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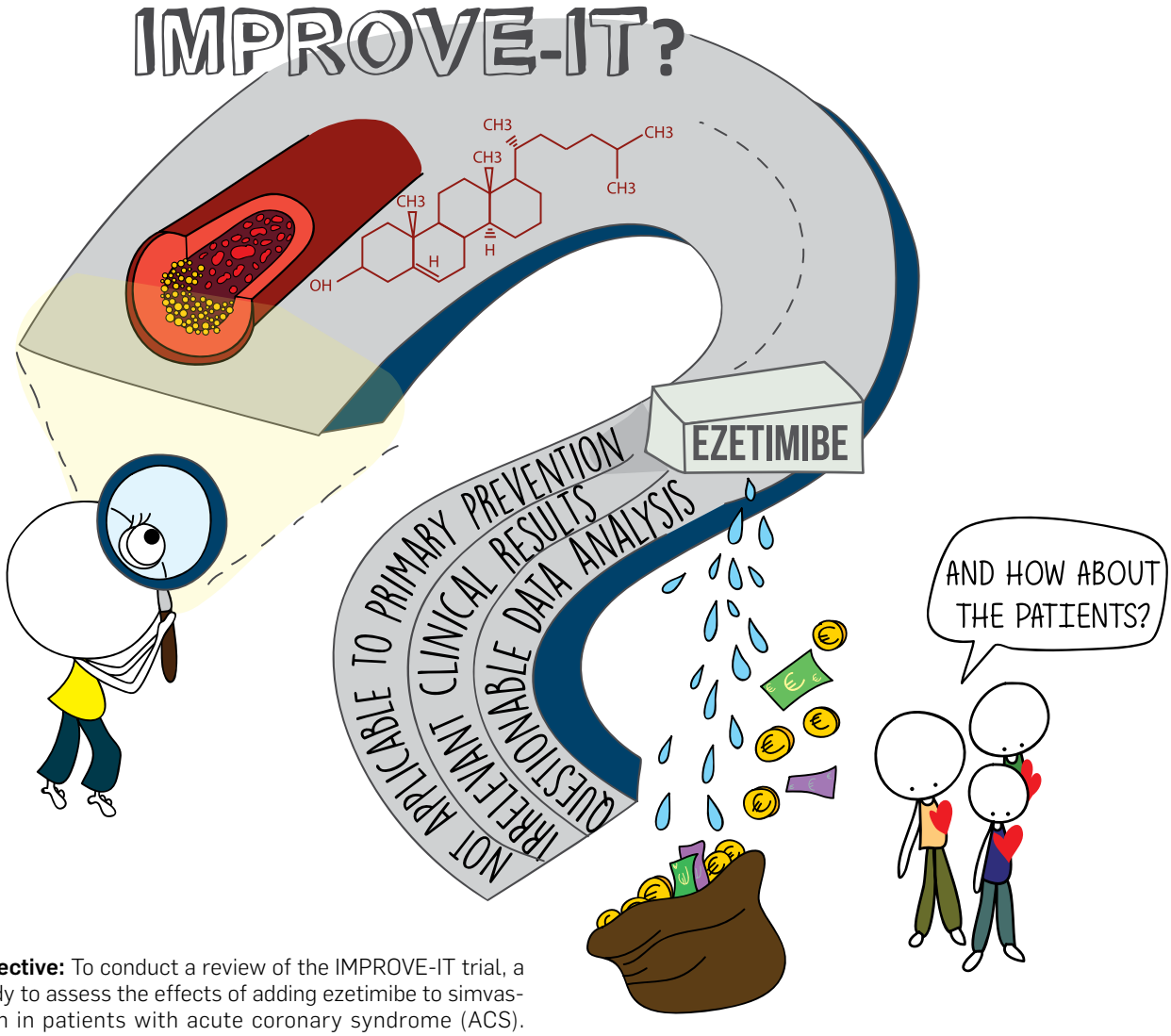

abstract

Objective: To conduct a review of the IMPROVE-IT trial, a study to assess the effects of adding ezetimibe to simvastatin in patients with acute coronary syndrome (ACS). **Methods:** The review is based on data from the article published in the journal *The New England of Medicine* and available from the reports of regulatory agencies. **Results and Conclusions:** The IMPROVE-IT trial enrolled patients for secondary prevention. Its results are not directly applicable to primary prevention of cardiovascular disease in high-risk patients. Results also cannot be extrapolated directly to all ACS patients, due to the strict inclusion and exclusion criteria applied in the trial. Similarly, the results are not applicable to secondary prevention of atherosclerotic disease other than after ACS. According to pre-defined criteria of the researchers who designed the study protocol, differences observed between ezetimibe and placebo were clinically irrelevant. Statistical significance was inappropriately attained after imputing data to patients for whom ACS-episode data were lacking. The IMPROVE-IT trial does not provide sufficient evidence supporting the use of ezetimibe in combination with a statin for ACS. The FDA advisory committee recommended prohibiting the pharmaceutical company from promoting the addition of ezetimibe to simvastatin to reduce cardiovascular events.

