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Effect of ezetimibe co-administered with statin therapy in Swiss outpatients

Results of patients with coronary artery disease and diabetes mellitus

Summary

Background: Ezetimibe impairs the intestinal absorption of dietary and biliary cholesterol and has been shown to significantly decrease low-density-lipoprotein-cholesterol (LDL-C) levels either as a monotherapy or when co-administered with a statin.

Aim: The aim of the present analysis of the observational program was to assess the efficacy of ezetimibe co-administered with statins in patients at high-risk for coronary artery disease (CAD) in daily practice.

Methods: In outpatients with hypercholesterolemia either a combined lipid-modifying therapy consisting of ezetimibe (10 mg) and a statin (varying dose) was initiated for those not currently on statin therapy, or ezetimibe was added to previously established statin therapy. Total cholesterol (TC), LDL-C, high-density-lipoprotein-cholesterol (HDL-C), and triglycerides (TG) before initiation of ezetimibe (baseline) and after an individual treatment duration (follow-up visit) were assessed by the treating physician.

Results: There were 601 patients classified as high-risk according to the guidelines of the Working group Lipids/Atherosclerosis of the Swiss Society of Cardiology (WGLA/SSC). In 52 of these patients the newly initiated therapy consisting of ezetimibe and a statin resulted in a mean TC reduction from 7.2 to 5.1 mmol/L (–29%; p <0.001) and a mean LDL-C reduction from 4.7 to 3.0 mmol/L (–38%; p <0.001) after a treatment duration of 45 ± 21 days. In 374 high-risk patients the co-administration of ezetimibe with ongoing unchanged statin therapy resulted in an additional TC reduction of 21 to 23% (p <0.001 for all statins) and an additional LDL-C reduction of 28 to 31% (p <0.001 for atorvastatin, simvastatin, pravastatin; p = 0.001 for fluvastatin) depending on the statin used after a treatment duration of 57 ± 49 days. On average, TC levels decreased from 6.3 to 4.9 mmol/L and LDL-C levels from 3.9 to 2.7 mmol/L. Of 310 high-risk patients not achieving a LDL-C level of ≤2.6 mmol/L with statin monotherapy and requiring up to 40% LDL-C reduction 59% reached this goal after an 8-weeks period of co-administration therapy with ezetimibe and a statin.

Conclusions: Co-administration of ezetimibe and a statin is highly efficacious in patients with CAD and/or diabetes mellitus. The significant results of randomised trials can also be seen in daily practice in a typical outpatient setting.

Key words: low-density-lipoprotein; cholesterol; statin; ezetimibe

Introduction

Coronary artery disease (CAD) is still the leading cause of mortality and morbidity in the Western world despite advances in treatment [1, 2]. In the United States there were more than 3 million hospital discharges for unstable angina, acute coronary syndrome, and myocardial infarction in 2001 [2]. Hypercholesterolemia is a major risk factor for the development and progression of CAD [3]. One principal goal of primary and secondary prevention is the correction of elevated low-density-lipoprotein-cholesterol (LDL-C) levels by lifestyle changes and lipid-lowering drugs [4]. Treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has been shown to be associated with a significant reduction in LDL-C levels as well as cardiovascular endpoints in both primary and secondary prevention [5–9], and statins are thus a cornerstone of lipid-modifying therapy. Recent

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studies suggest highest benefit from the most aggressive LDL-C reduction [10, 11]. The progression of coronary atherosclerosis assessed by sequential intravascular ultrasound examinations has been shown to be stopped by very intensive lipid-modifying therapy with statins [11]. Currently, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III and the American Heart Association and American College of Cardiology recommend a target LDL-C level of less than 100 mg/dL (2.6 mmol/L) for patients with CAD [5]. However, many patients, especially those at the highest risk for CAD do not reach these LDL-C goals by lifestyle changes and statin monotherapy despite good compliance [12, 13]. For these patients the co-administration of two lipid-altering drugs with complementary mechanisms of action offers an advantage over monotherapy and may allow achievement of a lower LDL-C level, thus reducing cardiovascular risk [14]. However, utilisation of previously available lipid-modifying agents (eg statins and fibrates) in combination is limited by the significantly higher risk of side effects associated with combination therapy [15].

