Impact of Ezetimibe on Atherosclerosis: Is the Jury Still Out?

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Ezetimibe is a new lipid-lowering agent that inhibits intestinal absorption of dietary cholesterol. It substantially lowers low-density lipoprotein cholesterol levels when used alone or in combination with statins. However, its effect on cardiovascular mortality remains unknown. We reviewed peer-reviewed published literature on the effect of ezetimibe on different phases of atherosclerosis. MEDLINE, EMBASE, BIOSIS, and other Web of Knowledge databases were searched for relevant abstracts and articles published in the English language that compared ezetimibe and statins as modulators of atherosclerosis. On the basis of the available evidence, ezetimibe appears to reduce inflammation when used in combination with statins, but its effect on endothelial function is mixed and less clear. The effect of ezetimibe on coronary disease progression or prevention of cardiovascular events is currently unknown. Use of ezetimibe as a second- or third-line agent to achieve low-density lipoprotein cholesterol treatment goals seems appropriate on the basis of the available evidence.

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CAD = coronary artery disease; CIMT = carotid artery intima-media thickness; CVD = cardiovascular disease; ENHANCE = Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression; FMD = flow mediated dilatation; FBF = forearm blood flow; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LDL-C = LDL cholesterol; NPC1L1 = Niemann-Pick C1-like 1 protein

Remarkable progress has been made in the understanding and treatment of blood lipid abnormalities in the past 3 decades. The development of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) in particular has led to substantial improvements in the treatment of lipid abnormalities. Statins improve cardiovascular disease (CVD) outcomes by lowering low-density lipoprotein cholesterol (LDL-C) levels[1,2] and also by affecting the process of atherosclerosis through several possible nonlipid mechanisms, such as reduction of inflammation[3] and reversal of endothelial dysfunction.[4] In part because of concerns of the relatively common occurrence of adverse effects from statins, intense efforts are ongoing to develop effective and well-tolerated lipid-altering agents.

Ezetimibe is a new lipid-lowering agent that inhibits intestinal cholesterol absorption and substantially reduces LDL-C levels when used alone or in combination with statin therapy.[5] However, the role of ezetimibe in lipid management has been debated in view of limited evidence defining the impact of ezetimibe on major adverse cardiac events. Proponents of the LDL-C level lowering position point out that ezetimibe would be expected to lower cardiovascular risk because it lowers LDL-C levels, and they cite many studies that have shown a reduction in cardiovascular events with any amount of reduction in LDL-C level, independent of the mechanism of that reduction.[6] Others take a more conservative stance and suggest that ezetimibe should be used only as a second- or third-line agent until more evidence is available regarding the impact of ezetimibe on CVD events,[7] particularly since evidence shows that an alternative therapy (statin therapy) has beneficial effects on CVD events. Until longer-term outcome studies of ezetimibe are available, these 2 viewpoints may not ever be reconciled, leaving physicians to judge the role of ezetimibe using currently available evidence. To help clarify the potential role of ezetimibe in lipid management and in risk reduction strategies, we reviewed published reports on ezetimibe and its impact on various steps in the process of atherosclerosis.

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METHODS

We performed a computerized search to identify clinical trials that compared the effect of ezetimibe and statins as modulators of traditional CVD risk factors (lipid levels, blood pressure, glycemic control), novel risk factors (inflammation, thrombosis, lipid peroxidation), markers of subclinical atherosclerosis (coronary calcification, endothelial dysfunction, arterial intima-media thickness), and clinical events. MEDLINE (from 1966 to October 2008), EMBASE (from 1980 to October 2008), BIOSIS, Cochrane Collaborative databases, and Web of Knowledge databases (including www.clinicaltrials.gov and www.scopus.com)