The IMPROVE-IT trial (ezetimibe added to simvastatin for acute coronary syndrome). A critical appraisal

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Introduction

Ezetimibe was approved in Spain in April 2003 on the basis of its ability to reduce plasma cholesterol levels. However, this drug has been used for more than 12 years without evidence that it reduces morbidity or mortality. Since 2003, three clinical trials of clinical effectiveness have been published.

The first trial, ENHANCE, was published in April 2008. It involved 720 patients with familial hypercholesterolemia who received either ezetimibe 10 mg or placebo for 2 years.[1] The primary endpoint was the change in carotid artery intima-media thickness. No statistically significant differences were observed in the primary endpoint. Mortality data were not published in this trial.

The SEAS trial was published in September 2008.[2] SEAS included 1,873 patients with mild-to-moderate aortic-valve stenosis. The primary endpoint was a combination of: cardiovascular death, aortic-valve replacement, nonfatal myocardial infarction (MI), hospitalization for unstable angina, heart failure, coronary revascularization, percutaneous coronary intervention or non-hemorrhagic stroke. After 4 years of ezetimibe 10 mg vs placebo in combination with simvastatin 40 mg, no statistically significant differences were found in the combined primary endpoint, nor for cardiovascular mortality or total mortality.

The SHARP trial, published in June 2011, involved 9,270 patients with chronic kidney disease.[3] The primary endpoint was a combination of nonfatal MI, coronary mortality, hemorrhagic stroke or any arterial revascularization. SHARP compared the effects of ezetimibe/simvastatin (10/20 mg) vs placebo for five years. The combination of ezetmibe/simvastatin reduced the primary endpoint vs placebo (11.3% vs 13.4%; RR= 0.85, 95%CI 0.74-0.94). The absolute risk reduction of 2.1% over 5 years corresponds to an annual ARR of 0.43%. No statistically significant differences were observed for cardiovascular mortality or total mortality.

IMPROVE-IT, published in June 2015, is the largest trial of ezetimibe combined with simvastatin.[4] It enrolled 18,144 patients hospitalized for acute coronary syndrome (ACS) with associated cardiovascular risk factors. Participants were randomized to ezetimibe 10 mg/simvastatin 40 mg or to placebo/simvastatin 40 mg for up to 7 years (median 6 years).

To date, there is no evidence that ezetimibe provides any benefit in primary prevention. Nor has it been observed that ezetimibe alone has any positive effect in secondary prevention.

In Navarre, with a population of 640,000 inhabitants, 4,158 patients (6.5 per 1,000) were receiving ezetimibe as of 09/12/2015. Of these, 2,642 (63.5%) received ezetimibe alone, the remainder ezetimibe with a statin. 2,183 (52.5%) used ezetimibe for secondary prevention of cardiovascular disease, 1,865 (44.8%) for primary cardiovascular prevention, and 110 (2.6%) for familial hypercholesterolemia. The cost of ezetimibe was 1.7 million Euros in Navarre in 2015.

This analysis reviews the IMPROVE-IT trial and analyzes the reported morbidity and mortality data.

Methods

In early October 2015, Bit Navarra requested the European Medicines Agency (EMA) to provide a Clinical Study Report on the IMPROVE-IT trial. On 22/10/2015, the EMA responded that the ezetimibe/simvastatin combination includes a drug (ezetimibe) that was approved nationally, but not centrally by EMA. Ezetimibe had been evaluated by the German Medicines Agency, but evaluation data on this drug were not available from the EMA.

On 17/12/2015, the FDA Endocrinologic and Metabolic Drugs Advisory Committee[5] published a review that included data provided in the FDA Clinical Study Report from the IMPROVE-IT trial. Our review utilizes data reported in the FDA review and in the The New England Journal of Medicine publication of the IMPROVE-IT trial.

Description of the IMPROVE-IT trial

Research question

Is the addition of ezetimibe to simvastatin effective in patients hospitalized for acute coronary syndrome with associated CV risk factors?

Design

Randomized, multicenter, parallel-group, double-blind, clinical trial with a minimum duration of 2.5 years.