Ezetimibe is a new lipid-lowering drug with a distinct mechanism of action. Beyond hepatic *de novo* synthesis, which is inhibited by statins, a substantial amount of serum cholesterol originates from intestinal absorption, which is not influenced by statins. Ezetimibe inhibits the absorption of dietary cholesterol and reabsorption of biliary cholesterol in the intestinal lumen [15]. The molecular mechanism of the inhibition of cholesterol absorption by ezetimibe has very recently been shown to be linked to the Niemann-Pick C1 Like 1 protein [16], a structural protein on the brush border of intestinal enterocytes, which mediates the intestinal absorption of cholesterol. Ezetimibe has been shown to lower LDL-C levels when given as monotherapy compared to placebo [17, 18]. More interestingly, several randomised, controlled trials documented an additional benefit of ezetimibe regarding LDL-C and TG reduction when co-administered with a statin as compared to the effects of statin monotherapy at the same dose [19–23]. This effect has been observed when ezetimibe has been co-administered with atorvastatin [20], simvastatin [21], pravastatin [22], and lovastatin [23]. It has been demonstrated that ezetimibe does not interfere with the absorption of fat-soluble vitamins and bile acids [15, 17, 24].

The aim of our observational program was (1.) to assess the efficacy of ezetimibe in co-administration with a statin in a typical outpatient setting in Switzerland, (2.) to determine whether the impressive results of randomised clinical trials concerning LDL-C reduction could be mirrored in daily practice, and (3.) to find out how many patients could reach their LDL-C goal due to additional ezetimibe co-administration.

Patients and methods

Patients and lipid parameters

The present observational program was performed in Switzerland between December 2002 and March 2004. Physicians were asked to report on outpatients with primary hypercholesterolemia in whom a therapy with ezetimibe was initiated. All patients meeting this criterion were eligible for the observational program, there were no exclusion criteria. A standardised questionnaire was completed to assess demographic data, cardiovascular risk profile, lipid status if available, and lipid lowering therapy. For characterisation of the patients' cardiovascular risk physicians had to report on the following items: CAD, diabetes, hypertension, obesity, family history of CAD, and cigarette smoking. For all these items no formal definitions were given, but the physicians had to answer based on the patients' previous medical history. Information on the items "older age" (men >50 years, women >60 years) and "hypertriglyceridemia" was derived from the demographic data and laboratory results respectively.

The patients were divided in two groups: (1.) initiation of ezetimibe 10 mg (Ezetrol®, Merck/Schering-Plough Pharmaceuticals, Inc., Kenilworth, NJ, USA) in co-administration with a statin in patients not currently on statin therapy, and (2.) co-administration of ezetimibe 10 mg in patients already taking a statin. Lipid status and lipid lowering therapy were documented at the baseline and follow-up visit. The interval between baseline and follow-up visit was determined by the individual physician. Lipid-lowering therapy was initiated by the treating physician. Monitoring and follow-up visits depended on the patient's underlying medical condition and the treatment prescribed, according to the physician's routine practice.

Patients were included in the present analysis if they were classified as *high-risk* for CAD according to the guidelines of the Working group Lipids/Atherosclerosis of the Swiss Society of Cardiology (WGLA/SSC) released in 1999 [25], ie those with documented CAD and/or diabetes mellitus.

Statistics

Statistical analysis was performed using a commercially available software package (SPSS version 11.5 for windows). Continuous data are expressed as the mean value ± standard deviation (or only the mean value for easier reading). The Wilcoxon rank sum test was used to compare lipid parameters before and after ezetimibe therapy. A two sided p-value of <0.05 was considered statistically significant.

Safety and adverse events

Safety information was collected through spontaneous reporting by the participating physicians. In addition, at the end of the program, a reminder letter was sent to report any potentially unreported adverse events. For the evaluation of the tolerability profile of ezetimibe 10 mg all questionnaires received in this program have been included in the analysis.

