IQWiG Reports – Commission No. A18-83

Ezetimibe for the prevention of cardiovascular events[1]

Extract

[1] Translation of the executive summary of the rapid report A18-83 *Ezetimib zur Prävention kardiovaskulärer Ereignisse* (Version 2.0; Status: 3 September 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Ezetimibe for the prevention of cardiovascular events

Commissioning agency:
Federal Joint Committee

Commission awarded on:
22 November 2018

Internal Commission No.:
A18-83

Address of publisher:
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

This rapid report was prepared in collaboration with external experts.

The responsibility for the contents of the report lies solely with IQWiG.

According to §139 b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Appendix D of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

External experts

- Birgit Linnemann, University Hospital Regensburg, Germany

IQWiG thanks the external expert for her collaboration in the project.

IQWiG employees

- Katharina Wölke
- Gertrud Egger
- Marco Knelangen
- Sabine Ostlender
- Cornelia Rüdig
- Sibylle Sturtz
- Volker Vervölgyi

Keywords: Ezetimibe, Secondary Prevention, Coronary Artery Disease, Acute Coronary Syndrome, Benefit Assessment, Systematic Review

Executive summary

On 22 November 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess ezetimibe for the prevention of cardiovascular events.

Research question

The aims of the present investigation are

- the benefit assessment of treatment with ezetimibe plus a statin versus treatment with a statin alone (research question 1) and
- the benefit assessment of treatment with ezetimibe plus a statin versus treatment with a statin plus another drug influencing lipid metabolism (research question 2)

for risk reduction of cardiovascular events in patients with a history of coronary heart disease (CHD) or acute coronary syndrome (ACS) with regard to patient-relevant outcomes.

Methods

The assessment included studies with patients with a history of CHD or ACS. The test intervention was ezetimibe plus a statin for risk reduction of cardiovascular events. The comparator intervention was either a statin alone (research question 1) or a statin plus another drug influencing lipid metabolism (research question 2). In order to derive a benefit of ezetimibe, it was necessary that the 2 study arms differed only in terms of the drugs to be compared, but not in other factors (e.g. different low-density lipoprotein cholesterol [LDL-C] target value strategies).

The following patient-relevant outcomes were considered for the investigation:

- Mortality
  - all-cause mortality
- Morbidity
  - cardiovascular morbidity
  - cerebrovascular morbidity
  - vascular non-cardiovascular and non-cerebrovascular morbidity
- Health-related quality of life
- Adverse effects
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - myopathy and rhabdomyolysis

- severe liver toxicity

Only randomized controlled trials (RCTs) were included in the benefit assessment. The minimum study duration was 12 months (52 weeks).

A recent systematic review by Zhan et al. 2018, as well as the rapid report commissioned by the G-BA, investigated ezetimibe for the prevention of cardiovascular disease and death. The assessment of research question 1 was primarily to be based on the 2 largest studies described in the systematic review (IMPROVE-IT: 18,144 randomized patients, median observation period: 6 years; HIJ-PROPER: 1734 randomized patients, median observation period: 3.86 years). Together, these comprise more than 90% of all participants and about 98% of the median patient years from the studies in the systematic review that are potentially eligible for the assessment of research question 1. The examination of the study documents showed, however, that due to the study design the HIJ-PROPER study is not suitable for answering research question 1 of the benefit assessment, and is therefore not relevant for the present benefit assessment on research question 1.

The comprehensive information retrieval described in the following sections was originally intended to be used to check whether, compared with the studies investigated in Zhan et al. 2018, there is evidence from further studies that, due to the study size, could challenge the results of the IMPROVE-IT and HIJ-PROPER studies, or whether additional outcomes (e.g. health-related quality of life) were reported. However, due to the study design the HIJ-PROPER study was not relevant. As the certainty of conclusions is limited due to the availability of only a single study, all studies identified in the information retrieval (including the studies considered in the systematic review by Zhan et al. 2018) were also examined to see whether they were able to challenge the findings of the IMPROVE-IT study or increase the certainty of conclusions.

A systematic literature search for studies was conducted in MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in MEDLINE, Embase, the Cochrane Database of Systematic Reviews, and the HTA Database.

