

# Half-dose ezetimibe add-on to statin therapy is effective in improving resistant hyperlipidaemia in Asian patients with ischaemic heart disease

Chong E, Shen L, Poh K K

## ABSTRACT

**Introduction:** Ezetimibe at full dose (10-mg) is used for lipid lowering. We hypothesised that ezetimibe at half dose is effective in achieving percentage improvement in lipid profile among Asian patients with severe hyperlipidaemia.

**Methods:** This was a prospective cohort study conducted between 2006 and 2008. 105 patients with hyperlipidaemia not reaching target level with statin treatment alone were given add-on ezetimibe 5-mg daily treatment. Lipid profiles were compared at pre- and post-ezetimibe therapy.

**Results:** The mean age of the patients was 56.0 +/- 10.3 years. 79.0 percent were male and 62.9 percent had hypertension, 39 percent had diabetes mellitus with a mean HbA1c of 7.7 percent. 58.1 percent had a history of myocardial infarction. The median simvastatin equivalent dose was 40 (range 5–80) mg. Duration of ezetimibe treatment was 102 +/- 60 days. We observed improvements in total cholesterol (TC) (from 5.31 +/- 1.02 to 4.33 +/- 1.11 mmol/l, 16.4 percent reduction, p-value less than 0.0005), low density lipoprotein (LDL) (from 3.43 +/- 0.87 to 2.52 +/- 0.95 mmol/l, 24.0 percent reduction, p-value less than 0.0005) and TC to LDL ratio (from 4.92 +/- 1.42 to 4.03 +/- 1.16, 16.2 percent reduction, p-value less than 0.0005). The percentage improvement of lipid profile was comparable to that of the published data based on 10-mg dosing.

**Conclusion:** A 5-mg dose of daily ezetimibe add-on treatment is effective in improving lipid profiles in Asian patients with severe hyperlipidaemia not reaching target with statin monotherapy.

**Keywords:** Asian, ezetimibe, half-dose, lipid, statin  
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## INTRODUCTION

Ezetimibe (Ezetrol™, MSD-Schering-Plough®, Whitehouse Station, NJ, USA) is a cholesterol absorption inhibitor.<sup>(1)</sup> At full dose of 10-mg once daily, ezetimibe is commonly used as an add-on therapy to improve lipid treatment in patients not reaching their therapeutic target with statin monotherapy alone.<sup>(2)</sup>

The National Cholesterol Education Program Adult Treatment Panel III (ATP III) recommends a low-density lipoprotein (LDL) level < 100 mg/dL (2.6 mmol/l) in patients with established vascular or coronary disease; an LDL target of < 80 mg/dL (2.1 mmol/l) may be considered for those at very high risk.<sup>(3)</sup> While statins are the cornerstone of LDL-lowering therapy, some patients fail to achieve their goals despite statin therapy. Ezetimibe can be used as monotherapy or in combination with simvastatin as Vytorin™. During the development of ezetimibe, various doses were evaluated (0.625–40 mg); 5-mg dosage was found to significantly lower LDL (15%–20%).<sup>(4)</sup> Despite this, ezetimibe is available only in 10-mg tablets. Our institution has recommended all ezetimibe prescriptions to be started at 5-mg, prescribed as 10-mg split in half. Mandated conversion of existing 10-mg prescriptions to 5-mg was, however, not instituted.

We hypothesised that ezetimibe at half dose (5-mg) daily is effective in achieving percentage improvement in the LDL profile of Asian patients with hyperlipidaemia not reaching target by statin treatment alone, and that ezetimibe may hence be administered in a more cost-effective way.

## METHODS

This was a prospective cohort study conducted at National University Hospital, Singapore. Patients with established coronary artery disease (CAD) who were attending the cardiology outpatient clinic were enrolled between September 2006 and February 2008. The inclusion criteria were patients with a history of CAD and who had undergone coronary angioplasty. All patients were given statins and were found to have

National University Heart Centre, National University Hospital, Yong Loo Lin School of Medicine, National University of Singapore, 1E Kent Ridge Road, Singapore 119228

Chong E, MBBS, MRCP, FAMS  
Cardiology Consultant

Poh KK, MBBChir, MRCP, FAMS  
Cardiology Consultant and Research Director

Biostatistics Unit

Shen L, PhD  
Senior Biostatistician

Correspondence to:  
Dr Eric Chong  
Tel: (65) 9382 7396  
Fax: (65) 6284 4977  
Email: ericchong80@hotmail.com