Results

Baseline characteristics

There were 142 participating physicians (54% cardiologists, 15% endocrinologists, 9% internists, 4% angiologists, 1% nephrologists, and 16% with other specialities). The analysis was based on the questionnaires from 897 patients, comprising 37% women and 63% men. According to the WGLA/SSC guidelines [25], 601 patients were classified in the *high-risk* group (67%). In table 1, the risk profile of the *high-risk* patients is presented.

Of these 601 patients belonging to the *high-risk* group 93 patients were either given ezetimibe as a monotherapy mainly due to statin intolerance (n = 77) or had to be excluded due to different treatment regimen (n = 16). Accordingly, 508 *high-risk* patients (age 62 ± 10 years) receiving a combination of a statin and ezetimibe could be included in the final analysis. Mean treatment duration was 56 ± 47 days for all *high-risk* patients receiving ezetimibe and a statin (n = 498). Treatment duration was unknown for 10 *high-risk* patients. Ninety percent (n = 456) of these *high-risk* patients were already on lipid lowering therapy with a statin, when therapy with ezetimibe was initiated at the baseline visit (table 2). In 374 of these 456 patients the statin dose remained unchanged when ezetimibe was initiated.

Table 1
Risk profile of 601 high-risk patients, ie those with coronary artery disease (CAD) and/or diabetes mellitus.

CAD, no diabetes mellitus	325 (54%)
Diabetes mellitus, no CAD	162 (27%)
CAD and diabetes mellitus	114 (19%)
Other risk factors	
Older age *	475 (79%)
Hypertension	337 (56%)
Hypertriglyceridaemia	301 (50%)
Obesity	240 (40%)
Family history of CAD	222 (37%)
Cigarette smoking	256 (26%)

* Men >50 years, women >60 years.

Statin doses

The mean doses of the statins used for initiation of a therapy in co-administration with ezetimibe were atorvastatin 15 ± 9 mg (n = 28), simvastatin 29 ± 19 mg (n = 13), pravastatin 21 ± 11 mg (n = 10), and fluvastatin 20 mg (n = 1). Patients with ongoing statin therapy and unchanged statin dose at the baseline visit were taking on average atorvastatin 37 ± 21 mg (n = 115), simvastatin 37 ± 21 mg (n = 114), pravastatin 36 ± 14 mg (n = 125), and fluvastatin 66 ± 20 mg (n = 20) at the time that ezetimibe was co-administered.

Table 2
High-risk patients classified according to simultaneous initiation of combined lipid-modifying therapy or co-administration of ezetimibe to an ongoing statin therapy. The percentage of administered statins is given.

Patients at high-risk (n = 601)			
Ezetimibe in co-administration with a statin (n = 508)		**ezetimibe-monotherapy (n = 77)**	**other treatment (n = 16)**
Ezetimibe added to statin (n = 456; 90%)	**initiation of ezetimibe + statin (n = 52; 10%)**		
34% Atorvastatin	54% atorvastatin		
30% Simvastatin	25% simvastatin		
31% Pravastatin	19% pravastatin		
5% Fluvastatin	2% fluvastatin		
ezetimibe added to unchanged statin dose (n = 374; 82%)	ezetimibe added to changed statin dose (n = 82; 18%)		

Table 3
Baseline characteristics of high-risk patients treated with ezetimibe in co-administration with a statin.

	patients at high-risk ezetimibe in co-administration with a statin (n = 508)	
	ezetimibe added to unchanged statin dose (n = 374)	**simultaneous initiation of ezetimibe + statin (n = 52)**
Age (years)	62 ± 10	65 ± 10
Total cholesterol (mmol/L)	6.3 ± 1.2	7.2 ± 1.9
LDL cholesterol (mmol/L)	3.9 ± 1.0	4.7 ± 1.6
HDL cholesterol (mmol/L)	1.3 ± 0.6	1.3 ± 0.4
Triglycerides (mmol/L)	2.8 ± 2.9	3.3 ± 4.5

LDL = low-density-lipoprotein; HDL = high-density-lipoprotein.