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were searched for relevant journal articles. We also manually searched the references of cited articles for pertinent material. The following search terms were used: *ezetimibe*, *statins* or *HMG-CoA reductase inhibitors*, *inflammation*, *high-sensitivity CRP* (C-reactive protein), *endothelial function/dysfunction* or *flow mediated dilatation* (FMD), *intima-media thickness* or *IMT*, *lipid peroxidation*, *platelet aggregation*, *coronary calcification*, *blood pressure*, and *hyperglycemia* or *hypoglycemia*. The search was restricted to articles and abstracts published in the English language. The abstracts of the cited articles were reviewed and summarized by 1 of the authors (F.J.A.) to determine relevance. All studies that were found by the authors to meet the criteria of our review were retrieved for further consideration. Studies were included in this review if they were from prospective trials, compared ezetimibe in one arm (alone or in combination with statins) with statins in the other arm (irrespective of the agent or dose used), and reported adequate data to allow comparison of both study arms on the end point in question. In addition, studies were included if they assessed the impact of ezetimibe on at least 1 of the pathway steps in the process of atherosclerosis. When an abstract from a meeting and a full article referred to the same trial, only the full article was included in the analysis. When there were multiple reports from the same trial, we used the most complete and/or most recently reported data. The quality of each study included in our review was individually evaluated by 1 of the authors (F.J.A.) using the criteria outlined by Jadad et al.[8]

MECHANISMS OF ACTION FOR EZETIMIBE

Ezetimibe is the first of a new class of highly selective cholesterol absorption inhibitors. Through a mechanism that is not yet fully elucidated, ezetimibe appears to block a protein transporter called Niemann-Pick C1-like 1 protein (NPC1L1)[9] that is located at the apical membrane of the small intestine enterocytes. The result of ezetimibe's action on NPC1L1 in the small intestine is to decrease the absorption of dietary and biliary cholesterol in the small intestine and subsequently decrease the delivery of LDL to the liver.[10] Increased clearance of plasma LDL through the liver ensues through up-regulation of LDL receptors on the surface of hepatocytes.[11] Statins lower serum LDL levels through up-regulation of LDL receptors in the liver, albeit through a different mechanism (inhibition of HMG-CoA reductase). In addition, statins reduce serum LDL levels by reducing hepatic cholesterol production. Furthermore, NPC1L1 is expressed in human hepatocytes and is similarly blocked by ezetimibe. However, the clinical effects and possible off-target effects of the interaction between ezetimibe and hepatic NPC1L1 are unclear.

EVIDENCE OF EZETIMIBE'S IMPACT ON ATHEROSCLEROSIS

To help clarify the potential clinical role of ezetimibe based on currently available evidence, particularly its role in CVD risk reduction, one needs to consider the published evidence regarding ezetimibe's impact on the major risk factors and pathophysiologic steps in the process of atherosclerosis (Figure).

TRADITIONAL CVD RISK FACTORS

Effects on Blood Lipids

Ezetimibe substantially reduces LDL-C levels (–17.2% to –22.3%) when used alone compared with placebo.[12,13] When used in combination with different statins, an additive reduction in LDL-C levels[14,15] is observed (–6% to –20%), along with favorable changes in high-density lipoprotein cholesterol, triglycerides, and apolipoprotein B100 levels in hyperlipidemic patients.[11]

Effects on Other Traditional CVD Risk Factors

Limited studies have suggested a potential beneficial effect of ezetimibe on glucose metabolism in both animal[16] and human[17] models, although the results are somewhat mixed[18] and preliminary. Whether ezetimibe therapy is associated with a reduced incidence of type 2 diabetes mellitus is unclear. No published reports could be identified that assessed the potential impact of ezetimibe therapy on other traditional CVD risk factors, including blood pressure and obesity.

The limited data on ezetimibe's effects on glucose and blood pressure mirror a similarly unclear picture of the effect that statins have on these factors. Some limited reports suggest that pravastatin is associated with a lower incidence of diabetes[19] and a neutral effect on glycemic indices.[20] In contrast, atorvastatin use led to worse blood glucose control compared with pravastatin.[21]

NOVEL CVD RISK FACTORS

Several investigators have studied the potential impact of ezetimibe on novel CVD risk factors, including its effect on inflammatory markers, thrombotic factors, and lipid peroxidation.

