

Ezetimibe treatment in the elderly to reduce cardiovascular events

Abstract:

Elderly people are the most fragile subgroup among patients with cardiovascular diseases. In patients 75 years and older treatment efficacy with statins is controversially debated. A secondary analysis of IMPROVE-IT demonstrates that adding ezetimibe to simvastatin in patients 75 years and older lowers not only LDL-cholesterol levels, but also cardiovascular events. This stands in line with previous findings that low-cholesterol absorption is associated with better survival and fewer cardiovascular events in elderly patients. These findings further add to the concept of “individualized lipid-lowering therapy”, in which determination of markers of cholesterol metabolism guide a personalized addition of ezetimibe.

Keywords: Acute coronary syndrome . Cholesterol . IMPROVE-IT . EWTOPIA 75 . Simvastatin-ezetimibe

Abbreviations

ACS: Acute Coronary Syndrome; CVD: Cardiovascular Disease; LDL: Low-Density Lipoprotein

Introduction

Elderly people are the most fragile subgroup among patients with cardiovascular diseases. In patients 75 years and older treatment efficacy with statins is controversially debated. A recently published secondary analysis of the IMPROVE-IT trial aimed to evaluate the effect of higher intensity lipid-lowering therapy with ezetimibe combined with simvastatin vs. simvastatin monotherapy on hard cardiovascular outcomes in patients with recent ACS. The primary results of this trial further add to the concept of “individualized lipid-lowering therapy” in order to improve cardiovascular outcomes.

ACS in Elderly

Patients 75 years and older have the highest cardiovascular risk, especially in the setting of an Acute Coronary Syndrome (ACS) [1]. In large clinical trials such as GRACE, CRUSADE and NRMI, patients over 75 years compose up to 40% of ACS cases and ACS complication rates increase with age [2].

The appropriate management of dyslipidemias in patients with ACS is a cornerstone in the treatment to reduce subsequent cardiovascular events. The current EAS/ESC-guidelines on the management of dyslipidemias recommend initiation of a high intensity statin [3], as statin treatment in this high-risk population has been shown to reduce cardiovascular events [4,5]. However, in patients 75 years and older recommendations are less clear [3].

Cholesterol Metabolism and Cardiovascular Diseases in Elderly Patients

Cholesterol absorption increases with age, which is mainly explained by an age-related increase of NPC1L1-a key protein responsible for cholesterol absorption in the small intestine [6,7]. On the other hand, it is well-known that cholesterol synthesis declines with age [7]. Hence, cholesterol absorption becomes more important in the elderly population.

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IMPROVE-IT and EWTOPIA 75-Benefits of Ezetimibe in Elderly Patients

IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) is an international, multicenter, randomized double-blind clinical trial involving over 18,000 patients in 39 countries from October 2005 through July 2010. The study aimed to evaluate the effect of higher intensity lipid-lowering therapy with ezetimibe combined with simvastatin vs. simvastatin monotherapy on hard cardiovascular outcomes in patients with recent ACS. The primary results [8] demonstrated a significant reduction in LDL-cholesterol levels, as well as an improvement in cardiovascular outcomes in patients, who received a combined lipid-lowering with ezetimibe and a statin. A recently published secondary analysis of IMPROVE-IT assessed treatment efficacy of a combined lipid-lowering strategy in an age-related analysis [9]. Bach and colleagues reported that treatment efficacy with ezetimibe on top of a statin increased with age: In patients over 75 years of age the number needed to treat was 11, whereas it was not as 125 in patients younger than 75 years.

Similar results were published only recently in a population of primary prevention. The EWTOPIA 75 (Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or older)-a prospective multicenter study – demonstrated that ezetimibe monotherapy in the elderly reduced not only LDL-C levels, but also cardiovascular outcomes even more effectively than expected [10]. These findings are of particular interest since results from ALLHAT-LTT-a study that investigated the effects of a statin on primary prevention among older adults-demonstrated that pravastatin did not prevent primary outcomes and all-cause mortality [11].

Discussion

Individual differences in cholesterol absorption affect cardiovascular risk. Strandberg and colleagues demonstrated in the DEBATE study (Drugs and Evidence-Based Medicine in the Elderly) that in patients 75 years and older lower cholesterol absorption was associated with fewer cardiovascular events [12]. The authors speculated that this patient population could benefit in particular by a combined lipid-lowering strategy with a statin and a cholesterol absorption inhibitor. Moreover, our group reported that in patients older than 70 years, high cholesterol absorption and low cholesterol synthesis is associated with the severity of coronary artery disease [13].

Lipka and colleagues have previously shown that a combination of ezetimibe with a statin result in more effective LDL-C lowering

compared to statin monotherapy [14]. In the EASE-trial addition of ezetimibe to a statin was safe and achieved LDL-C goals without a change in dose or potency of the statin [15].

Miettinen and colleagues demonstrated in the landmark trial 4S that patients with high cholesterol absorption did not benefit from statin monotherapy [16]. He postulated that increased cholesterol absorption could be detrimental and that especially patients characterized as “high-cholesterol absorbers” should be treated with a cholesterol absorption inhibitor. This hypothesis has been proven by HIJ-PROPER only recently [17-19]. In this study pitavastatin and ezetimibe demonstrated a significant reduction in cardiovascular events compared to pitavastatin monotherapy only in those patients with high cholesterol absorption. Patients with low cholesterol absorption did not benefit from the addition of ezetimibe.

Taking into account that cholesterol absorption increases with age, it is plausible to speculate that ageing is associated with “hyper absorption” and that inhibition of cholesterol absorption in patients 75 years and older is an effective strategy to reduce cardiovascular events.

Conclusion

IMPROVE-IT as well as EWTOPIA 75 demonstrated the usefulness of ezetimibe treatment in patients 75 years and older. Results of these trials further add to the concept of “individualized lipid – lowering therapy” in order to improve primary and secondary prevention of cardiovascular diseases.

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Mini Review

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