Dual Inhibition of Cholesterol Synthesis and Absorption by Statins and Ezetimibe: a New Approach to Treatment for Dyslipidemia

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ABSTRACT. In clinical practice, clinicians may not increase statin dose levels out of concern for potential adverse events or because titration of statin doses provides only limited additional effectiveness. Ezetimibe, a novel agent inhibiting cholesterol absorption, can be effectively and safely co-administered with any dose of any statin and, compared with the single inhibition of cholesterol production, afforded by statins alone, provides consistently greater reductions in LDL-C through dual inhibition of both cholesterol production and absorption. The aim of our study was to evaluate the additional effectiveness and safety of Ezetimibe in high risk patients with documented coronary heart disease who were not at goal with starting doses of a statin.

Materials and Methods. The including criteria of 127 patients, enrolled in the study were the presence of established CHD plus type 2 diabetes of at least 3 months duration and/or other major risk factors, LDL-C > 100 mg/dl and < 250 mg/dl, high triglycerides (TG) ≥200 mg/dl and <400 mg/dl. Patients had to have been receiving therapy with a stable dose of baseline statin, either simvastatin 20 mg or atorvastatin 10 mg, for at least 4 weeks. At randomization, patients were assigned to switch to ezetimibe/atorvastatin 10mg/10mg (Gr. 1) or to continue baseline statin at double the dose: simvastatin 40mg or atorvastatin 20 mg (Gr. 2).

Results. After 12 week follow up analysis of the study showed that 72.6% of patients (45 from 62) in Gr. 1 achieved LDL-C < 100 mg/dl vs 27.7% of patients (18 from 65) in Gr. 2 (P<0.001). 29.0% of patients (18 from 62) from Gr. 1 reached More lower LDL-C goal of below 70 mg/dl vs 4.6% (3 from 65) of patients in Gr. 2 (P<0.01). Patients from Gr. 1 experienced an additional mean LDL-C reduction of 29.2% after 12 weeks vs 12.3% in Gr. 2 (P<0.001). No statistically significant differences were observed between the 2 treatment groups with respect to musculoskeletal or overall adverse experiences.

Conclusions. According to our study we conclude that for high risk patients with CHD who did not achieve LDL-C goal on their starting dose of statin therapy, ezetimibe/atorvastatin combination provided superior lipid-lowering efficacy vs doubling the dose of the baseline statin after 12 weeks of study. Therapy with ezetimibe/atorvastatin was generally well tolerated. Dual inhibition of hepatic cholesterol synthesis and intestinal cholesterol absorption may be a new and practical approach to today's treatment for dyslipidemia. © 2009 Bull. Georg. Natl. Acad. Sci.

Key words: atherosclerosis, treatment for dyslipidemia, dual inhibition of cholesterol synthesis and absorption, Ezetimibe.

INTRODUCTION. Cardiovascular disease is a major cause of disability and premature death throughout the world, and contributes substantially to the escalating costs of health care. Of an estimated 58 million deaths globally from all causes in 2005, cardiovascular disease (CVD) accounted for 30%. This proportion is
equal to that due to infectious diseases, nutritional deficiencies, and maternal and perinatal conditions combined [1]. It is important to recognize that a substantial proportion of these deaths (46%) were of people under 70 years of age, in the more productive period of life; in addition, 79% of the disease burden attributed to cardiovascular disease is in this age group [2].

Atherosclerosis eventually leads to cardiovascular disease (CVD), resulting in a variety of clinical manifestations including: coronary heart disease (CHD) (angina pectoris, MI, and sudden cardiac death), cerebrovascular disease (transient ischemic attacks [TIA] and stroke) and peripheral vascular disease (PVD) (intermittent claudication and gangrene). Atherosclerosis develops over many years and is usually advanced by the time symptoms occur, generally in middle age. Acute coronary and cerebrovascular events frequently occur suddenly, and are often fatal before medical care can be given. Statistics have shown that the probability at birth of eventually dying from major CVD in the USA is 47%, compared with 22% for cancer, 3% for accidents, 2% for diabetes and 0.7% for HIV [3].

An estimated 79,400,000 American adults (one in three) have one or more types of cardiovascular disease (CVD), of whom 37,500,000 are estimated to be age 65 or older. Mortality data show that CVD (100-199) as the underlying cause of death accounted for 36.3 percent of all 2,398,000 deaths in 2004, or one of every 2.8 deaths in the United States. CVD “total mention” mortality (1,408,000 deaths) accounted for about 58 percent of all deaths in 2002 [4].

The most significant clinical manifestation, in terms of morbidity and mortality, is CHD. Table 1 shows that the death rates resulting from CVD and CHD vary greatly in different countries, with the highest rates in the Russian Federation and the lowest in Japan [5].