Setting

1,147 sites in 39 countries (North America, Europe, Australia, New Zealand, Asia, Latin America).

Patients

Patients hospitalized within the previous ten days for acute coronary syndrome with associated CV risk factors such as diabetes mellitus, previous coronary angiography or percutaneous coronary intervention during the index hospitalization.

Inclusion/exclusion criteria

Patients aged ≥ 50 years with LDL-C 50-125 mg/dL (1.3-3.2 mM) for patients who had not received previous lipid-lowering therapy, and 50-100 mg/dL (1.3-2.6 mM) for patients who had been receiving previous lipid-lowering therapy. The main exclusion criteria included planned elective CABG surgery and elevated creatinine clearance.

Intervention

18,144 patients were randomized: 9,067 to simvastatin (40 mg/day) plus ezetimibe (10 mg/day) vs 9,077 to simvastatin (40 mg/dL) plus placebo.

In both groups, patients with LDL-C >79 mg/dL (1.3 mM) received a higher dose of simvastatin (80 mg/day) without breaking the blinding. Following a FDA warning in June 2011 the dose was reduced to 40 mg/day for patients not previously tolerating 80 mg/d for over 1 year.[6] If LDL-C ≤100 mg/dl (1.3 mM) was not reached, simvastatin was discontinued and a more potent statin was provided. The analysis was performed by intention to treat.

Outcome Measures

Primary endpoint
Combined endpoint of cardiovascular death, nonfatal acute myocardial infarction, unstable angina requiring hospitalization, coronary revascularization (≥30 days following randomization) and nonfatal stroke.

Secondary endpoints:
- death from any cause or major coronary event or nonfatal stroke;
- death from coronary disease or nonfatal infarction or emergency coronary revascularization ≥30 days following randomization;
- death from cardiovascular disease or nonfatal infarction or hospitalization for unstable angina or any revascularization ≥30 days following randomization or nonfatal stroke.

Results

A total of 18,144 patients were followed up for 7 years (median, 6 years). The main results are described in table 1. No significant differences were observed in terms of safety. After six-year follow-up, 42% of patients had discontinued therapy in both groups.

Authors' conclusion

Ezetimibe administered in combination with a statin improves LDL-C reduction and cardiovascular outcomes. Also, a LDL-C reduction below the established limit provides an additional clinical benefit.

Promotor's role

This trial was funded by Merck, which owns ezetimibe patent.

Table 1. Main results of the IMPROVE-IT trial.

	No. Patients (%)		
Variable	SIMVAS (N=9,077)	SIMVAS+EZE (n=9,067)	Hazard ratio (95%CI)
Primary endpoint			
Cardiovascular death or major coronary event or nonfatal stroke	2,742 (34.7)	2,572 (32.7)	0.936 (0.89-0.99)
Secondary endpoints:			
Death from any cause or major coronary event or nonfatal stroke	3,246 (40.3)	3,089 (38.7)	0.95 (0.90-1.0)
Death from coronary disease or nonfatal infarction or coronary revascularization	1,448 (18.9)	1,322 (17.5)	0.91 (0.85-0.98)
Death from cardiovascular disease or nonfatal acute myocardial infarction or hospitalization for unstable angina or any revascularization ≥30 days following randomization or nonfatal stroke	2,869 (36.2)	2,716 (34.5)	0.95 (0.90-1.0)

Review of IMPROVE-IT trial based upon FDA data analysis

Study Design

Although IMPROVE-IT was a double-blind, randomized trial, the paper does not provide any data on the blinding and randomization concealment methods used.

One group received a single lipid-lowering drug (simvastatin), whereas the other received two lipid-lowering drugs (simvastatin/ezetimibe). Obviously, the reduction in cholesterol levels was expected to be greater in the group receiving two lipid-lowering drugs. In such trials, blinding can be broken. Study personnel with access to LDL-C results could deduce the treatment that each patient was receiving.

Study population

IMPROVE-IT trial enrolled patients for secondary prevention. The results are not applicable directly to high-risk patients in primary prevention of cardiovascular disease.

The results also cannot be extrapolated to all ACS patients nor are they directly applicable to secondary prevention after atherothrombotic events other than ACS, for example stroke or TIA.

Outcomes

Effectiveness

The reported results show modest effectiveness for the composite endpoint after treatment for a median of 6 years: NNT=50 (27-289). No benefit for total mortality was observed, placebo/simvastatin: 1231 (15.3%), ezetimibe/simvastatin: 1215 (15.4%), RR = 0.99 (CI95%, 0.91-1.07). No benefit for death from cardiovascular causes was observed either, placebo/simvastatin: 538 (6.8%), ezetimibe/simvastatin: 537 (6.9%), RR = 1.00 (CI95%, 0.89–1.13).[5]

Figure 1. Patients treated with simvastatine + placebo.

