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Co-administration of ezetimibe and simvastatin in acute myocardial infarction

F. Chenot[*], P. F. Montant[*], O. Marcovitch[*], M. Blaimont[*], A. de Meester[*] and O. S. Descamps[*†]

[*]Department of Internal Medicine, [†]Centre for Medical Research, Centre Hospitalier Jolimont-Lobbes, Haine Saint-Paul, Belgium

Abstract

Background Recent trials in acute myocardial infarction indicate that intensive and early statin therapy that lowers low-density lipoprotein cholesterol (LDL-C) to ≤ 70 mg dL^{-1} is beneficial. The combination of statins with ezetimibe, a newly developed cholesterol-absorption inhibitor, can lead to a further reduction in LDL-C of up to 26%. In this study, we examined the rapidity and intensity of the lipid-lowering effect of ezetimibe co-administered with simvastatin immediately after myocardial infarction.

Materials and methods Sixty patients admitted for acute myocardial infarction were randomized to receive either simvastatin 40 mg (SIMVA), a combination of simvastatin 40 mg and ezetimibe 10 mg (EZE/SIMVA), or no lipid-lowering drugs (NLLD) and had their lipid levels assessed 2, 4 and 7 days later.

Results At baseline, cardiovascular risk factors were similar in all three groups [mean (SD) LDL-C of 141 (36) mg dL^{-1}]. At days 2 , 4 and 7 there was no significant change in mean LDL-C levels in the NLLD group (–10%, –6%, and –9%, all $P > 0{\cdot}09$), while there were significant reductions with SIMVA (–15%, –27%, and –25%, respectively, all $P < 0{\cdot}001$ vs. day 0) and even greater reductions with co-administration of EZE/SIMVA (–27%, –41%, and –51%, respectively, all $P < 0{\cdot}001$ vs. day 0). The percentages of patients achieving LDL-C below 70 mg dL^{-1} at days 4 and 7 were substantially greater with EZE/SIMVA (45% and 55%, respectively) than with SIMVA (5% and 10%, respectively), while no NLLD patient reached this goal. Triglyceride levels showed a progressive increase in the NLLD group (+45% at day 7, $P < 0{\cdot}05$ vs. day 0), no change in the SIMVA group, but a decrease in the EZE/SIMVA group (–17% at day 7, $P < 0{\cdot}05$ vs. day 0). No significant difference in HDL-C levels, tolerability, or clinical events was observed between the three groups.

Conclusions The co-administration of ezetimibe 10 mg with simvastatin 40 mg, by inhibiting cholesterol absorption and production, allowed more patients with acute myocardial infarction to reach LDL-C ≤ 70 mg dL^{-1} as early as the fourth day of treatment. The effects of such rapid and intense reduction in LDL-C on cardiovascular morbidity and mortality need to be evaluated in future clinical endpoint studies.

Keywords Cardiovascular disease, ezetimibe, LDL-cholesterol, myocardial infarction, simvastatin, triglycerides.
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F. Chenot, P. F. Montant and O. S. Descamps have contributed equally to this work.

Department of Internal Medicine (F. Chenot, P. F. Montant, O. Marcovitch, M. Blaimont, A. de Meester, O. S. Descamps); Centre for Medical Research, Centre Hospitalier Jolimont-Lobbes, Haine Saint-Paul, Belgium (O. S. Descamps).

Correspondence to: Dr Olivier Descamps, Department of Internal Medicine, Centre Hospitalier Jolimont-Lobbes, Rue Ferrer 159, B-7100 Haine Saint-Paul, Belgium. Tel.: +32 64 23 42 15; fax: +32 64 23 38 42; e-mail: descaoli@skynet.be

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Table 1 Baseline patient characteristics randomized between the three regimes