Effects of ezetimibe initiated in co-administration with a statin in high-risk patients

Fifty-two *high-risk* patients (age 65 ± 10 years; table 3) were initiated on a lipid modifying therapy consisting of ezetimibe in co-administration with one of several statins (atorvastatin 5–40 mg, simvastatin 10–80 mg, pravastatin 10–40 mg, fluvastatin 20 mg). For all treatment groups mean TC levels were reduced from 7.2 to 5.1 mmol/L (–29%; p <0.001) and mean LDL-C levels were reduced from 4.7 to 3.0 mmol/L (–38%; p <0.001) after a treatment duration of 45 ± 21 days (fig. 1). The mean TG levels decreased from 3.3 to 2.2 mmol/L (–20%; p <0.001) with a simultaneous increase in the mean HDL-C levels from 1.3 to 1.4 mmol/L (+11%; p = 0.118).

Mainly due to statin intolerance, 77 *high-risk* patients (age 65 ± 11 years) were initiated on ezetimibe 10 mg monotherapy, which resulted in a mean TC reduction from 6.8 to 5.5 mmol/L (–18%; p <0.001) and a mean LDL-C reduction from 4.3 to 3.3 mmol/L (–23%; p <0.001). Mean HDL-C levels remained unchanged at 1.4 mmol/L, whereas mean TG levels decreased from 2.7 to 2.3 mmol/L (–9%; p <0.001).

Effects of ezetimibe added to established statin therapy in high-risk patients

At the time of ezetimibe initiation 456 of the *high-risk* patients (age 62 ± 10 years; table 3) were already on an established statin regimen, which remained unchanged in 374 (82%) of them (table 2). Co-administration of ezetimibe in patients with ongoing unchanged statin therapy resulted in a mean TC reduction from 6.3 to 4.9 mmol/L for all treatment groups after a treatment duration of 57 ± 49 days. Additional TC reduction was –21% for ezetimibe in co-administration with atorvastatin 10–80 mg (p <0.001), –23% for ezetimibe and simvastatin 10–80 mg (p <0.001), –22% for ezetimibe and pravastatin 10–80 mg (p <0.001), and –23% for ezetimibe and fluvastatin 40–80 mg (p <0.001) (fig. 2A).

The co-administration of ezetimibe with ongoing statin therapy resulted in a mean LDL-C reduction from 3.9 to 2.7 mmol/L for all treatment groups. Levels for LDL-C were lowered by an additional 30% with ezetimibe in co-administration with atorvastatin (p <0.001), by 31% with ezetimibe and simvastatin (p <0.001), by 28% with ezetimibe and pravastatin (p <0.001), and by 28% with ezetimibe and fluvastatin (p = 0.001) (fig. 2B). The effects of ezetimibe in patients with established statin therapy on HDL-C levels were an increase by an additional 0.3% when added to atorvastatin (p = 0.506), by 7% when added to simvastatin (p = 0.340), by 5% when added to pravastatin (p = 0.071), and by 2% when added to fluvastatin (p = 0.450). Mean HDL-C levels for