Inflammation

Inflammation is recognized as a major component of the process of atherogenesis and a contributor to plaque rupture.[22,23] Higher levels of circulating markers of systemic inflammation, mainly high-sensitivity (hs) CRP, are associated with an increased risk of myocardial infarction and

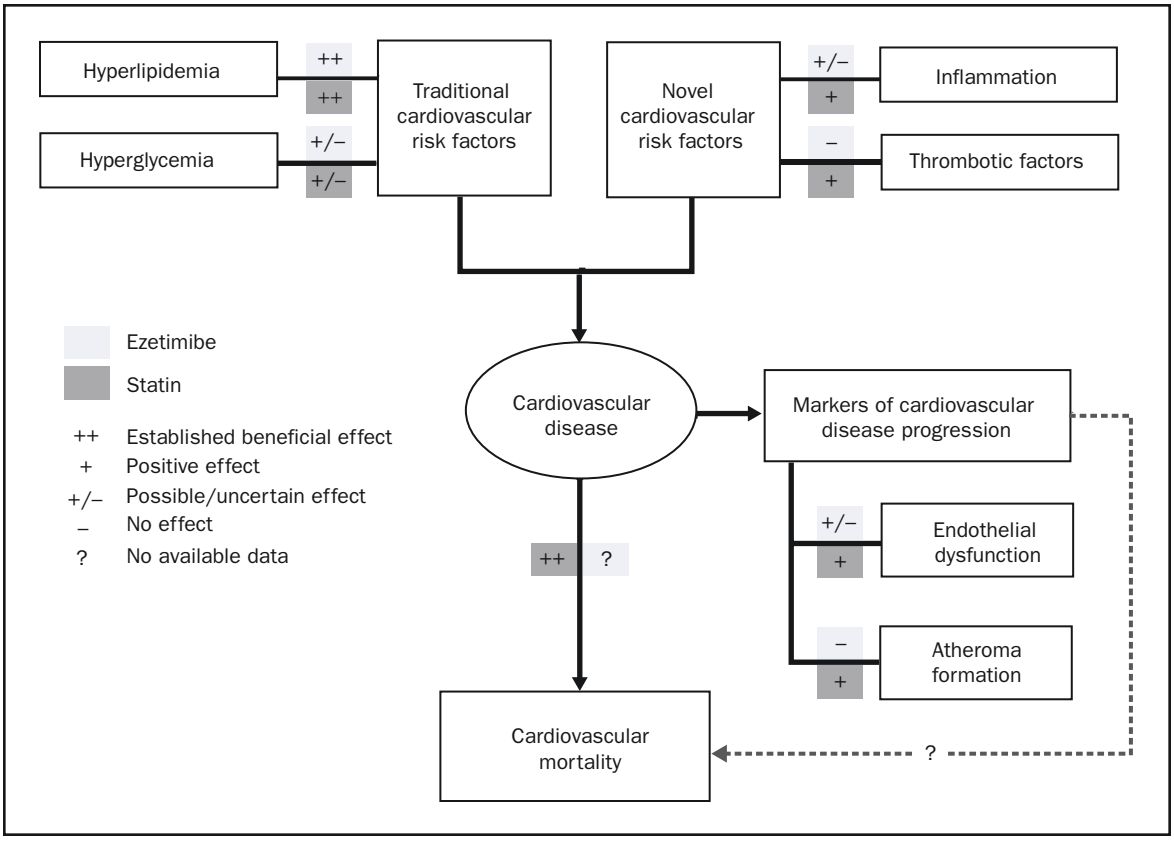

FIGURE. Impact of ezetimibe and statin therapy on various steps in the process of atherosclerosis.

ischemic stroke in asymptomatic patients[24] and a heightened risk of major adverse cardiac events in those with established disease.[25] Measurement of hs-CRP levels in patients with an intermediate 10-year risk of CVD appears to be helpful in further risk stratification of such patients.[26] A recently published study,[27] JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), found that statin therapy lowers cardiovascular risk in persons with elevated hs-CRP levels. However, debate continues regarding the most appropriate role for hs-CRP as a risk indicator, particularly in its potential role as a target of preventive therapies.[28]

Key findings from published reports of ezetimibe therapy and inflammation are as follows. First, several studies have shown that ezetimibe monotherapy produced overall a modest, nonsignificant reduction in hs-CRP levels compared with placebo[29] (7.4% vs –2.8%). Pearson et al[30] pooled data from 3 randomized controlled trials[5,31,32] that compared the efficacy and safety of ezetimibe-simvastatin combination therapy relative to simvastatin monotherapy. In 2541 hyperlipidemic men and women, ezetimibe-simvastatin combination therapy was more effective in lowering hs-CRP levels than simvastatin alone (–31% vs –14.3%; $P<.001$). This effect was noticed across all available simvastatin dosages, with an additional 14.1% to 19.4% reduction in hs-CRP levels with 10 mg of ezetimibe combined with any simvastatin dose. In contrast, in a small study of 40 hyperlipidemic patients, Efrati et al[33] reported that adding ezetimibe to ongoing therapy with 40 mg of simvastatin was less effective in reducing the hs-CRP level than doubling the statin dose. The dissimilar results in these 2 studies may be due to the differences in study design, particularly the smaller number of participants in the latter study.