In the USA CHD is the single largest killer of men and women [6]. Approximately 15.8 million people have a history of MI or angina pectoris. CHD caused one of every five deaths in the United States in 2004. CHD mortality in 2004 was 452,327. MI mortality in 2004 was 157,559. About every 26 seconds, an American will suffer a coronary event, and about every minute someone will die from one. About 38 percent of the people who experience a coronary attack in a given year will die from it [7].

50 percent of men and 64 percent of women who died suddenly of CHD had no previous symptoms of this disease. Between 70 percent and 89 percent of sudden cardiac deaths occur in men, and the annual incidence is three to four times higher in men than in women. However, this disparity decreases with advancing age. People who have had a heart attack have a sudden death rate that is four to six times that of the general population [8].

It has been estimated that in the USA more than 100 million people have elevated total cholesterol levels of ≥200 mg/dl (5.2 mmol/l) and more than 40 million have levels of ≥240 mg/dl (6.2 mmol/l) [9]. Early trials have shown that a reduction in total cholesterol results in a reduction in the incidence of CHD events. In addition, a recent meta-analysis of 38 trials [10] has shown that for every 10% reduction in total chol-
terol, CHD mortality is reduced by 15% and total mortality by 11% (both p<0.001). Similar reductions were seen with all lipid-lowering treatments studied. Thus, total cholesterol is a modifiable risk factor for CHD and total mortality.

Low-density lipoprotein (LDL) cholesterol is strongly associated with the development atherosclerosis and CHD events in patients with established CHD (history of angina pectoris, MI etc.) and in those without CHD [11]. It has been recognised as a prime target for lipid intervention to prevent CHD. A 10% increase in LDL cholesterol is associated with an approximate 20% increase in risk for CHD [11] but most patients with elevated LDL are untreated in USA. Upon analysis of NHANES III data Jacobson and colleagues found that approximately 28.4 million Americans required drug therapy according to ATP II guidelines while only an estimated 4.5 million were receiving drug therapy [12].

The intensity of intervention depends not only on raised cholesterol or LDL cholesterol but also on the presence of a number of other risk factors for CHD, such as low HDL cholesterol, smoking, hypertension and diabetes [13].

Modification of risk factors has been shown to reduce mortality and morbidity in people with diagnosed or undiagnosed cardiovascular and/or CHD diseases.

A recent update to the American Heart Association/American College of Cardiology (AHA/ACC) guidelines for secondary prevention includes recommendations regarding lipid management [14] and further supports the intensive reduction of LDL-C in patients with CHD and other atherosclerotic vascular disease. The recommended LDL-C treatment goal in these patients is <100 mg/dl, but a target of <70 mg/dl is now considered a reasonable strategy [14]. Any person at high risk who has lifestyle-related risk factors is a candidate for therapeutic lifestyle changes (TLC) to modify these risk factors, regardless of LDL-C level. Whenever the baseline LDL-C concentration is ≥100 mg/dl, initiation of an LDL-C-lowering drug and dietary therapy is recommended. If baseline LDL-C is 70 to 100 mg/dl, it is now reasonable to lower it to <70 mg/dl [14] (Table 2).

Clinical trial evidence led to proposed modifications of ATP III LDL-C goals and cut points for TLC and drug therapy [15]. Factors that place patients in the very high-risk category include the presence of established cardiovascular disease (CVD) plus the following: 1) multiple major risk factors, especially diabetes; 2) severe and poorly controlled risk factors, especially continued cigarette smoking; 3) multiple risk factors of the metabolic syndrome, especially high triglycerides (TG) ≥200 mg/dl plus non–high-density lipoprotein cholesterol (HDL-C) ≥130 mg/dl with HDL-C <40 mg/dl; and 4) acute coronary syndromes [15]. For high-risk patients, the recommended LDL-C treatment goal remains <100 mg/dl. However, an optional target of <70 mg/dl is a reasonable clinical strategy for persons considered to be at very high risk [15]. Any person at high risk who has lifestyle-related risk factors is a candidate for TLC to modify these risk factors, regardless of LDL-C level. As before, whenever the baseline concentration is ≥130 mg/dl, simultaneous initiation of an LDL-C-lowering drug and dietary therapy is recommended. If LDL-C is 100 to 129 mg/dl, the same interventions now hold [15] (Table 2).