	No lipid-lowering drug $N = 20$	Simvastatin 40 mg $N = 20$	Ezetimibe 10 mg + simvastatin 40 mg $N = 20$
Women/Men, *n*	12/8	6/14	11/9
NSTEMI/STEMI, *n*	7/13	3/17	3/17
Age, years	59 ± 23	61 ± 10	64 ± 11
BMI, kg m^{-2}	26·0 ± 4·9	27·2 ± 5·3	25·3 ± 4·7
Diabetes, %	15%	10%	20%
Hypertension, %	70%	60%	60%
Smoking, %	45%	75%	65%
Family history, %	30%	30%	50%
Cholesterol, mg dL^{-1}	211 ± 42	223 ± 51	216 ± 46
LDL-C, mg dL^{-1}	133 ± 31	145 ± 36	146 ± 32
HDL-C, mg dL^{-1}	52 ± 14	45 ± 10	46 ± 14
Triglycerides, mg dL^{-1}	125 ± 67	165 ± 110	149 ± 88
Lp(a)	24 ± 26	18 ± 14	14 ± 18
Fibrinogen (mg dL^{-1})	393 ± 185	375 ± 131	387 ± 176
Hs-CRP (mg dL^{-1})	2·9 ± 3·0	2·3 ± 1·5	2·9 ± 3·2

STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitive CRP; Lp(a), lipoprotein (a).

Introduction

Several studies have established that statin therapy in secondary prevention reduces morbidity and mortality [1–3]. More recently, the advantage of an early administration of statins after acute myocardial infarction has been demonstrated extensively [4–7]. Such benefits have been primarily linked to the effects of low-density lipoprotein cholesterol (LDL-C) lowering. Additional effects of statins (i.e. anti-inflammatory properties, antithrombotic effects, endothelial function improvement), also called 'pleiotropic effects', could as well play a favourable role [8–15]. A strong linear relationship between LDL-C and cardiovascular outcomes has emerged from all studies, suggesting that the lower LDL-C, the better the outcome [16]. Recently, the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial and Treat to New Targets (TNT) trial studies showed that morbidity and mortality drastically decreases when LDL-C is lowered to 70 mg dL^{-1} or less [5,16–18].

Ezetimibe, a cholesterol absorption inhibitor, has been shown to have an impressive additional LDL-C-lowering effect when co-administered with a statin [19–23]. In the recent Ezetimibe Add-On to Statin for Effectiveness (EASE) study, the addition of ezetimibe to ongoing statin therapy resulted in a mean additional lowering of LDL-C by 26% [19]. However, the lipid-lowering effect of ezetimibe after acute myocardial infarction and its eventual clinical effects on morbidity and mortality after such an event have so far not been investigated.

We performed a comparison of lipid profiles in the first seven days following a myocardial infarction during treatment with one of three regimes: ezetimibe co-administered with simvastatin, simvastatin alone, or no lipid-lowering drug.

Materials and methods

Patients

Between November 2004 and August 2005, we enrolled the patients admitted for acute myocardial infarction (with or without ST-segment elevation) in the coronary unit of the Centre Hospitalier Jolimont-Lobbes. Patients were eligible for inclusion if the first pain occurred in the previous 24 h before admission. Patients were excluded if they had a secondary cause of lipid profile abnormality (e.g. thyroid disorders, inflammatory diseases, neoplasia, serious hepatic diseases, creatinine level above 1·7 mg dL^{-1} or Cockcroft-Gault creatinine clearance < 30 mL min^{-1}), creatine kinase more than three times the normal value and non-related to myocardial infarction, previous lipid-lowering therapy, baseline LDL-C < 90 mg dL^{-1}, and patients receiving strong cytochrome P450–3A4 inhibitors.

A total of 60 patients (31 men, 29 women, average age 61 years) were recruited. The baseline lipid profiles and the other cardiovascular risk factors are presented in Table 1. They were similar across the treatment groups, with the exception of significantly more men ($P = 0·001$) and a higher proportion of smokers in the simvastatin group ($P = 0·002$). The severity of myocardial infarction, in terms of proportion of ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) (Table 1) and of creatine-kinase elevation (data not shown), was similar across the three treatment groups. Overall there were 49 patients (82%) with STEMI and 11 patients (18%) with NSTEMI, both similar in terms of mean age, sex distribution or baseline lipid profiles. Medications administered during the study were similar in the three treatment groups: aspirin (100%), low-molecular weight heparin (100%), clopidogrel or ticlopidine (91%), tirofiban (15%), angiotensin-converting enzyme inhibitors

or angiotensin II type 1 blockers (91%), and beta blockers (85%). Revascularization methods used were thrombolysis in 66% of patients with STEMI, percutaneous intervention in 76% of all patients, and surgical revascularization in 8% of patients.