**Table I. Baseline patient characteristics (n = 105).**

Baseline characteristic	No. (%)
Mean age $\pm$ SD (yrs)	56 $\pm$ 10.3
Race	
Chinese	65 (61.9)
Malay	33 (31.4)
Indian	7 (6.7)
Female gender	22 (21)
Hypertension	66 (62.9)
Diabetes mellitus	41 (39)
Mean HbA1c $\pm$ SD (%)	7.77 $\pm$ 1.68
Smoking	41 (39)
Renal impairment	6 (5.7)
Stroke	6 (5.7)
History of myocardial infarction	61 (58.1)
History of coronary artery disease	105 (100)

SD: standard deviation

unsatisfactory LDL-lowering results. A total of 105 patients who fulfilled the criteria were recruited into the study. Patients who received statin monotherapy initially but were unable to reach the target LDL level were given an additional ezetimibe 5-mg daily treatment instead of the usual 10-mg dosage. The target LDL level for the CAD patients was < 100 mg/dL (2.6 mmol/dl). We compared the LDL levels of patients on ezetimibe 5-mg dose with those of previous studies using a 10-mg dose.

In addition to LDL, other serum lipid parameters, including total cholesterol (TC), high-density lipoprotein (HDL), triglycerides (TG) and TC/HDL ratio, were also measured. The measurements were performed in three steps: Step 1 – at baseline before statin treatment; Step 2 – at mid stage after three months of statin treatment but before ezetimibe was added; and Step 3 – post three months of ezetimibe 5 mg add-on therapy. Serum liver function, creatinine (Cr) and creatinine kinase (CK) levels were monitored as surrogate markers for potential side effects of hepatic transaminitis, renal dysfunction and myositis. The patients were followed up clinically at regular 6–12 weekly intervals.

Data collection was performed by independent research nurses who were unaware of the purpose of the study. Baseline demographic and clinical data were collected from clinical case notes and computer records. Dose and duration of lipid-lowering therapy were documented. Follow-up blood tests, including lipid, liver and renal panels as well as CK levels before and at three months after the respective treatments, were retrieved from the laboratory records. The primary study end-points were percentage reduction in LDL level, absolute change in LDL level and the percentage of patients reaching target ATP III LDL goal after additional ezetimibe therapy. The secondary end-points

**Table II. Medication and statin usage in the study population (n = 105).**

Baseline characteristic	No. (%)
Other lipid-lowering drugs	
Niaspan	0 (0.0)
Fenofibrates	4 (3.8)
Antiplatelets	105 (100)
Hydrochlorothiazides	9 (8.6)
Calcium blockers	14 (13.3)
B blockers	92 (87.7)
ACE inhibitor	64 (61.0)
Angiotensin receptor blocker	14 (13.3)
Diabetes mellitus drugs	41 (39.0)
Sulphonoureas (glipizide)	25 (61.0)
Metformin	23 (53.7)
Acarbose	1 (2.4)
Insulin	4 (19.8)
Lovastatin	14 (13.3)
Median dose; range (mg)	40; 20–80
Simvastatin	83 (79.0)
Median dose; range (mg)	40 5–80
Atorvastatin (lipitor)	5 (5.8)
Median dose; range (mg)	20; 20–40
Rousuvastatin (crestor)	10 (2.9)
Median dose; range (mg)	10; 5–10
Pre-treatment simvastatin equivalent dose; range (mg)	40; 5–80
Mean duration of stable statin monotherapy $\pm$ SD (days)	100 $\pm$ 45
Mean duration of ezetrol plus statin combination therapy $\pm$ SD (days)	102 $\pm$ 60

SD: standard deviation; ACE: angiotensin-converting enzymes

included percentage change in other lipid parameters, including TC, HDL, TG and TC/HDL ratio. Potential adverse events such as development of myositis, renal dysfunction and hepatic transaminitis were monitored.

Continuous data was reported as mean value  $\pm$  standard deviation, unless otherwise specified. Categorical data was presented as absolute values and percentages. Comparison of continuous variables between pre- and post treatment was performed by paired *t*-test. McNemar test was performed for comparison of paired categorical variables. A *p*-value < 0.05 was considered to be statistically significant. Analysis was conducted using the Statistical Package for the Social Sciences version 16.0 (SPSS Inc, Chicago, IL, USA).