Second, Ballantyne et al[34] compared atorvastatin-ezetimibe combination therapy with atorvastatin alone and reported an overall larger reduction in hs-CRP levels with the combination therapy compared with atorvastatin monotherapy (–41% vs –31%; $P<.01$). Unlike the findings in the aforementioned simvastatin studies, addition of ezetimibe produced an incremental reduction in the hs-CRP level with only the higher 80-mg atorvastatin dose (–62% vs –43%; $P<.01$) but not with the lower 10-mg dose (–25% vs –27%), despite the consistent benefit observed with LDL-C level lowering across the whole dosing range of atorvastatin.

Third, ezetimibe-simvastatin combination therapy was also compared with atorvastatin monotherapy.[35] Investiga-

tors observed no further reduction in hs-CRP levels with the addition of ezetimibe to simvastatin compared with the corresponding dose of atorvastatin in 1902 patients with above-target LDL-C values. They concluded that the reduction in hs-CRP levels was similar in the 2 treatment groups (24.8% vs 25.1%). This conclusion should be interpreted with caution because the degree of reduction in LDL-C levels differed between the treatment groups.[36] When comparing dosages that achieved equivalent reductions in LDL-C levels, atorvastatin alone produced greater reductions in hs-CRP levels than ezetimibe-simvastatin combination therapy.

Fourth, Catapano et al[37] reported a greater reduction in LDL-C levels with ezetimibe-simvastatin combination therapy relative to rosuvastatin but a similar change in hs-CRP levels in both groups. A study by Ballantyne et al[38] compared rosuvastatin monotherapy to rosuvastatin-ezetimibe combination therapy and found a significant reduction in hs-CRP levels with the combination therapy compared with statin monotherapy (–46% vs 29%; $P<.001$).

In summary, currently available data suggest that ezetimibe may have a synergistic effect on hs-CRP levels when combined with statins, a finding that is consistent with the results of a recent meta-analysis.[39] However, the mechanism of this effect and the interaction of ezetimibe with different statins are still in need of clarification. In addition, the high correlation between the change in LDL-C levels and that in hs-CRP levels suggests that most of the anti-inflammatory effect of LDL-C–lowering therapies is related to the magnitude of change in LDL-C, rather than an LDL-independent effect of statins or other lipid-lowering therapies. The clinical importance of pleiotropic benefits of statins and ezetimibe in prevention of vascular disease has not been firmly elucidated.

Thrombotic Factors

Patients with hyperlipidemia have increased platelet aggregation,[40] which may contribute to CVD risk in these patients. Although therapy with statins has been associated with reduced platelet aggregation through a mechanism that is LDL independent,[41] data from 2 studies suggest no such effect with ezetimibe therapy. Piorkowski et al[42] showed that atorvastatin (40 mg) produced greater reduction in markers of platelet activation than atorvastatin (10 mg) combined with ezetimibe, 10 mg/d, in patients with stable coronary artery disease (CAD) despite achieving a similar LDL-C reduction in both groups. Similar findings were also reported by Hussein et al[43] despite considerable methodological variation in the 2 studies.

Lipid Peroxidation

Oxidation of LDL particles has been identified as an early step in the process of atherosclerosis. Oxidized LDL is less likely to be taken up by hepatic LDL receptors and more likely to be taken up by monocytes in the arterial wall. This latter phenomenon initiates a cascade of events that results ultimately in endothelial injury and dysfunction.[44] Statins have been reported to have a possible positive effect on LDL oxidation.[45] In one report,[43] ezetimibe lowered the peroxidation tendency of LDL in 22 hyperlipidemic patients. In addition, ezetimibe therapy was shown to reduce the serum level of oxidized cholesterol significantly (>50%) in 7 healthy volunteers fed an oxidized cholesterol-rich diet.[46] The clinical importance of this observation is unknown.