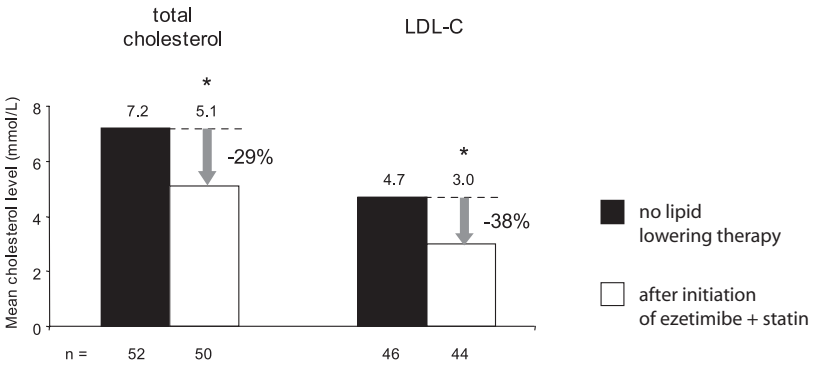

Figure 1
Reduction of total cholesterol and low-density-lipoprotein-cholesterol (LDL-C) in high-risk patients due to simultaneous initiation of ezetimibe and statin therapy. Data pooled for all doses of all statins (atorvastatin 5–40 mg, simvastatin 10–80 mg, pravastatin 10–40 mg, fluvastatin 20 mg).
* p <0.001 vs no lipid lowering therapy for all statins pooled.

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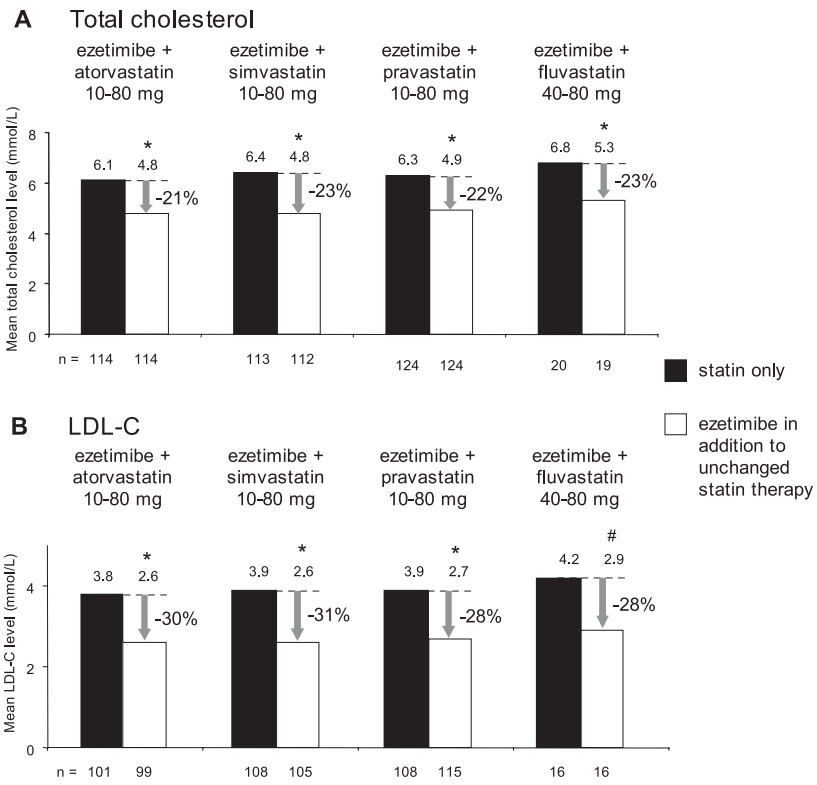

Figure 2
Additional reduction of total cholesterol (A.) and low-density-lipoprotein-cholesterol (LDL-C) (B.) in high-risk patients due to co-administration of ezetimibe to ongoing statin therapy. Data pooled for all doses of one statin.
* p <0.001 vs. statin only; # p = 0.001 vs statin only.

all treatment groups remained unchanged at 1.3 mmol/L. Triglyceride levels decreased by an additional 9% when ezetimibe was co-administered with atorvastatin (p <0.001), by 10% when ezetimibe was co-administered with simvastatin (p <0.001), by 7% when ezetimibe was used together with pravastatin (p = 0.001), and by 19% when ezetimibe was co-administered with fluvastatin (p = 0.008). For all treatment groups co-administration of ezetimibe to established statin therapy resulted in a mean decrease of triglycerides from 2.8 to 2.2 mmol/L.