## RESULTS

Baseline demographic characteristics are shown in Table I. Mean age of the patients was 56.0  $\pm$  10.3 years. Nearly 80% were men. 65 (61.9%) patients were Chinese, 33 (31.4%) were Malay and seven (6.7%) were Indian. Slightly over 60% of patients had hypertension, while nearly 40% had diabetes mellitus with a mean HbA1c

**Table III. Results of lipid-lowering therapies.**

Lipid profile (mmol/l)	Mean $\pm$ SD			% reduction	p-value
	Before statin monotherapy	Post statin monotherapy	Combination therapy*		
TC	5.42 $\pm$ 1.33	5.31 $\pm$ 1.02	4.33 $\pm$ 1.11	16.7	< 0.0005
TG	1.84 $\pm$ 0.96	1.66 $\pm$ 0.71	1.57 $\pm$ 0.74	1.14	0.383
HDL	1.09 $\pm$ 0.24	1.12 $\pm$ 0.24	1.11 $\pm$ 0.23	0.11	0.409
LDL	3.41 $\pm$ 1.23	3.43 $\pm$ 0.87	2.52 $\pm$ 0.95	24.3	< 0.0005
TC/LDL ratio	5.17 $\pm$ 1.79	4.92 $\pm$ 1.42	4.03 $\pm$ 1.16	15.7	< 0.0005

\* Combination therapy consists of statin + ezetimibe 5-mg.

SD: standard deviation; TC: total cholesterol; TG: triglycerides; HDL: high-density lipoprotein; LDL: low-density lipoprotein

**Table IV. Comparison of liver, renal and muscle enzyme levels.**

Blood marker	Mean $\pm$ SD		
	Before treatment	Statin monotherapy	Combination therapy*
AST (U/L)	53.59 $\pm$ 83.19	37.52 $\pm$ 55.68	26.78 $\pm$ 9.59
ALT (U/L)	32.99 $\pm$ 22.31	32.73 $\pm$ 20.42	32.63 $\pm$ 16.26
CK (U/L)	210.9 $\pm$ 290.12	196.09 $\pm$ 348.83	170.76 $\pm$ 248.63
Cr (umol/l)	92.65 $\pm$ 26.74	90.71 $\pm$ 22.12	98.51 $\pm$ 27.14

\* Combination therapy consists of statin + ezetimibe 5-mg.

p-value is not statistically significant for all markers.

SD: standard deviation; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CK: creatinine kinase; Cr: creatinine

of 7.7%. 58% had a history of confirmed myocardial infarction. All patients had a diagnosis of CAD based on coronary angiography, which showed significant coronary artery stenosis. These patients had also undergone coronary angioplasty to the culprit lesions.

The pharmacological characteristics of statin and ezetimibe use are shown in Table II. The median simvastatin-equivalent dose was 40 (5–80) mg. To define the simvastatin-equivalent dose, the following formulae were used: 1 lovastatin = 0.5 simvastatin; 1 atorvastatin = 2 simvastatin; 1 rosuvastatin = 4 simvastatin. In all, 79.1%, 4.8% and 2.9% of patients were on simvastatin, atorvastatin and rosuvastatin, respectively. The mean duration of ezetimibe treatment was 102  $\pm$  60 days.

All patients were compliant to the ezetimibe 5-mg add-on treatment. Table III shows the lipid profile before and after the treatment. We observed significant improvement in TC (from 5.31  $\pm$  1.02 to 4.33  $\pm$  1.11 mmol/l,  $p$  < 0.0005), LDL (from 3.43  $\pm$  0.87 to 2.52  $\pm$  0.95 mmol/l,  $p$  < 0.0005) and TC/LDL ratio (from 4.92  $\pm$  1.42 to 4.03  $\pm$  1.16,  $p$  < 0.0005). The mean absolute reductions of TC, LDL and TC/LDL ratio were 0.94 (95% confidence interval [CI] 0.71–1.16), 0.90 (95% CI 0.70–1.11) and 0.90 (95% CI 0.66–1.15), respectively. The mean percentage reductions of TC, LDL and TC/LDL ratio were 16.7% (95% CI 12.71%–20.17%), 24.3%

(95% CI 18.79%–29.25%) and 15.7% (95% CI 12.02%–20.32%), respectively.

Prior to the start of any statin treatment, 14 (13.3%) patients had achieved the LDL goal of < 2.6 mmol/l (100 mg/dL) and three (2.8%) patients had LDL < 2.1 mmol/l (80 mg/dL). Post statin monotherapy, the percentages of patients who reached the respective goals were 14.3% (< 2.6 mmol/l) and 2.8% (< 2.1 mmol/l). Post ezetimibe 5-mg/statin combination therapy, the percentages of patients who reached the respective goals were 63.8% (< 2.6 mmol/l) and 40% (< 2.1 mmol/l). The percentage increment of patients reaching therapeutic LDL target post ezetimibe was statistically significant, with  $p$ -values < 0.001. All patients who had achieved their LDL goals after statin monotherapy maintained their LDL levels after the addition of ezetimibe 5-mg.