Table 2

<table>
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<tr>
<th>Intensive LDL-C goals for high-risk patients</th>
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<tr>
<th>ATP III Update 2004</th>
<th>AHA/ACC guidelines for patients with CHD</th>
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<tr>
<td>&lt;100 mg/dl: Patients with CHD or CHD risk equivalents (10 year risk ≥20%)</td>
<td>&lt;100 mg/dl: Goal for all patients with CHD</td>
</tr>
<tr>
<td>&lt;70 mg/dl: Therapeutic option for very high risk patients</td>
<td>&lt;70 mg/dl: A reasonable goal for all patients with CHD</td>
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* and other forms of atherosclerotic disease

1 Factors that place a patient at very high risk: established cardiovascular disease (CVD) plus multiple major risk factors (especially dyslipidemia), severe and poorly controlled risk factors (e.g., cigarette smoking), metabolic syndrome (hypertriglyceridemia [TG] ≥200 mg/dl, non-HDL-C ≥130 mg/dl, with HDL-C <40 mg/dl), and acute coronary syndromes


Widely used in lipid lowering therapy, HMG CoA reductase inhibitors (even when administered at high doses) are frequently insufficient to achieve guideline-recommended LDL-C goals for many patients with hypercholesterolemia in everyday clinical practice [16]. At starting doses, statins provide LDL-C reductions of 25% to 40% [17]. For many patients and especially those at high risk with high LDL-C, however, these reductions are inadequate for achieving goal LDL-C levels on initial statin therapy [18]. In clinical practice, clinicians may not increase statin dose levels out of concern for potential adverse events or because titration of statin doses provides only limited additional effectiveness [19]. The majority of these patients do not reach their goal after 6 months. As a consequence, a wide therapeutic gap exists between targets LDL-C levels and those typically achieved in clinical practice. A recent and more effective therapeutic hypocholesterolemic strategy is to treat the two main sources of cholesterol simultaneously (production of cholesterol, mainly in the liver, and absorption of cholesterol in the intestine) with a complementary mechanism of action, by co-administering Ezetimibe, a novel agent inhibiting cholesterol absorption, with a statin, which inhibits cholesterol production in the liver [20]. Ezetimibe can be effectively and safely co-administered with any dose of any statin and, compared with the single inhibition of cholesterol production, afforded by statins alone, provides consistently greater reductions in LDL-C through dual inhibition of both cholesterol production and absorption [21, 22, 23] (Table 3).

Ezetimibe is the first in a class of cholesterol-lowering agents with a mechanism of action that is very different from other lipid lowering therapies, including bile acid sequestrants. By inhibiting cholesterol absorption at the level of the brush border of the intestine, ezetimibe reduces the amount of lipoprotein cholesterol circulated to the liver. In response to reduced cholesterol delivery, the liver reacts by upregulating LDL-C receptors, which in turn leads to increased clearance of cholesterol from the blood [24].

Adding Ezetimibe to ongoing statin therapy led to a substantial additional reduction in LDL cholesterol levels, facilitating attainment of NCEP goals. In patients with hypercholesterolemia not at goal on statin therapy alone, the Ezetimibe Add-On to Statin for Effectiveness (EASE) trial [25, 26] demonstrated that co-administering ezetimibe (10 mg) with any dose of statin reduced LDL-C levels by an additional 25%, compared with the usual 6% attained by titration the statin dose and improved LDL-C goal attainment from 20% on statin monotherapy to 71% vs 18.9% on statin alone, p<0.001 (20).

Ezetimibe-based therapy represents an exciting new area in the treatment of dyslipidemia.

PURPOSE. The aim of our study was to evaluate the additional effectiveness and safety of Ezetimibe in high risk patients with documented coronary heart disease and hypercholesterolemia who were not at goal with starting doses of a statin.

MATERIALS AND METHODS. The including criteria of 127 patients, enrolled in the study were the presence of established CHD plus type 2 diabetes of at least 3 months duration and/or other major risk factors, LDL-C > 100 mg/dl and < 250 mg/dl, high triglycerides (TG) ≥200 mg/dl and <400 mg/dl.

Patients had to have been receiving therapy with a stable dose of baseline statin, either simvastatin 20 mg or atorvastatin 10 mg, for at least 4 weeks.

At randomization, patients were assigned to continue baseline statin at double the dose (simvastatin 40 or atorvastatin 20 mg) or to switch to ezetimibe/atorvastatin 10/10 mg.

The primary study end point was the percentage of patients who achieved LDL-C below 100 mg/dl after 12 weeks of study treatment. In an additional efficacy analysis, the percentage of patients who achieved a lower LDL-C goal of less than 70 mg/dl was evaluated. Secondary end points were percentage reductions in total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and the ratio of total cholesterol to HDL-C.

In addition, data for safety profile and tolerability evaluations were also collected throughout the study period.

Patients randomized to ezetimibe/simvastatin (Gr. 1, n=62) and doubling of their baseline statin dose (Gr. 2, n=65) were well matched with respect to age and gender, and baseline characteristics, including medical history. No statistically significant differences between the 2 treatment groups were reported.
At baseline, mean LDL-C was 124 mg/dl in the ezetimibe/simvastatin group and 128 mg/dl in the doubling the statin group.