Study design

At entry into the coronary care unit, eligible patients were randomly assigned to one of three treatment regimes: ezetimibe 10 mg day^{-1} co-administered with simvastatin 40 mg day^{-1} (EZE/SIMVA), simvastatin 40 mg day^{-1} (SIMVA), or no lipid-lowering drugs (NLLD). All patients received the usual diet prescribed in the coronary care unit and were managed with usual medical treatment. Lipid profiles, high-sensitivity C-reactive protein (hs-CRP) and fibrinogen were assessed at admission (day 0) and at days 2, 4, and 7. Cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides were assessed using an Olympus AU600 autoanalyser and respective reagents (Olympus Diagnostica, GmbH, Clare, Ireland). LDL-C was calculated by the formula of Friedewald [LDL-C = TC – (HDL-C + TG/5); all in mg dL^{-1}]. Fibrinogen was measured by chronometric methods (Dade Behring, Marburg, Germany) and hs-CRP was measured by immunoturbidimetry methods using Olympus system and reagents (Olympus Diagnostica, GmbH).

Other daily systematic assessments included cardiac enzymes, full blood count, electrolytes, creatinine, urea, liver function tests, and muscular enzymes. Thyroid stimulating hormone (TSH), T3, and T4 were measured at day two. Each patient underwent continuous cardiac monitoring and a complete clinical examination and electrocardiogram were performed each day.

The protocol was approved by the ethical committee of the hospital and written informed consent was obtained from all patients.

Statistical analysis

The primary study endpoints were changed from baseline in LDL-C at days 2, 4 and 7 and the proportion of patients with an LDL-C level < 70 mg dL^{-1}.

Our strategy was to compare LDL-C levels between day 0 and successive days for the treatment regimes and to compare the difference in LDL-C reduction between each of the regimes. Based on published studies, we expected an average difference in LDL-C reduction of about 40% between no treatment and SIMVA and an average difference of about 20% between EZE/SIMVA and SIMVA. For baseline LDL-*C*-values of 100 and 140 mg dL^{-1} (with standard deviations of 20 and 30 mg dL^{-1}, respectively), we estimated a minimal sample size of 18 patients in each group to detect a 20% difference between two groups with a two-sided significance level of 0·05 and a statistical power of 80%.

In the three groups, we analysed the difference between day 0 and successive days by paired two-tailed Student's *t*-test. We also compared two-by-two the mean concentrations of lipids in the groups by unpaired two-tailed Student's *t*-test at each day.

Secondary endpoints were changes in other lipid measures (total cholesterol, HDL-C, and triglycerides) and changes in inflammatory markers (hs-CRP and fibrinogen), the occurrence of drug toxicity and clinical events (symptoms, clinical examination findings, electrocardiogram findings, and events on cardiac monitoring).

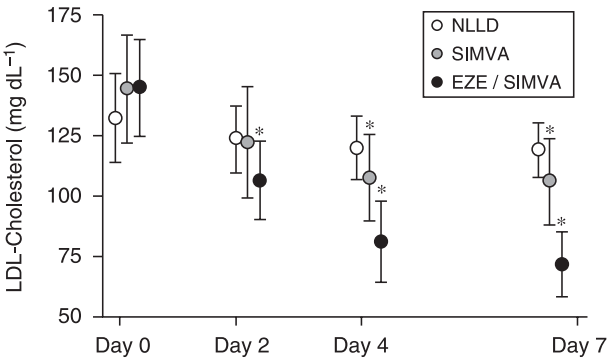

Figure 1 LDL-C levels during treatment with no lipid-lowering drug (NLLD, $N = 20$), simvastatin 40 mg day^{-1} (SIMVA, $N = 20$), or ezetimibe 10 mg day^{-1} co-administered with simvastatin 40 mg day^{-1} (EZE/SIMVA, $N = 20$) after an acute myocardial infarction (*$P < 0·05$ compared to day 0).