In addition, the following information sources and search techniques were considered: study registries, inquiries to the manufacturer, publicly available documents from regulatory authorities, the G-BA and IQWiG websites, and the screening of reference lists of the systematic reviews identified.

The selection of relevant studies was carried out independently by 3 persons. The results of this selection were summarized after the full-text assessment. Data were extracted into standardized tables. In order to assess the qualitative certainty of results, risk-of-bias criteria were assessed across outcomes and specific to outcomes and then classified as low or high. The results of the individual studies were organized and described according to outcomes.

If the studies were comparable with regard to the research question and relevant characteristics and no relevant heterogeneity was observed, it was planned to summarize the individual results quantitatively using meta-analyses.

For each outcome, a conclusion was drawn on the available evidence of the (greater) benefit and (greater) harm in 4 levels with regard to the respective certainty of conclusions: There was either proof (highest certainty of conclusions), an indication (medium certainty of conclusions), a hint (weakest certainty of conclusions), or none of these 3 situations applied. The latter was the case if no data were available or the data available did not allow any of the other 3 conclusions to be drawn. In this case, the conclusion "there is no hint of a (greater) benefit or (greater) harm" was drawn.

Results

Results of the comprehensive information retrieval

The information retrieval identified a total of 8 RCTs, 7 for research question 1 (ezetimibe + statin vs. statin) and 1 for research question 2 (ezetimibe + statin vs. statin + another drug influencing lipid metabolism) that met the inclusion criteria of the benefit assessment. For research question 1, no additional evidence was identified by the information retrieval compared with the recent systematic review by Zhan et al. 2018. Furthermore, 3 ongoing studies relevant to research question 1 were identified. The last search was conducted on 4 February 2019.

The HIJ-PROPER study was, contrary to plan, not considered for the benefit assessment, as the effects of the different LDL-C target value strategies between treatment groups on the results of the study cannot be estimated and therefore it is unclear to what extent observed effects are attributable to ezetimibe. Therefore, all other studies included by the information retrieval were evaluated to determine whether they were able to challenge the results of the IMPROVE-IT study or increase the certainty of conclusions.

The assessment of research question 1 is ultimately based only on the IMPROVE-IT study. The assessment of research question 2 is based on the COMBO II study.

Results for research question 1

Studies whose results are not considered in the benefit assessment

Due to the study size and the only medium qualitative certainty of results in each of the 6 other studies identified, none of them can challenge the result of the benefit assessment on research question 1 on the basis of the IMPROVE-IT study or increase the certainty of conclusions. The results of these studies are therefore not considered in the benefit assessment.

Study characteristics of the study included in the assessment

The IMPROVE-IT study is a randomized, double-blind, actively controlled, 2-arm parallel group study comparing ezetimibe plus simvastatin with simvastatin plus placebo. Adult patients

were included who had been hospitalized for ACS (unstable angina pectoris, myocardial infarction without ST-segment elevation, or myocardial infarction with ST-segment elevation) within 10 days prior to randomization. The LDL-C levels of patients who had not received lipid-lowering therapy prior to the qualifying ACS event were to lie between 50 and 125 mg/dl. The LDL-C levels of patients who had already received lipid-lowering therapy prior to the ACS event were to lie between 50 and 100 mg/dl.

A total of 9067 patients were randomized to the ezetimibe/simvastatin arm of the study and 9077 to the simvastatin + placebo arm. Patients in both study arms were treated according to the summaries of product characteristics. Lipid-lowering pretherapy was generally permitted in the IMPROVE-IT study, but the potency of LDL-C lowering therapy prior to hospitalization was not allowed to exceed that of 40 mg simvastatin/day.

The primary outcome of the IMPROVE-IT study was a combined outcome of cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, hospitalization due to unstable angina pectoris, and revascularization via percutaneous coronary intervention or coronary artery bypass surgery at least 30 days after randomization. Secondary outcomes were further outcomes from the categories “morbidity”, “mortality” and “adverse effects”.

The study duration was to be at least 2.5 years, provided that at that time a primary outcome event had occurred in at least 5250 patients. The actual median observation period was 6 years. The median treatment duration was 4.4 years.