SUBCLINICAL MARKERS OF ATHEROSCLEROSIS

Various markers of atherosclerosis have been developed to help identify otherwise healthy individuals who show evidence of early atherosclerosis and who are at risk of future CVD events. Such markers include noninvasive measurement of carotid artery intima-media thickness (CIMT), endothelial function, arterial stiffness, coronary calcification, and ankle-brachial index. Limited available data on the impact of ezetimibe on measures of subclinical atherosclerosis are described subsequently.

Carotid Artery Intima-Media Thickness

Numerous studies have reported that CIMT is associated with the risk of CVD,[47] and CIMT has been used in several studies as a subclinical marker of atherosclerosis[48] and as a surrogate end point of CVD.[49] In addition, serial CIMT measurements, as a marker of CVD progression and/or regression, were used to study the effect of various interventions on CVD.[50-61] The advent of more advanced imaging techniques and software has made this imaging modality even more attractive in accurately detecting and quantifying changes in CIMT.

Data are limited on ezetimibe and changes in CIMT. One recent study that used CIMT measurements to assess the impact of ezetimibe therapy on atherosclerosis produced as many questions as answers. In the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) study,[59] the effect of ezetimibe-simvastatin on CIMT was investigated by Kastelein et al in persons with familial hypercholesterolemia who were randomized to receive simvastatin, 80 mg, and either ezetimibe, 10 mg, or placebo. The primary end point was a change in CIMT after 24 months of treatment. At the conclusion of the study, the group receiving simvastatin-ezetimibe combination therapy had significantly reduced LDL-C (–39.1% vs 55.6%; $P<.01$) and hs-CRP (–49.2% vs –23.5%; $P<.01$) levels compared with the simvastatin group. However, despite the difference in

TABLE 1. **Baseline and Maximum CIMT Change in Various Studies Evaluating CIMT as an End Point**[a]

Reference	Intervention	Duration	No. of patients	Mean ± SD baseline CIMT[b] (mm)	Δ CIMT (% of baseline)	Study quality[c]
Nolting et al,[51] 2003	Simvastatin (80 mg)[d]	2 y	153	0.92	–5.4[e]	1
Terpstra et al,[55] 2003	Nifedipine[d]	26 wk	131	1.03±0.23	–7.6[e]	1
Langenfeld et al,[52] 2005	Pioglitazone (45 mg) vs glimperide (1-6 mg)	24 wk	173	0.95±0.15	–5.9[e]	2
Lonn et al,[53] 2001	Ramipril (2.5 or 10 mg) vs placebo	4.5 y	732	1.15±0.34	NA	4
Okada et al,[54] 2004	Therapeutic lifestyle changes	2 y	1390	0.86	–4.8 to –16	1
Kastelein et al,[59] 2008	Simvastatin/ezetimibe (80/10 mg) vs simvastatin (80 mg)	24 mo	720	0.7±0.2	+1.2	5
CASHMERE,[58] 2008	Atorvastatin (80 mg) vs placebo	12 mo	398	0.69±0.12	+2.9	NA
Smilde et al,[60] 2001	Atorvastatin (40 mg) vs simvastatin (20 mg)	2 y	330	0.93±0.2	–3.3[e]	5
Taylor et al,[61] 2002	Atorvastatin (80 mg) vs pravastatin (40 mg)	12 mo	138	0.94±0.65 (atorvastatin arm)	–14.7[e]	4
Crouse et al,[57] 2007	Rosuvastatin (40 mg) vs placebo	24 mo	738	1.16±0.2	–0.24[e]	4

[a] CASHMERE = Carotid Atorvastatin Study in Hyperlipidemic Post-menopausal Women: A Randomized Evaluation; CIMT = carotid artery intima-media thickness; NA = not available.
[b] Maximum CIMT when specified.
[c] Quality of studies assessed using the criteria outlined by Jadad et al.[8]
[d] Nonrandomized design.
[e] Significant change ($P<.05$) from baseline.