Results

LDL-C levels

The greatest reductions in LDL-C were observed in the EZE/SIMVA group: at days 2, 4 and 7, reductions from baseline were –27%, –41% and –51% (all $P < 0·001$) (Fig. 1). LDL-C was also reduced significantly in the SIMVA group: –15%, –27% and –25%, respectively (all $P < 0·001$). There was no significant change in LDL-C in the NLLD group at day 2 (–10%, $P = 0·09$), day 4 (–6%, $P = 0·09$) or day 7 (–9%, $P = 0·16$).

The mean LDL-C levels achieved in the EZE/SIMVA group were significantly lower than in the SIMVA group at day 4 (82 ± 37 mg dL^{-1} vs. 108 ± 35 mg dL^{-1}, respectively, $P = 0·03$) and day 7 (72 ± 29 mg dL^{-1} vs. 107 ± 36 mg dL^{-1}, respectively, $P = 0·002$).

The percentage of patients achieving the LDL-C goal of ≤ 70 mg dL^{-1} was substantially greater in the EZE/SIMVA group compared with the SIMVA group at day 4 (45% vs. 5%, respectively) and day 7 (55% vs. 10%, respectively) (Fig. 2). The difference at days 4 and 7 between the EZE/SIMVA and SIMVA groups persisted in multivariate adjusting for factors that could potentially influence lipoprotein levels such as age, sex, diabetes, weight, body-mass index (BMI), and smoking status (data not shown).

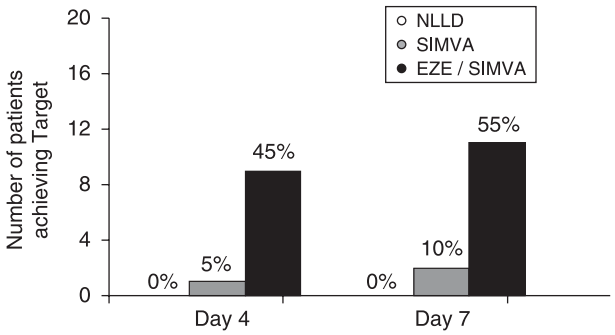

Figure 2 Percentage of patients achieving a goal LDL-C level of < 70 mg dL^{-1} during treatment with no lipid-lowering drug (NLLD, $N = 20$), simvastatin 40 mg day^{-1} (SIMVA, $N = 20$), or ezetimibe 10 mg day^{-1} co-administered with simvastatin 40 mg day^{-1} (EZE/SIMVA, $N = 20$) after an acute myocardial infarction.

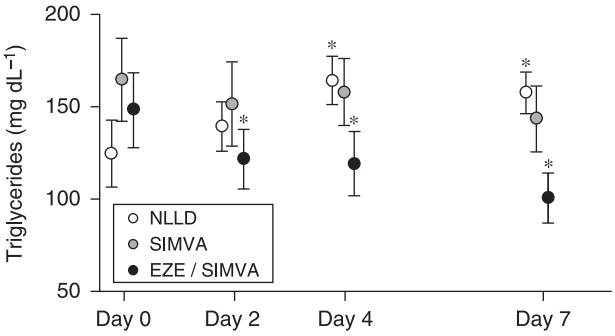

Figure 3 Triglyceride levels during treatment with no lipid-lowering drug (NLLD, $N = 20$), simvastatin 40 mg day^{-1} (SIMVA, $N = 20$), or ezetimibe 10 mg day^{-1} co-administered with simvastatin 40 mg day^{-1} (EZE/SIMVA, $N = 20$) after an acute myocardial infarction (*$P < 0{\cdot}05$ compared to day 0).

