plus ezetimibe regimen in patients who are treatment-naïve is also efficient at reducing plasma LDL-C.

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