LDL-C level lowering, the primary outcome, CIMT change, did not differ between the treatment groups (+0.0033 mm for simvastatin vs +0.0182 mm for simvastatin-ezetimibe; $P=.15$). Although these results suggest that ezetimibe did not promote additional CIMT improvement, 81% of the study participants were already receiving statin therapy before the start of the study. This fact may have affected CIMT stabilization and/or regression for study participants even before the study began, thus dampening the potential impact of ezetimibe on CIMT change during the study. In support of this concern, the mean maximum CIMT at baseline in participants in the ENHANCE study was only 0.70 mm, a value significantly smaller than the corresponding CIMT values from other studies in which a treatment benefit on CIMT was reported (Table 1).

Some commentators have questioned the use of CIMT as an end point in the ENHANCE study,[62] using the results of the previously reported CASHMERE (Carotid Atorvastatin Study in Hyperlipidemic Post-menopausal Women: A Randomized Evaluation)[58] to support this point. In CASHMERE, 398 postmenopausal women (average age, 56 years) were randomized to receive either atorvastatin, 80 mg, or placebo and were followed up for 12 months using CIMT as an outcome measure. Reportedly, no changes in atherosclerosis burden could be detected at the end of the study, even with the use of atorvastatin therapy. This study has several limitations: (1) it involved a small number of postmenopausal women with moderate hyperlipidemia, relatively high levels of high-density lipoprotein cholesterol, and low CIMT measures at baseline; (2) it had a high dropout rate in both the treatment and the placebo groups; (3) study duration was too short to detect changes in CIMT, especially in a population at low risk of progression of atherosclerosis; and (4) it has not yet been published in a peer-reviewed journal. Recently, a secondary analysis from SANDS (Stop Atherosclerosis in Native Diabetics Study[63]) was released.[64] One-third of patients (Native Americans without prior CVD who had diabetes) randomized to an aggressive LDL-C goal of less than 70 mg/dL required ezetimibe to reach the treatment goal. Among patients in the aggressive arm, 62% of those who received ezetimibe plus a statin and 61% of those who received statin therapy only showed either no change or a reduction in CIMT at 36 months of follow-up compared with 39% of patients in the arm of a standard LDL-C goal of less than 100 mg/dL ($P<.001$). In this nonprespecified secondary analysis, the magnitude of LDL-C level lowering was similar in both groups of the aggressive arm: –32.3 in patients who received statin monotherapy and –31.1 in the group that received the statin-ezetimibe combination therapy. In addition, multivariate analysis showed that change in LDL-C level independently affected CIMT change, whereas ezetimibe use did not.

Endothelial Function and Arterial Stiffness

Since endothelial dysfunction is considered an early step in the current understanding of atherogenesis[65] and a key player in plaque progression and rupture,[66] detection of endothelial function impairment that predates the presence of clinically important plaque burden may help identify a subgroup of patients at higher risk of future development of cardiovascular events.[67] Similarly, increased arterial stiffness is predictive of coronary disease and stroke even after

adjustment for other CVD risk factors.[68] Statin therapy has been reported to improve measures of arterial function.[69-71] Several studies have also explored the potential impact of ezetimibe on arterial function.

Settergren et al[72] demonstrated a comparable reduction in LDL-C and hs-CRP levels in patients with stable CAD and dysglycemia who were treated with either simvastatin (80 mg) or simvastatin (10 mg) and ezetimibe (10 mg) combination therapy. In addition, both groups had similar improvement in FMD, a measure of endothelial function, after 6 weeks of therapy (+0.9% vs +1.5%, *P*=.39). In another report,[73] 60 patients from a similar population were randomized according to their statin status. Statin-naive patients were randomized to receive either ezetimibe alone or atorvastatin, 40 mg, alone. Patients who were receiving a long-term dosage of simvastatin at 20 mg/d had 10 mg of ezetimibe added to their ongoing simvastatin therapy and those receiving 10 mg of atorvastatin were switched to 40 mg/d of atorvastatin. All patients received study medication for 4 weeks. Forearm blood flow (FBF) was measured by the venous occlusion plethysmography technique to assess endothelial function. Study investigators found that patients in the ezetimibe or simvastatin (20 mg)–ezetimibe combination groups had no improvement in their FBF after 4 weeks of therapy, whereas a statistically significant increase in FBF was noted among participants in the 2 atorvastatin groups (statin naive and statin exposed). They concluded that ezetimibe use in patients with stable CAD was not associated with improvement in endothelial function, whereas use of atorvastatin was associated with improved endothelial function.