Cholesterol target achievement with ezetimibe added to established statin therapy in high-risk patients

According to the new WGLA/SSC guidelines [26], the LDL-C target level for *high-risk* patients is ≤2.6 mmol/L. At baseline 310 of 374 *high-risk* patients were not at their LDL-C goal with statin monotherapy. After co-administration of ezetimibe with ongoing unchanged statin therapy the LDL-C target achievement was investigated in relation to the initial LDL-C values (fig. 3). In 57 patients (18%) LDL-C levels were between 2.6 and 3.25 mmol/L under statin monotherapy, and these patients thus needed up to 20% LDL-C reduction to reach the LDL-C target of 2.6 mmol/L. By co-administration of ezetimibe to the ongoing statin therapy 77% of patients in this group were able to reach their LDL-C goal. Seventy-nine patients (25%) had LDL-C values between 3.25 and 3.7 mmol/L while receiving statin monotherapy, and thus needed 21–30% LDL-C reduction to reach their LDL-C target. Through co-administration of ezetimibe with the established statin regimen 71% of these patients reached their LDL-C goal. In 85 patients (27%) LDL-C values were between 3.7 and 4.3 mmol/L under statin monotherapy, and these patients thus needed 31–40% LDL-C reduction to reach the LDL-C target. Co-administration of ezetimibe to the ongoing statin therapy resulted in LDL-C goal achievement in 37%. Thus, 71% of the patients had LDL-C values in the range of 2.6 to 4.3 mmol/L needing up to 40% LDL-C reduction, and 59% of these patients could reach the LDL-C target of 2.6 mmol/L.

Safety and adverse events

A total of 44 adverse event (AE) reports were received where ezetimibe was considered to be possibly related. The reports involved 44 different patients (5% of whole patient population in program), and all events were non-serious. In 20% of these AE reports ezetimibe was given as monotherapy, and in 80% of them ezetimibe was given in combination with a statin. The majority of AE reported for ezeti-

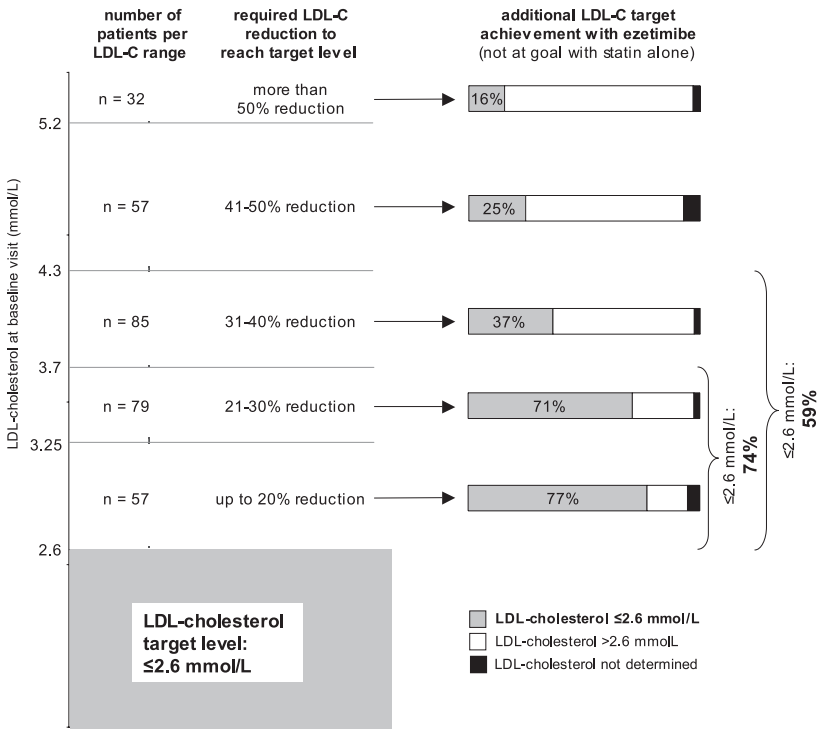

Figure 3
Additional low-density-lipoprotein-cholesterol (LDL-C) target achievement in high-risk patients in dependence on their initial LDL-C values.

mibe monotherapy were gastrointestinal complaints. The majority of AE reported for ezetimibe in combination with a statin were gastrointestinal disorders, followed by skin disorders, musculo-skeletal disorders, nervous system disorders and pathological laboratory values. Ezetimibe as monotherapy as well as in combination with a statin was generally well tolerated, and the reported AE corresponded to the current information included in the Swiss Physicians' Desk Reference of ezetimibe [27].

