CORRESPONDENCE

Ezetimibe-Statin Combination Therapy: Efficacy and Safety as Compared With Statin Monotherapy—A Systematic Review

by Barbara Nußbaumer MSc BSc, Dr. med. Anna Glechner, Dr. med. Angela Kaminski-Hartenthaler, Dr. med. Peter Mahlknecht, and Prof. Dr. med. Gerald Gartlehner, MPH in issue 26/2016

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No Indication for Routine Administration

The authors (1) reach the conclusion—strongly based on the IMPROVE-IT trial (2)—that ezetimibe-statin combination therapy for high-risk patients (and specifically, those with diabetes) with acute coronary syndrome lowers the risk of cardiovascular events as compared to statin monotherapy.

This prospective controlled randomized trial, with a median duration of six years, involved 18 144 patients, 4933 of whom had diabetes (27.2%).

Nonfatal cardiovascular events occurred in 46% of patients in the statin group, and in 40% of the ezetimibe-statin combination group. Thus, the absolute risk reduction (ARR) by ezetimibe addition is 6%. The number needed to treat (NNT) over the course of six years is therefore 17 (e.g., 100 divided by 6).

In other words: of 17 diabetic patients treated with the combination over six years, only one patient has the chance of avoiding an additional cardiovascular event. Thus, 16 patients would have been treated with no additional benefits. This is described by the acronym “NTN” (number treated needlessly), of 15 (16 minus 1). Whether this is clinically relevant should perhaps be decided by each person individually.

It must be particularly emphasized that the combination treatment did not reduce either the cardiovascular mortality or the all-cause mortality for persons with diabetes.

Originally, the trial was to be carried out with 10 000 patients over two years. To avoid a foreseeable negative result, the amount of registered patient information was drastically increased in Amendment 3, to 18 000 patients over a six-year interval (3).

Despite these expansions, no advantages were observed by the combination treatment even for the “non-diabetic” patients. In my opinion, there is still no indication for routine administration of ezetimibe.

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No Clinical Relevance

It requires great deal of optimism to draw therapy-relevant conclusions from the results of IMPROVE-IT, the key trial addressing a potential benefit of the addition of ezetimibe to simvastatin therapy (1):

- No prolongation of life (total mortality, $P = 0.78$)
- No survival benefit by reduction of fatal cardiovascular disease events (cardiovascular mortality, $P = 1.00$)
- No protection against hemorrhagic insults ($P = 0.11$)
- An enormous number needed to treat (NNT) of 143 for ischemic stroke
- A composite primary endpoint including so many diseases (five) that there is mathematically already a high probability for statistical significance. This is not relevant for patients, as having numerous medical conditions is not statistically significant.
- An NNT of 50 for the primary endpoint—only one patient is certain to receive protection, while the remaining 49 have no benefit despite also taking the combination therapy.

Unfortunately, the authors have not extrapolated the NNT to larger numbers of patients, which would expose the entire debacle (2). Of 5000 patients, only 100 will be guaranteed protection, while 4900 will not have this benefit, despite also being treated with ezetimibe-simvastatin for seven years.

Therefore, no clinical relevance for combination therapy can be assumed, based on the cited data from IMPROVE-IT.

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In Reply:

We would like to thank Prof. Dr. Meyer and Dr. Traut for their comments on our article (1). Both comments relate to the interpretation of the results of the IMPROVE-IT trial (2).

Both note that the combination therapy (statin plus ezetimibe) did not reduce the cardiovascular mortality or the all-cause mortality as compared to statin monotherapy, and that the benefits in terms of cardiovascular events are low. The clinical relevance of the combination therapy is therefore questioned.

Even though the cardiovascular mortality and all-cause mortality were not reduced by combination therapy in the IMPROVE-IT trial (2), the primary endpoint (a combination of cardiovascular events)—adjusted for the number of participants in the trial and for power calculations—showed that the combination therapy provided a statistically significant advantage, of an absolute risk reduction of 2 percentage points (number needed to treat [NNT], 50 over 7 years). This reduction is not great in absolute terms. Nonetheless, if we take into account the relevance of a myocardial infarction, a stroke, or a revascularization with hospitalization for the affected person, it is likely that even such low absolute risk reductions become important for these individuals. Still, we agree that routine administration of ezetimibe cannot be based on this evidence. In our view, however, it is also important to inform patients, as part of shared decision-making, about additional endpoints as well as the effectiveness of a drug, and not to only fixate on reduction of mortality. This is especially true considering that patient preferences are sometimes differently assessed by physicians than by the patients themselves (3).

Prof. Dr. Meyer points out that the number of enrolled patients was increased from 10 000 to 18 000 in the IMPROVE-IT trial. This protocol change was made transparent and was justified (4). Without this increase, the statistical power could not have been achieved. We see this action as positive, as it prevented the lack of statistical power that was problematic for the other trials in our systematic review. If statistical power cannot be obtained, it remains unclear whether a lack of

statistical significance is due to the fact that there really is no significant difference or due to a sample size that is too small.

Dr. Traut notes that the composite endpoint has no patient-relevant significance, because some components of the composite endpoint considered individually did not show statistically significant differences. We agree that the use of composite endpoints can be problematic, especially when a composite endpoint was not defined a priori. However, the IMPROVE-IT trial defined the composite endpoint already in its initial description in the trials registry (5). We therefore do not believe that this endpoint was designed post-hoc to produce statistical significance.

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Conflict of interest statement

The authors of all contributions declare that no conflicts of interest exists.