Landmesser et al[74] evaluated the role of ezetimibe on endothelial function in patients with heart failure by using FMD measurements, expressed as the percentage of dilatation of radial artery after relief of wrist arterial occlusion. Patients were randomized to receive either 10 mg of ezetimibe or 10 mg of simvastatin. At the end of 4 weeks, both groups had a similar reduction in LDL-C level (15.6% vs 15.4%), whereas only the patients receiving simvastatin had an improvement in endothelial function based on FMD improvements.

Mäki-Petäjä et al[75] assessed changes in arterial function, using FMD and arterial stiffness, as measured by arterial pulse wave velocity in a cohort of patients with rheumatoid arthritis but no concomitant CVD, renal disease, or diabetes. Patients were randomized to receive either 10 mg of ezetimibe or 20 mg of simvastatin in a double-blind, crossover manner. Despite a larger reduction in LDL-C levels in the simvastatin group (–38.7% vs –17.9%; *P*=.001), patients in both groups had substantial improvement in arterial pulse wave velocity (–7.23% vs –7.40%) and FMD (37.2% vs 64.9%; *P*=.10). In contrast, Efrati et al[33] found no improvement in augmentation index with ezetimibe use, either singly or in combination with simvastatin therapy. Table 2 summarizes the clinical studies that evaluated the effect of ezetimibe on arterial health, including an assessment of the quality of these studies using the criteria outlined by Jadad et al.[8]

In summary, studies with more rigorous methods[72,75] showed comparable improvement in endothelial function and arterial stiffness with both ezetimibe monotherapy and combination therapy, whereas the studies with less rigorous methods did not.[33,73,74] However, the latter group of studies has multiple methodological concerns that limit the strength of their conclusions. The results of the study by Mäki-Petäjä et al[75] may not be applicable to the general population because it was exclusively performed in persons with rheumatoid arthritis, a condition that is in itself highly associated with inflammation and endothelial dysfunction.[77]

On the basis of currently available evidence, ezetimibe appears to have a positive, protective effect on endothelial function, although this association needs to be further confirmed by additional long-term clinical trials.

Other Measures of Atherosclerosis

Several other methods to assess subclinical CVD have been developed, including coronary calcification scanning and measurement of the ankle-brachial blood pressure index. In addition, quantifying changes in atherosclerotic burden over time is now feasible with intravascular ultrasonography, which has been used to assess CAD progression or regression. We identified no published studies that have addressed the effect of ezetimibe therapy on these markers of atherosclerosis.

Cardiovascular Events

To date, the long-term effect of ezetimibe on cardiovascular events is largely unknown. The SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study,[78] a placebo-controlled study designed primarily to assess the possible effect of intensive lipid lowering with simvastatin-ezetimibe combination therapy on aortic valve stenosis, showed a trend toward reduction in ischemic events (a secondary end point of the study) in the treatment group relative to placebo (15.7% vs 20.1%; *P*=.02) during a median follow-up of 52 months. However, it is possible that this reduction was due to the effects of simvastatin, not ezetimibe. IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), a randomized, prospective, placebo-controlled clinical trial comparing the impact of simvastatin monotherapy with simvastatin-ezetimibe combination therapy on cardiovascular outcomes in patients with acute

TABLE 2. **Studies Comparing the Effects of Ezetimibe and Statin Therapies on Endothelial Function and Arterial Stiffness**[a]