One patient developed myalgia symptoms, with peak CK at 837 U/L. This level was, however, less than three times the upper limit of CK ( $3 \times 350 = 1,150$  U/L); hence, it was not considered an event of myositis. There were no significant differences in CK, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and serum creatinine at both pre- and post-ezetimibe therapy. No patient experienced clinical rhabdomyolysis and drug-induced transaminitis or hepatic dysfunction. These laboratory results are shown in Table IV.

## DISCUSSION

Ezetimibe has often been used as a second-line or add-on therapy for lipid lowering when patients fail to achieve the target LDL level after initial statin therapy.<sup>(5)</sup> Patients with known CAD need to achieve a lower LDL level of < 2.6 mmol/l as compared to patients without CAD. Ezetimibe is an expensive medicine under the current pharmaceutical patent. A report has found that a 5-mg dosage can be equally effective as a 10-mg dosage in the western population.<sup>(6)</sup> However, to date, minimal study in this regard has been conducted on Asian patients. Hence, it is reasonable to investigate the effectiveness of ezetimibe in an Asian group of patients to determine if the effectiveness of half-dose ezetimibe is comparable to the full dose. This could potentially improve the cost-effectiveness of lipid-lowering treatment by using a starting dose of 5-mg instead of 10-mg ezetimibe. In addition, taken at a higher dose, ezetimibe has a higher risk of hepatotoxicity.<sup>(7)</sup> At a lower dose, it would have lower side effects besides being more cost-effective.

In pharmacological studies, combinations of full-dose ezetimibe with all available statins have been attempted, and LDL reductions of approximately 20%–25% as additive effects to any statin dose alone have been demonstrated.<sup>(8)</sup> In a meta-analysis that included five randomised controlled trials involving 5,039 patients, the weighted mean difference between treatments significantly favoured the ezetimibe/statin combination over placebo/statin for TC reduction (16.1%; 95% CI 14.8%–17.3%;  $p < 0.0001$ ) and LDL reduction (23.6%; 95% CI 21.7%–25.6%;  $p < 0.0001$ ).<sup>(8)</sup> Small, additional increases in HDL (2%–3%) and reductions in TG (10%–15%) have also been observed.<sup>(9)</sup> Although our study, which used half the dose, did not reproduce the significant changes in the HDL and TG levels, it showed a consistent improvement of LDL level by about 24%. TC and TC/HDL ratio were also significantly improved by approximately 16%. Prior to ezetimibe treatment, the target LDL of < 2.6 mmol/l was reached only in 14.3% of patients, but the target LDL was reached by 63.8% ( $p < 0.001$ ) post ezetimibe treatment.

With regard to the safety profile, there was no change in CK and Cr after ezetimibe treatment. No patients developed myositis or rhabdomyolysis. Liver enzymes showed a reverse trend of further lowering/improvement of ALT and AST. This could be attributable to the reversal of fatty liver as a result of improvements in the lipid profile. There was no incidence of hepatic toxicity or significant induction of liver enzymes by three times the upper limit. Hence, the safety profile in our study was comparable to that of previous published studies.<sup>(10,11)</sup>

Our study showed that in Asian patients, the 5-mg ezetimibe add-on therapy is comparable to 10-mg ezetimibe (based on historical data), with respect to percentage reduction of LDL levels and achievement of ATP III LDL goals. Widespread adoption of this low-dose strategy could result in millions of dollars of cost savings annually. At the price of approximately US\$70 per month for 10-mg ezetimibe tablets, substantial savings will be generated through the implementation of this strategy in institutions, and should hence be considered.<sup>(12)</sup> As this was a single-arm study with no control group using a 10-mg dosage, historical published data using a 10-mg dosage was used as a comparison. However, for the purpose of this study, a single-arm analysis could provide valuable information on the effectiveness and safety of 5-mg dosing in Asian patients.

In conclusion, 5-mg daily ezetimibe treatment is safe and effective in improving lipid profiles in Asian patients with CAD and significant hyperlipidaemia not reaching target LDL level with statin monotherapy. 5-mg ezetimibe add-on therapy reduced LDL level by 24%, which is comparable to the results of published studies conducted using 10-mg ezetimibe. Hence, the use of half-dose ezetimibe can be considered a cost-effective, first-line add-on therapy in patients with persistent hyperlipidaemia.

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