Other measures

At day 7, triglyceride levels decreased significantly from baseline in the EZE/SIMVA group (–48 mg dL^{-1}, –17%, $P < 0{\cdot}01$), showed no significant change in the SIMVA group, and significantly increased in the NLLD group (+40 mg dL^{-1}, +45%, $P < 0{\cdot}05$) (Fig. 3). At day 7, mean total cholesterol levels achieved in the EZE/SIMVA group were significantly lower than in the SIMVA group at day 4 (140 ± 39 mg dL^{-1} vs. 177 ± 41 mg dL^{-1}, respectively, $P = 0{\cdot}006$) and day 7 (126 ± 40 mg dL^{-1} vs. 168 ± 31 mg dL^{-1}, respectively, $P = 0{\cdot}01$) (Fig. 4). There was no difference between treatments in HDL-C levels ($P = 0{\cdot}15$).

No significant variation was noted in inflammatory markers (C-reactive protein and fibrinogen). Symptoms, clinical examinations, electrocardiograms, continuous monitoring, and general treatments also showed no significant difference between treatment groups. One treatment-related side-effect

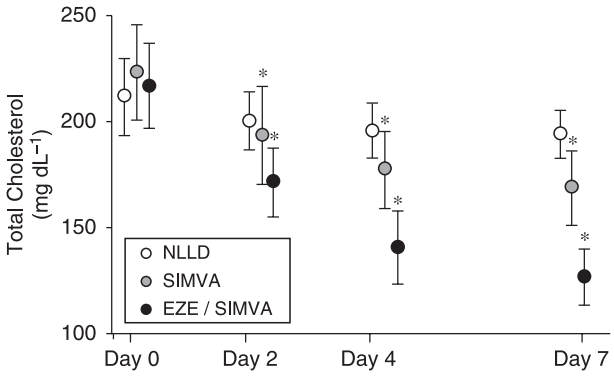

Figure 4 Total cholesterol levels during treatment with no lipid-lowering drug (NLLD, $N = 20$), simvastatin 40 mg day^{-1} (SIMVA 40 mg, $N = 20$), or ezetimibe 10 mg day^{-1} co-administered with simvastatin 40 mg day^{-1} (SIMVA 40 + EZETROL 10, $N = 20$) after an acute myocardial infarction (*$P < 0{\cdot}05$ compared to day 0).

was observed in the SIMVA group (one patient experiencing transitory cytolytic hepatitis, which resolved after discontinuation of simvastatin). No cases of myalgia or rhabdomyolysis were observed.

Discussion

The co-administration of ezetimibe with simvastatin resulted in significantly greater reductions in LDL-C compared with simvastatin alone, and allowed a greater proportion of patients to achieve the goal of LDL-C levels. The rapidity and magnitude of the LDL-C reductions seen with co-administration were impressive, with significant LDL-C reduction compared with baseline by day 2, and greatly superior LDL-C lowering compared with simvastatin alone by day 4. By day 7, LDL-C was reduced by 51% in the group receiving ezetimibe co-administered with simvastatin, compared with only 25% in the simvastatin group. Treatment guidelines have suggested an LDL-C target level of < 70 mg dL^{-1} as a goal for high-risk patients [16]. Almost half of the patients in this study achieved an LDL-C level of ≤ 70 mg dL^{-1} with ezetimibe co-administered with simvastatin by day 4, compared with only 10% achieving this goal with simvastatin alone at day 7. As cardiovascular prognosis after myocardial infarction has been related to the early reduction of LDL-C levels [4,17,24], such impressive reductions in LDL-C achieved within a week of treatment could be of great benefit to patients.