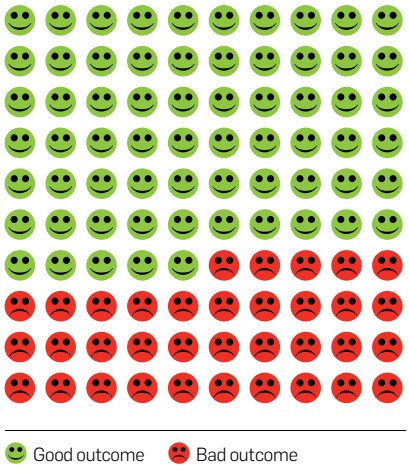

Figure 2. Patients treated with simvastatine + ezetimibe.

Figures 1 and 2 show the effects of adding ezetimibe in absolute terms. Green faces represent patients who did not experience any of the primary endpoint events. Red faces represent patients who experienced a primary endpoint. Blue faces (Figure 2) represent patients who did not experience any episode of the primary endpoint as a result of adding ezetimibe to simvastatin.

Statistical significance of outcomes and clinical relevance of the data published

All outcomes for the primary and secondary endpoints are close to the pre-defined margin of statistical significance. The originally intended duration of the study was 2.5 years. However, on completion of this study period, no statistically significant differences were observed in the primary endpoint. The original protocol was then modified five times and the IMPROVE-IT study duration was increased from 2.5 years to a median follow-up of 6 years. The original sample size was also increased by 80%. This was presumably an attempt to increase statistical power to capture a small but statistically significant difference. Nevertheless, no differences were observed between ezetimibe and placebo during follow-up of up to 7 years, according to the mid-study analyses performed prior to study completion. Although the original protocol provided that two mid-study analyses would be performed during the trial, eventually a third mid-study analysis was performed without prior justification.[5]

Questionable effectiveness of ezetimibe

In its review of the trial, the FDA Advisory Committee for Endocrinologic and Metabolic Drugs[5] the FDA statistical reviewers seriously questioned the validity of the statistical analysis, which concluded that statistically significant differences were obtained with ezetimibe+simvastatin.

Missing data are common in clinical trials. However, for IMPROVE-IT, primary endpoint data (whether or not a patient experienced a primary endpoint event during the study) were missing for 11% of patients. To solve this problem and include these patients in the statistical analysis, the authors impute data to these patients. Thus, the patients with missing data are imputed reasonable data similar to real data reported for other matched study patients. As a result, imputed primary endpoint data were assigned to around 2,000 patients in the IMPROVE-IT trial.

Additionally, most missing data corresponded to patients lost to follow-up. These individuals were assigned imputed real outcomes from patients who had completed the trial. In the study there were sufficient data from patients who had discontinued the treatment and had been followed-up until study completion and for whom primary endpoint data were also available. It would have been more reasonable to impute data from these patients to those lost to follow-up for whom endpoint data were missing since both shared a similar profile. Had the IMPROVE-IT authors taken this more conservative approach, the overall differences between the two groups would not have been statistically significant. A more sensible approach to the management of missing endpoint data would not have found ezetimibe more effective than placebo when added to simvastatin for patients presenting with ACS.

On 14/12/2015, the FDA advisory committee recommended prohibiting the pharmaceutical company from claiming that the addition of ezetimibe to simvastatin reduces the incidence of cardiovascular events.[7,8]

Safety

Few safety data are provided in the publication of the IMPROVE-IT trial.[4] Serious adverse effects are not reported in the NEJM article, nor in the supplementary appendix published with it. However, the FDA briefing[5] provides comprehensive information on adverse effects, and it seems that there were no significant differences between the two groups.

In clinical and patient experience, myopathy is a common and disabling adverse effect of statins. Yet clinical trials deliberately exclude capturing most affected patients by defining myopathy by criteria requiring both muscle pain or weakness and CPK levels > 10 times upper limit of normal. IMPROVE-IT also defined myopathy as "CPK ≥ 10 x ULN with unexplained muscle symptoms consistent with myopathy (weakness, pain, soreness not due to new exercise, unusual physical activity, or trauma)." All such trials probably underestimate myopathy, since people with muscle weakness or pain that limits daily activities and exercise seldom have CPK levels much higher than 1.5-2 times ULN.