Risk of bias

The risk of bias across outcomes was rated as low for the IMPROVE-IT study. The outcome-specific risk of bias was considered high for the results of the combined outcome “major adverse cardiovascular event” (MACE) due to high and time-differentiated discontinuation rates between treatment groups. The outcome-specific risk of bias was assessed as low for the results of all other relevant outcomes. For the outcome MACE, at best hints of a greater or lesser benefit or harm can therefore be derived from the available data, and at best indications for all other relevant outcomes.

Results for patient-relevant outcomes

The combined cardiovascular outcome MACE used for the assessment is composed of the individual components of cardiovascular death (defined as CHD death, death from atherosclerotic vascular disease or death from other non-atherosclerotic cardiovascular diseases), non-fatal myocardial infarction, and non-fatal stroke. The MACE outcome is operationalized as the time to first occurrence of an event for 1 of the 3 individual components. For this outcome, there was a statistically significant difference between treatment groups in favour of ezetimibe/simvastatin versus simvastatin. This was shown in statistically significant differences between treatment groups in favour of ezetimibe/simvastatin versus simvastatin for the single components of non-fatal myocardial infarction and non-fatal stroke.

In contrast, no statistically significant difference between treatment groups was shown for the single component of cardiovascular death; the effect estimate was hazard ratio (HR) = 1.00 with a 95% confidence interval of [0.89; 1.13]. For the combined outcome MACE, due to the high outcome-specific risk of bias, the data provide a hint of a greater benefit of ezetimibe/ simvastatin versus simvastatin.

The IMPROVE-IT study showed no statistically significant differences between treatment groups for the other outcomes (all-cause mortality, hospitalization due to unstable angina pectoris, hospitalization due to heart failure, SAEs, discontinuation due to AEs, myopathy and rhabdomyolysis). For these outcomes, the data thus provide no hint of a greater or lesser benefit or harm from ezetimibe/simvastatin versus simvastatin. The outcome of health-related quality of life was not recorded in the study, nor were patient-relevant outcomes on vascular non-cardiovascular and non-cerebrovascular morbidity. No usable data were available for the outcome of severe liver toxicity.

Summary of evidence

For the combined outcome MACE, the data provide a hint of a greater benefit of ezetimibe/ simvastatin versus simvastatin. This is reflected in statistically significant differences for the individual components of non-fatal myocardial infarction and non-fatal stroke.

The data provide no hint of a greater or lesser benefit or harm from ezetimibe/simvastatin versus simvastatin for the outcomes of all-cause mortality, hospitalization due to unstable angina pectoris, hospitalization due to heart failure, SAEs, discontinuation due to AEs, myopathy and rhabdomyolysis. No data were reported on vascular non-cardiovascular and non-cerebro-vascular morbidity or on health-related quality of life. No usable data were available for the outcome of severe liver toxicity.

Results for research question 2

Study characteristics

The COMBO II study is a randomized, double-blind, actively controlled, 2-arm parallel group study comparing ezetimibe and alirocumab, each plus a statin. The study included patients with a high to very high cardiovascular risk (CHD or peripheral arterial occlusive disease, ischaemic stroke, moderate renal failure, type 1 or 2 diabetes with at least 2 other risk factors) whose LDL-C levels were insufficiently controlled with existing statin therapy (≥ 70 mg/dl).

A total of 241 patients were randomized to the ezetimibe arm and 479 to the alirocumab arm in a 1:2 ratio.

The doses of ezetimibe and alirocumab were as specified in the respective summary of product characteristics. The present benefit assessment is based on the data from the final analysis after 104 weeks of treatment.

The primary outcome of the study was the change in the LDL-C level after 24 weeks versus the LDL-C level at baseline. Patient-relevant outcomes were mainly determined by means of the analysis of AEs.

Subpopulation relevant for the benefit assessment

Alirocumab is only approved for patients who do not reach the LDL-C target values with a maximum or maximally tolerated statin pretherapy. According to the approval status, treatment with ezetimibe for the prevention of cardiovascular events requires a history of CHD or ACS.