We did not find any significant changes on fibrinogen and hs-CRP. We must acknowledge, however, that our study has probably not the statistical power to rule out a modification of these parameters. As a matter of fact, the inflammatory status secondary with the acute myocardial infarction produced a high level of hs-CRP with a very high standard deviation (see Table 1). In larger series, statins as well as ezetimibe [26,27] have been shown to lower hs-CRP. This non-lipid-related effect like other effects, currently called

'pleiotropic effects' [25], are thought to contribute also to the clinical benefits of statins. Although ezetimibe therapy has failed to demonstrate all the spectrum of pleiotropic properties than statin (for example, statin improved endothelial vasodilator function, but ezetimibe did not) [28,29]), it is not excluded that, in acute myocardial infarction, benefits arising from the pleiotropic activities of statin could be further enhanced by a potential anti-inflammatory action of ezetimibe.

The early and intensive treatment regimes used in this study were well tolerated, with the exception of one occurrence of mild and transitory cytolytic hepatitis (ALAT $\times$ 2·5, ASAT $\times$ 1·5). This hepatic abnormality resolved after the arrest of simvastatin which was only motivated by the end of the study and by the fact that there was no argument to further carry on statin treatment in this patient as he had LDL-C at 75 mg dL^{-1} (thus below the recommended 100 mg dL^{-1}). We must admit however, that the transaminase values of this patient reached the recommended limit for statin discontinuation (two to three times the normal values) [30].

It is noteworthy that in the group receiving no lipid-lowering treatment, LDL-C and HDL-C levels did not change significantly, whereas triglyceride levels significantly increased. In previous studies, the 'natural variation' of these lipid levels after myocardial infarction is fairly heterogeneous [31–35]. While it is recognized that LDL-C levels may fall after a myocardial infarction, we could not detect any significant decrease in LDL-C in the no lipid-lowering treatment arm of our study, possibly due to a lack of statistical power in detecting small changes as those previous reported [31–35]. However, our observation of increased triglyceride levels after acute myocardial infarction in the group receiving no lipid-altering treatment has been described previously in the literature [31,33,34]. The pathophysiology of this variation is unclear, but inflammatory factors such as cytokines (tumour necrosis factor α, interleukin 1 and 6) are known to increase triglycerides by stimulating hepatic secretion and lipolysis [36]. Other factors may be psychological stress [37,38], or the beta b1ocker treatment which, in the case of bisopro1o1 used in our coronary unit, increased trig1ycerides up to 28% [39,40].

A surprising finding in the present study was that co-administration of ezetimibe with simvastatin produced a significant reduction in triglycerides, but simvastatin alone produced no change in triglyceride levels. Although this finding needs to be examined more thoroughly with a greater number of subjects (due to inter- and intra-individual variations of this lipid measurement), it is possible that this triglyceride-lowering effect might have potential benefit for patients' prognosis. Triglycerides are indeed often associated with thrombotic conditions [41,42], so lowering triglycerides may reduce the risk of complications after myocardial infarction such as venous thrombosis, cerebral ischaemic disease, coronary rethrombosis, or postdilation thrombosis. The mechanism underlying the reduction of triglycerides with ezetimibe is unclear [19–23], but it is possible that reduction in cholesterol absorption limits the production of chylomicrons and thus the entry of intestinal triglycerides into the circulation. This may suggest that after myocardial infarction, the mechanism behind the increase in triglycerides seen in the absence of treatment is in a large part dependent on the intestinal absorption of triglycerides rather than to adipose tissue lipolysis or hepatic lipogenesis. These hypotheses need to be examined more extensively in future studies.

The present study represents a preliminary step to the more extensive investigation of the clinical benefits of treatment with ezetimibe co-administered with simvastatin in the acute phase of myocardial infarction. A study of much longer duration is required to investigate the clinical effects of early lipid-lowering therapy. Also, our study lacked the statistical power to examine other interesting endpoints such as inflammatory measures.

In conclusion, this study demonstrated for the first time that the co-administration of ezetimibe with simvastatin, by inhibiting cholesterol absorption and production, after acute myocardial infarction produces a rapid and substantial reduction in LDL-C. Further clinical studies are required to investigate whether such rapid reduction in LDL-C in the days following a myocardial infarction results in long-term clinical benefit. If so, such findings could result in a new hypothesis in addition to 'the lower, the better' of 'the faster, the better'.

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