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Review Article

The effect of combined ezetimibe and statin therapy versus statin therapy alone on coronary plaque volume assessed by intravascular ultrasound: A systematic review and meta-analysis

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KEYWORDS:
Intravascular ultrasound;
Coronary atherosclerotic plaque;
Statin;
Ezetimibe therapy

BACKGROUND: Current guidelines recommend an intensive lipid-lowering therapy to achieve the low-density lipoprotein cholesterol (LDL-C) target in patients with high risk of cardiovascular disease. Former studies suggested adding ezetimibe to statin therapy in the above setting may promote plaque changes; however, this effect has not been consistently reported.

METHODS: Electronic searches were performed in MEDLINE, EMBASE, and Cochrane library and on November 30, 2017 to identify prospective trials assessing the effects of combined ezetimibe and statin therapy versus statin therapy alone on atheroma volume using intravascular ultrasound. The effect size between treatment groups within individual studies was assessed by weighted mean difference (MD) using a random-effects model.

RESULTS: Eight studies were obtained for systematic review and 6 of them compromising total of 583 subjects that meet the criteria were meta-analyzed. There was a significant reduction from baseline to follow-up in total atheroma volume with an MD of –3.71 mm^3 (95% confidence interval: −5.98 to −1.44, $P < .001$), whereas analysis for percent atheroma volume demonstrated weighted MD of –0.77% (−1.68 to 0.14, $P = .10$). A substantial decrease in LDL-C was observed with MD −16.75 mg/dL (−20.89 to −12.60, $P < .00001$).

CONCLUSION: The addition of ezetimibe to statin therapy is effective in reducing total atheroma volume assessed by intravascular ultrasound and also resulted in effective reduction of plasma LDL-C levels.

Introduction

Atherosclerotic coronary artery disease (CAD) remains a leading cause of morbidity and mortality worldwide.[1] Several well-established publications indicate that risk factors accelerate the development of atheroma, with hypercholesterolemia being a primary driver for plaque growth. A strong body of evidence, including Mendelian

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randomization studies, demonstrated the causality of low-density lipoprotein cholesterol (LDL-C) in CAD.[2] Furthermore, previous studies have shown a 20% reduction in 5-year incidence of adverse cardiac events per 1-mmol/L decrease in LDL-C concentration while on statin therapy.[3]

Ezetimibe is a cholesterol absorption inhibitor, exerting its effect through interaction with the Niemann-Pick C1-like protein 1 (NPC1L1) located in intestine, which leads to further reduction of circulating plasma LDL-C levels by 15–20%, when compared with statin therapy alone.[4,5] The clinical benefit of combining ezetimibe with statin therapy was confirmed in the IMPROVE-IT randomized trial, which demonstrated reduced cardiovascular events in those receiving combination therapy following presentation with an acute coronary syndrome.[6] However, the underlying mechanism of adding ezetimibe to statin therapy results in modification of cardiovascular outcome is unclear.

Atheroma (or plaque) volume is an important surrogate marker of future cardiovascular events and can be measured using a variety of imaging techniques, including intravascular ultrasound (IVUS) (Fig. 1).[7,8] Former studies using IVUS have widely recognized that statin therapy modifies the natural history of CAD by slowing plaque progression and may even result in regression of atheroma.[9,10] Although combination of ezetimibe with statins is well accepted in current cardiovascular therapeutic guidelines, the true benefits of this combination on atherosclerotic plaque in patients with existing cardiovascular disease remains to be established.[11,12]

Methods

Data sources and search strategy

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13] Comprehensive searches of EMBASE, MEDLINE, and The Cochrane Library along with trial registries and abstracts from major scientific meetings were conducted to identify suitable publications. Our search was restricted to studies published in English language only. The study protocol was prospectively registered with PROSPERO (CRD42017081249) and adhered to the PRISMA guidelines. An example search strategy for EMBASE is provided in Supplemental Table 1.

Study selection

Studies analyzed are only those meeting the following inclusion criteria:

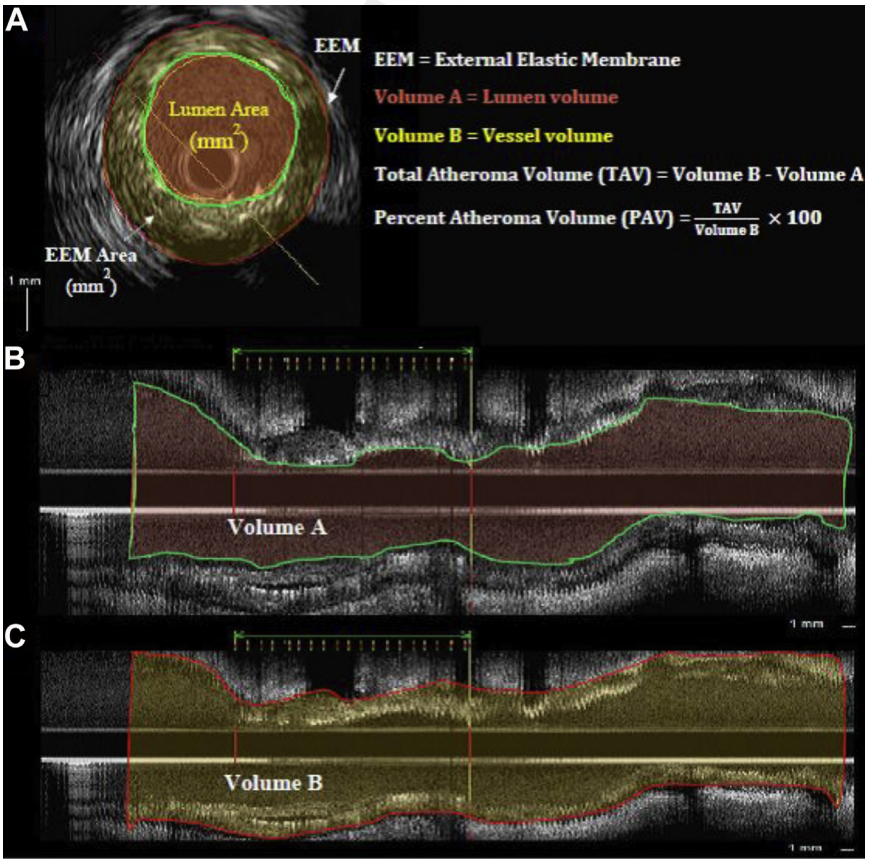

Figure 1 Intravascular ultrasound of coronary artery to assess plaque volume. (A) Planimetry of external elastic membrane (EEM) and lumen area; Formula to calculate TAV and PAV using lumen volume and vessel volume; (B) Longitudinal view of the same segment of coronary artery assessing lumen volume (Volume A); (C) Evaluation of vessel volume (Volume B). PAV, percent atheroma volume; TAV, total atheroma volume.