However, in the COMBO II study, at least 40% of patients in the total population were not shown to have been pretreated at the maximally tolerated statin dose. For the total population of the COMBO II study, therefore, the use of alirocumab according to the approval status is not ensured. However, for the early benefit assessment procedure for Commission A18-74, analyses were used for a subpopulation pretreated with maximum statin therapy at the start of the study (maximum statin therapy [mST] population). Moreover, in the mST population more than 90% of patients had CHD, so that the use of ezetimibe according to the approval status was ensured. For this reason, the analyses prepared for the early benefit assessment procedure for Commission A18-74 were requested from the manufacturer Sanofi-Aventis for the subpopulation described above, as these patients represent a sufficient approximation to the relevant population for research question 2 of the present benefit assessment.

The present benefit assessment is therefore based on the mST population as the relevant subpopulation of the COMBO II study, with 140 patients in the ezetimibe arm and 262 in the alirocumab arm. All data presented below refer to the mST population.

Risk of bias

The risk of bias across outcomes was rated as low for the COMBO II study. The outcome-specific risk of bias was also rated as low for the results on all relevant outcomes. For all relevant outcomes, at best indications of a greater or lesser benefit or harm can therefore be derived from the available data.

Results for patient-relevant outcomes

The combined cardiovascular outcome “major adverse cardiovascular event” (MACE) comprises the individual components of death due to CHD, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, and hospitalization due to unstable angina pectoris. For the combined outcome MACE, however, no data are available for the relevant subpopulation. Therefore, the individual components are used separately for the benefit assessment. However, the component of death due to CHD is not assessed separately because the outcome of all-cause mortality reflects deaths from any cause and therefore provides a more complete picture than mortality from specific causes.

There were no statistically significant differences between treatment groups for the individual components of non-fatal myocardial infarction, fatal and non-fatal stroke, and hospitalization

due to unstable angina pectoris. The data thus provide no hint of a greater or lesser benefit of ezetimibe + statin versus alirocumab + statin.

There were also no statistically significant differences between treatment groups for the outcomes of all-cause mortality, hospitalization due to heart failure, SAEs, discontinuation due to AEs, myopathy, rhabdomyolysis, allergic reactions, and local injection site reactions. The data thus provide no hint of a greater or lesser benefit or harm from ezetimibe + statin versus alirocumab + statin. The outcome of health-related quality of life was not recorded in the study, nor were patient-relevant outcomes on vascular non-cardiovascular and non-cerebrovascular morbidity. No usable data were available for the outcome of severe liver toxicity.

Summary of evidence

The data do not provide a hint of a greater or lesser benefit or harm from ezetimibe + statin versus alirocumab + statin for any of the relevant outcomes. In addition, the data are inadequate for the outcomes of all-cause mortality, non-fatal myocardial infarction, fatal and non-fatal ischaemic stroke, hospitalization due to unstable angina pectoris, and hospitalization due to heart failure, because the 95% confidence interval is so imprecise that neither a halving nor doubling of the effect can be ruled out. No data were reported on vascular non-cardiovascular and non-cerebrovascular morbidity and health-related quality of life. No usable data were available for the outcome of severe liver toxicity.

Conclusion

Research question 1: In patients with a history of CHD or ACS, the data provide a hint of a greater benefit of treatment with ezetimibe plus a statin versus treatment with a statin alone for risk reduction of cardiovascular events with regard to the combined cardiovascular outcome MACE. This advantage was shown in statistically significant differences for the 2 single-components of non-fatal myocardial infarction and non-fatal stroke. In contrast, for the third single component of cardiovascular death, no statistically significant difference was found, with the point estimate (hazard ratio) lying on the zero effect. For the other patient-relevant outcomes, the data provide no hint of a greater or lesser benefit or harm from treatment with ezetimibe plus a statin versus treatment with a statin alone for risk reduction of cardiovascular events.

Research question 2: In patients with a history of CHD or ACS, the data do not provide a hint of a greater or lesser benefit or harm from treatment with ezetimibe plus a statin versus treatment with alirocumab plus a statin for risk reduction of cardiovascular events with regard to any of the patient-relevant outcomes. Especially for the outcomes of cardiovascular events and all-cause mortality, the data were inadequate.

The full report (German version) is published under
https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-83-ezetimibe-for-the-prevention-of-cardiovascular-events-rapid-report.10779.html