Reference	Patient population	Intervention	End points assessed	Findings	Conclusion	Study quality[b]
Settergren et al,[72] 2008	43 With stable CAD and DM or IGT	Simvastatin (10 mg) + ezetimibe vs simvastatin (80 mg)	FMD and FBF[c] after 6 wk	FMD increased in both groups (0.9% vs 1.5%; *P*=.39)	Lipid lowering rather than pleiotropic effects of statins is important for improvement in endothelial function	5
Fichtlscherer et al,[73] 2006	60 With stable CAD	Ezetimibe vs combination simvastatin (20 mg) and ezetimibe vs atorvastatin (40 mg)	FBF after 4 wk	Atorvastatin but not other therapies increased FBF (*P*<.05)	Ezetimibe in patients with stable CAD does not improve endothelial function	1
Landmesser et al,[74] 2005	20 With NYHA III CHF	Ezetimibe vs simvastatin (10 mg)	FMD after 4 wk	Simvastatin but not ezetimibe increased FMD	Ezetimibe in CHF lowers LDL-C levels but does not improve endothelial function	1
Mäki-Petäjä et al,[75] 2007	20 With RA	Ezetimibe vs simvastatin (20 mg)	FMD and aPWV after 6 wk[d]	Δ aPWV (0.60 vs 0.71) (*P*=.90); FMD increased 1.36% vs 2.55% (*P*=.10)	Ezetimibe and statins reduced LDL-C levels and improved endothelial function and aPWV	3
Efrati et al,[33] 2007	40 With hyperlipidemia	Ezetimibe vs simvastatin (40 mg) vs combination simvastatin (40 mg) and ezetimibe vs simvastatin (80 mg)	AIx after 3 mo	Only simvastatin (40 mg) decreased AIx	Improved AIx with simvastatin in statin-naive patients but not with ezetimibe	1
Bulut et al,[76] 2005	14 (male) with MeTS with chest pain	Atorvastatin (40 mg) vs combination atorvastatin (10 mg) and ezetimibe	FBF after 8 wk	Atorvastatin + ezetimibe increased FBF more than atorvastatin (40 mg)	Combination therapy is more potent in improving endothelial function	1

[a] AIx = augmentation index; aPWV = aortic pulse wave velocity; CAD = coronary artery disease; CHF = congestive heart failure; DM = diabetes mellitus; FBF = forearm blood flow; FMD = flow mediated dilatation; IGT = impaired glucose tolerance; LDL-C = low-density lipoprotein cholesterol; MeTS = metabolic syndrome; NYHA = New York Heart Association; RA = rheumatoid arthritis.
[b] Study quality assessed using the criteria outlined by Jadad et al.[8]
[c] We measured FMD noninvasively with ultrasonography; FBF was measured using venous occlusion plethysmography.
[d] Study design included crossover.

coronary syndromes, is currently under way and will shed more light on the role of ezetimibe in hyperlipidemia management when the results become available in 2012.

Adverse Reactions

Clinical efficacy trials of ezetimibe, which were not powered to detect differences in adverse events, have shown no increased incidence of ezetimibe-induced muscle or liver injury relative to placebo or statin monotherapy.[79] Reports of serious ezetimibe-related myopathy[80] and liver toxic effects[81] exist in the literature, but to date it does not appear that ezetimibe exacerbates statin-induced myopathy.[82] Recent reports have raised concerns about an association between ezetimibe and an increased incidence of cancer.[78] However, analysis of pooled cancer data from 3 large ezetimibe trials found no sufficient evidence of an association between ezetimibe and cancer.[83]

CONCLUSION

Ezetimibe, a new lipid-lowering agent, can substantially lower LDL-C levels either alone or in combination with statin therapy. However, data are limited regarding the impact of ezetimibe on CVD morbidity and mortality. Until those data become available, the decision to use ezetimibe in a clinical role depends on extrapolation of studies that have assessed the impact of ezetimibe on important intermediate steps in the process of atherosclerosis.

Although ezetimibe lowers LDL-C levels, whether it affects any other traditional CVD risk factors is unclear. Limited reports suggest that ezetimibe may reduce the inflammatory process of atherosclerosis when used in combination with statin therapy, but ezetimibe appears to have no beneficial effects on thrombotic factors. Results of published studies on the effect of ezetimibe on markers of subclinical atherosclerosis are somewhat mixed. Studies assessing ezetimibe's impact on endothelial function and arterial stiffness have been generally positive. Data assessing the impact of ezetimibe on CIMT are limited.

On the basis of the limited published data, it appears appropriate to use ezetimibe as a second- or third-line agent while trying to achieve treatment targets of LDL-C. However, ezetimibe should be used with the understanding that evidence regarding its impact on the intermediate steps in the atherosclerotic pathway is somewhat mixed and that evidence regarding its impact on clinical cardiovascular

events is lacking. It is hoped that longer-term studies, when they become available, will help clarify the impact of ezetimibe on cardiovascular morbidity and mortality. Until that time, the jury is still out regarding its true impact on CVD pathways and outcomes.

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