The protocol was continuously modified

The protocol of the IMPROVE-IT trial was modified many times. The number of events for the primary endpoint was increased from 2,955 to 5,250. To achieve this, the sample size was increased from 10,000 to 12,500 in the second version of the protocol, and to 18,000 patients in the third version. The purpose of this increase was to be able to assign statistical significance to very small absolute differences (see table 2). Initially, the minimum clinically relevant difference between both groups was set at 3%. However, following mid-study analyses, the investigators reduced the "minimum clinically relevant absolute difference" to 1.5%.

During the study, two mid-study analyses were performed that had not been scheduled in the original trial protocol. In May 2012 (7 years after the start of study), the Data Safety Monitoring Board observed that the second mid-study analysis revealed no significant differences between the study groups. In March 2013 (8 years after the start of the study), a third mid-study analysis – not included in the initial protocol – was performed. Again, no statistically significant differences were identified. The study was completed in September 2014. Table 2 summarizes the modifications made to the initial protocol during the performance of the IMPROVE-IT trial.[5]

Table 2. Timeline of modifications to the protocol of the IMPROVE-IT trial.[5]

Date	Modification to the protocol	Sponsor's Rationale	Comments
October 2005	Recruitment starts		
April 2007	**First modification** Patients with CrCl<30 ml/min and patients with ACS requiring coronary bypass are excluded.		
September 2007	**Second modification** The number of events for the primary endpoint was increased from 2,955 to 5,250. The sample size was increased from 10,000 to 12,500. Recruitment of patients with myocardial infarction with elevated ST segment is stopped.	The number of events included for the primary endpoint is increased to 5,250 to improve the statistical power of the study in order to demonstrate a significant reduction of risk. The reason is that these patients were expected to account for a third of the sample, but at that point, they represented half the patients recruited.	The argument is not correct. The number of expected events and the sample size were increased by 78% and 25%, respectively. The predicted statistical power is still the same as in the previous version of the protocol (90%). What changes is the magnitude of the minimally relevant difference (initially set as 3%). Mid-study analyses found a risk difference only half the minimally relevant difference.
March 2008	**Third modification** The sample size was increased to 18,000 patients.	The sample size was increased to 18,000 patients to maintain statistical power.	The real purpose of increasing the sample size while maintaining a statistical power of 90% was that a risk difference much smaller than expected reached statistical significance. The sample size was increased by 80%.
March 2010	***First mid-study analysis*** The first mid-term analysis was performed after reaching 50% of the events expected.	The Safety Committee recommended trial continuation.	After five years of study, no differences were observed between the addition to simvastatin of ezetimibe 10mg/d and placebo.
June 2011	**Fourth modification** The administration of simvastatin 80 mg is interrupted. The modification led to a second mid-term analysis when 75% of the expected primary endpoint events had occurred.	This decision was based on a warning by the FDA against administration of simvastatin 80 mg/day.	
March 2012	***Second mid-term analysis***	The Safety Committee recommended trial continuation.	The study started 6.5 years ago. No differences are observed between ezetimibe and placebo. Another mid-term analysis not included in the initial protocol is scheduled at nine months (March 2013)
March 2013	***Third mid-term analysis***	The Safety Committee recommended trial continuation. The p value for multiple analyses is adjusted to approximately 0.0394 for the final analysis of primary endpoint outcomes.	The study started 7.5 years ago. No differences are observed between ezetimibe and placebo.
September 2014	Completion of the study		More than 9 years after the start of the study, statistically significant differences are obtained.
November 2014	Results are presented in the scientific sessions of the American Heart Association		
June 2015	On line publication. Publication in NEJM		

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Conclusions

The IMPROVE-IT trial assessed secondary prevention in high risk patients after acute coronary syndrome. The results are not directly applicable to primary prevention of cardiovascular disease, even in high-risk patients.

Results also cannot be extrapolated reliably to all ACS patients. Similarly, the results are not directly applicable to secondary prevention after other atherothrombotic syndromes such as ischemic stroke.

According to criteria for clinical significance that were pre-specified by the researchers who designed IMPROVE-IT, the absolute risk differences observed between ezetimibe and placebo were clinically irrelevant.

Statistical significance was inappropriately attained after assigning imputed data to the 11% of patients for whom primary outcome data were lacking during follow-up.

The IMPROVE-IT trial does not provide conclusive evidence to support the use of ezetimibe in combination with a statin after ACS.

The FDA advisory committee recommended prohibiting Merck from promoting the addition of ezetimibe to simvastatin to reduce the incidence of cardiovascular events.

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