Discussion

In the described Swiss observational program on the effects of ezetimibe in co-administration with statins in an unselected population of typical outpatients, we were able to mirror the results of prospective, randomised clinical trials in daily practice. In both, patients with initiation of lipid-modifying therapy consisting of a statin and ezetimibe, and patients receiving ezetimibe on-top of a previously established statin regimen, consistent reductions in TC as well as in LDL-C were achieved after a mean treatment period of 8 weeks (≤12 weeks in 89% of patients).

In the majority of *high-risk* patients ezetimibe was given in addition to previously established and unchanged statin therapy resulting in an additional LDL-C reduction of about 30% regardless of the type of co-administered statin. Only few clinical trials have investigated the effect of ezetimibe in this setting [19, 28] which in daily practice is certainly more frequent than the simultaneous initiation of statin and ezetimibe therapy. Our results are very similar to those of 769 patients with primary hypercholesterolemia (mean LDL-C level 3.6 mmol/L), in whom the addition of ezetimibe to ongoing statin therapy (one third atorvastatin, on third simvastatin, one third other statins) resulted in a LDL-C reduction of 25% after a 8-weeks period [19]. However, the comparison with the present data is limited by the fact, that treatment duration was longer than 8 weeks in a considerable number of our patients. Nevertheless, regarding the fact that doubling of a given statin dose has been shown to result in an additional LDL-C reduction of about 6% ("rule of six") [14], a LDL-C reduction of 30% in patients with ongoing statin therapy is remarkable. The fact that approximately 60% of patients with LDL-C levels of 2.6 to 4.3 mmol/L under statin monotherapy were able to reach the goal of 2.6 mmol/L is even more encouraging.

There is a growing body of evidence that the co-administration of a statin and ezetimibe is equal or even superior to a higher statin dose with respect to the cholesterol lowering effects. Interestingly, the addition of ezetimibe 10 mg to ongoing therapy with simvastatin 20 mg in diabetics has recently been shown to be more effective than doubling of the simvas-

tatin dose [29]. Similarly, patients given the combination of simvastatin 10 mg and ezetimibe 10 mg were less likely to need up-titration of their simvastatin dose, and were more likely to reach the LDL-C goal of ≤2.6 mmol/L compared to patients starting with simvastatin 20 mg [30]. Furthermore, the effect of ezetimibe and simvastatin has been shown to be superior to atorvastatin in the corresponding dose [31], suggesting that the additional use of ezetimibe might be an alternative to switching to a more potent statin.

In the minority of *high-risk* patients a combined cholesterol-modifying therapy with ezetimibe and a statin was simultaneously initiated with results comparable to those reported in the literature. The combination of ezetimibe with different doses of atorvastatin, simvastatin, or pravastatin in patients with baseline LDL-C levels of around 4.5 mmol/L during a 12-week treatment period has been shown to provide a LDL-C reduction of 53 to 61% for atorvastatin [20], 44 to 57% for simvastatin [21], and 34 to 41% for pravastatin [22]. In our patients receiving the combination of ezetimibe with atorvastatin, simvastatin, or pravastatin, the LDL-C reduction was somewhat lower (38% for the pooled results of all statins). However, the mean atorvastatin dose used in our patients (15 mg) was much lower than that in the trial by Ballantyne and coworkers (around 37.5 mg) [20], whereas the mean doses of simvastatin (29 mg *vs.* 37.5 mg [22]) and pravastatin (21 *vs* 23 mg [22]) were comparable to those in the published trials. In addition, our *high-risk* group only consisting of patients with CAD and/or diabetes was very different from the collective investigated in the studies published by the Ezetimibe Study Group [20–23] with only few patients having CAD or diabetes. This is a very important issue, since patients at the highest risk for CAD are known to be least likely to achieve their treatment goal [13]. However, due to the small number of patients fitting the above reported setting (simultaneous initiation of ezetimibe and statin) in our observational program conclusions are limited.