**RESULTS.** After 12 week follow up analysis of the primary end point of the study showed a significant advantage for ezetimibe/atorvastatin combination (Gr. 1) vs doubling the statin dose (Gr. 2) \((P<0.001)\): 72.6% (45 patients from 62) achieved LDL-C 100 mg/dl with ezetimibe/atorvastatin vs 27.7% of patients (18 from 65) receiving either simvastatin 40 mg or atorvastatin 20 mg.

29.0% (18 from 62) of patients from ezetimibe/atorvastatin group (Gr. 1) reached More lower LDL-C goal of below 70 mg/dl vs 4.6% (3 from 65) of patients in Gr. 2, doubling the dose of baseline statin to simvastatin 40 mg or atorvastatin 20 mg \((P<0.01)\) (Table 4).

Patients who were switched to ezetimibe/simvastatin from baseline statin therapy with simvastatin 20 mg or atorvastatin 10 mg experienced an additional mean LDL-C reduction of 29.2% (from 124 mg/dl to 96 mg/dl) after 12 weeks. In contrast, patients who had their dose of simvastatin or atorvastatin doubled experienced a mean LDL-C reduction of 12.3% (from 128 mg/dl to 114 mg/dl) after 12 weeks. The difference in LDL-C changes was statistically significant \((P<0.001)\) in favor of switching to ezetimibe/simvastatin (Table 5).

Similar changes from baseline to after 12 week treatment differences were observed between the groups for total cholesterol and the total cholesterol/HDL-C ratio, each of which were statistically significant \((P<0.01)\) in favor of switching to ezetimibe/simvastatin vs doubling the dose of baseline statin: 18.9% and 14.7% vs 7.8% and 6.9%, respectively (see Table 5).

Changes in triglycerides and HDL-C level were not significantly different between the 2 treatment groups.

No statistically significant differences were observed between the 2 treatment groups with respect to musculoskeletal or overall adverse experiences, or discontinuations of study therapy due to adverse experiences.

**DISCUSSION AND CONCLUSIONS.** Data from epidemiologic and clinical trials confirm a long-linear relationship between LDL-C and relative risk of CHD. Many high risk patients need significant LDL-C efficacy to reach recommended treatment goals. At starting doses, statins provide LDL-C reductions of less than

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**Table 4**

Effectiveness of Ezetimibe/Atorvastatin combination vs doubling the statin dose in achievement the LDL-C goals:

\(<100 \text{ mg/dl} \text{ and } <70 \text{ mg/dl}\)

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**Table 5**

Effectiveness of Ezetimibe/Atorvastatin combination (Gr. 1) vs doubling the statin dose (Gr. 2) after 12 week treatment in high risk patients with CHD

<table>
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<tr>
<th>Reduction of</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
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<tr>
<td>Total Cholesterol</td>
<td>18.90%</td>
<td>7.80%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>29.20%</td>
<td>12.30%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>1.80%</td>
<td>+2.20%</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.30%</td>
<td>3.70%</td>
<td>NS</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>14.70%</td>
<td>6.90%</td>
<td>&lt;0.01</td>
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</table>
50%. For many patients and especially those at high risk with high LDL-C, however, these reductions are inadequate for achieving goal LDL-C levels on initial statin therapy.

In the past few years, an innovative approach to cholesterol lowering therapy has been introduced. Ezetimibe-based therapy represents an exciting new area in the treatment of dyslipidemia.

According to our study we conclude that for high risk patients with CHD who did not achieve LDL-C goal on their starting dose of statin therapy, ezetimibe/atorvastatin combination provided superior lipid-lowering efficacy vs doubling the dose of the baseline statin. A significantly higher percentage of patients switched to ezetimibe/atorvastatin (72.6% and 29.0%) compared with patients whose dose of baseline statin was doubled (27.7% and 4.6%) achieved LDL-C below 100.0 mg/dl and 70.0 mg/dl after 12 weeks of study.

Switching to ezetimibe/atorvastatin also provided significantly greater reductions in mean LDL-C (29.2%) compared with doubling the baseline statin dose (12.3%) after 12 weeks among patients who had already been on stable statin therapy ($P<0.01$).

Therapy with ezetimibe/atorvastatin was generally well tolerated.

Dual inhibition of hepatic cholesterol synthesis and intestinal cholesterol absorption may be a new and practical approach to today’s treatment for dyslipidemia.
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ბულ. გერგ. ნაციонаლ. აკად., ვოლ. 3, ნო. 2, 2009

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REFERENCES:

3. CDS/NCHS computations from American Heart Association web site (www.americanheart.org).

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