For statins a strong correlation of LDL-C reduction and reduction in cardiovascular endpoints has been demonstrated [10, 11]. However, the statins also exhibit so-called non-lipid effects whose importance is currently not exactly known [32]. From the published data, including our observational program, we recognize a considerable potential of ezetimibe, especially when combined with statins, to reduce LDL-C levels, but data about non-lipid effects are sparse. One study reported a significantly more effective reduction of the high-sensitivity-C-reactive-protein (hs-CRP) by the combination of simvastatin and ezetimibe than by simvastatin monotherapy in the corresponding dose suggesting that ezetimibe might potentiate the hs-CRP-lowering effects of simvastatin [33]. Regarding the fact, that hs-CRP levels reflecting the degree of arterial inflammation in atherosclerosis have been shown to be strong prognostic predictors [34], and that hs-CRP and LDL-C reduction show only a very weak correlation [34] the co-administration of ezetimibe and a statin seems to be a very convenient combination to reduce cardiovascular risk. Since ezetimibe alone leads to a comparably weak LDL-C reduction (17–18% in clinical studies [18, 24] and 23% in our previously not treated *high-risk* patients receiving monotherapy) and has no effects on hs-CRP levels [33], monotherapy with ezetimibe should be considered only for patients with statin intolerance, whereas in all other cases combination therapy should be given.

The recently published Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 (PROVE-IT-TIMI 22) study revealed that in *high-risk* patients (acute coronary syndrome within 10 days before randomisation) the achievement of an even lower LDL-C level (1.8 mmol/L) than the recommended target level (2.6 mmol/L) by a more intensive lipid-lowering statin regimen (atorvastatin 80 mg *vs.* pravastatin 40 mg) resulted in a significant reduction in cardiovascular endpoints [10]. Therefore, there might be a trend to even lower LDL-C target levels. The use of drugs with different mechanism of LDL-C reduction (eg ezetimibe) offers the potential to achieve even lower levels. However, since endpoint studies do not exist today, the final proof is lacking, whether LDL-C reduction to the same level by either a high statin dose or ezetimibe combined with a low or moderate statin dose has the same benefit concerning hard endpoints.

In addition to the discussed limitations, the observational program has several methodological problems. The lack of a control group and the fact that efforts to modify cholesterol levels with diet and/or physical activity were not assessed and might have confounded the results, warrants careful interpretation of the data. Furthermore, the study duration, that is the time interval between the baseline and the follow-up visit, varied considerably. The management of the patients was not uniform, since monitoring was completely

left to the treating physician. It also is unknown how patients were selected by the physicians, and how many patients were judged not to be suitable for the present observational program.

Since neither measurements of hepatic enzymes and creatine phosphokinase levels were routinely documented, nor myalgia and tendinopathy were systematically assessed, the observational program does not allow conclusions about hepatotoxicity and myotoxicity, which are major concerns with statin therapy. In clinical studies, the overall safety profile of ezetimibe in co-administration with a statin was generally similar to that of the statin alone [19–23]. Under ezetimibe in co-administration with a statin, liver enzyme elevations or signs of myopathy were seen with the same frequency as in statin monotherapy [19–23].

Conclusions

Despite the fact that our analysis is based on an observational program with its inherent limitations, we have shown that the co-administration of ezetimibe with statin therapy in Swiss *high-risk* outpatients, either as simultaneously initiated combined lipid-modifying therapy, or added to a previously established statin regimen, is highly efficient in LDL-C reduction in daily practice and that data of controlled randomised trials are confirmed in a real life setting. Further studies to reveal the clinical benefit of ezetimibe-induced LDL-C correction are warranted. Ongoing endpoint studies with ezetimibe might add to our understanding of cholesterol-modifying therapy.

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