

IQWiG Reports – Commission No. 11-02

Ticagrelor – Benefit assessment according to § 35a Social Code Book V¹

Executive Summary

¹ Translation of the executive summary of the benefit assessment “Ticagrelor - Nutzenbewertung gemäß § 35a SGB V” (Version 1.0; Status: 29.09.11). 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.

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Executive summary

In its letter of 21 January 2011, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to perform a benefit assessment of the active ingredient ticagrelor in accordance with §35a Social Code Book V. The assessment is based on a dossier of the pharmaceutical company (PC). The dossier was transmitted to IQWiG on 4 July 2011.

The benefit assessment of ticagrelor + acetylsalicylic acid (ASA) was in comparison with

- Clopidogrel + ASA in patients with unstable angina pectoris and myocardial infarction without ST-segment elevation (unstable angina/NSTEMI),
- Clopidogrel + ASA in patients with myocardial infarction with ST-segment elevation (STEMI) who receive drug treatment,
- Prasugrel + ASA in patients with STEMI who had undergone percutaneous coronary intervention (PCI),
- ASA monotherapy in patients with STEMI who had been treated with a coronary artery bypass graft (CABG).

There was a total of 2 relevant studies (PLATO and TRITON). Both studies were double-blind, randomized and actively controlled. In the PLATO study, treatment with ticagrelor + ASA was compared with treatment with clopidogrel + ASA. In the TRITON study, treatment with prasugrel + ASA was compared with treatment with clopidogrel + ASA. On the basis of these studies (with direct and indirect comparison), data were available on 2 of the above 4 therapeutic indications (unstable angina/NSTEMI and STEMI [PCI]). No adequate data were available for the therapeutic indications “STEMI (drug treatment)” and “STEMI (CABG)”.

Both studies are approval studies for ticagrelor and prasugrel, respectively. In both cases, subgroup analyses led to restrictions in approval. The present assessment is therefore based on analyses which are largely restricted to patients treated in accordance with the current approval status of the drugs.

The following results were found for the above 4 therapeutic indications:

Unstable angina/NSTEMI

For the assessment of the therapeutic indication “unstable angina/NSTEMI”, only the PLATO study was available (direct comparison between ticagrelor + ASA and clopidogrel + ASA). The risk of bias was low, both at the study level and for the individual outcomes. Because of the high quality and adequate size of the PLATO study, it was possible to derive proof from the data, for example of added benefit, unless outcome-specific aspects weakened the informative value of the evidence.

Mortality

There was a statistically significant difference in favour of ticagrelor for overall mortality and cardiovascular mortality. This provides proof of added benefit for both outcomes.

Morbidity

There was a statistically significant difference in favour of ticagrelor for myocardial infarctions and the combined outcome of cardiovascular mortality, myocardial infarction and stroke.

Because of the operationalization of the outcome “myocardial infarction” (inclusion of myocardial infarctions which were solely diagnosed on the basis of enzyme changes), the level of the informative value of the evidence was reduced (from proof to indication). Thus, there is an indication of added benefit for the outcome “myocardial infarction”.

The result of the combined outcome will not be further considered, as there was an advantage for each of the two components “cardiovascular mortality” and “myocardial infarction” separately; in addition, for the third component, stroke, there was practically no numerical difference between the treatment groups.

The result for strokes was not statistically significant. An added benefit for the outcome “stroke” is not proven.

Health-related quality of life

The PC dossier contained no evaluable data on health-related quality of life. An added benefit for the outcome “health-related quality of life” is not proven.

Adverse effects

The results for severe bleeding, potentially fatal and fatal bleeding, as well as serious adverse events, were all not statistically significant. Greater harm for these 3 outcomes is not proven.

There was a statistically significant difference to the disadvantage of ticagrelor for adverse events and study discontinuations due to adverse events, as well as the individual adverse events of dyspnoea and bradycardia. Thus, this provides proof of greater harm for dyspnoea and study discontinuations due to adverse events. Because of the marginal effect size, no proof of greater harm is provided for the overall rate of adverse events and bradycardia.

STEMI (drug treatment)

The PLATO study also included patients who were treated with drugs after STEMI. Nevertheless, the PC did not submit separate results for STEMI (drug treatment). An added benefit is not proven.

STEMI (PCI)

For the assessment of the therapeutic indication “STEMI (PCI)”, there was no available study in which ticagrelor + ASA and prasugrel + ASA were directly compared. The assessment was based on an indirect comparison of the results of the PLATO study (ticagrelor + ASA vs. clopidogrel + ASA) and the TRITON study (prasugrel + ASA vs. clopidogrel + ASA). The risk of bias for both studies was low, both at the study level and at the level of the individual outcomes. Nevertheless, the informative value of the evidence is reduced by the indirect comparison.

Mortality, Morbidity

The results of the indirect comparison for the outcomes “overall mortality”, “cardiovascular mortality”, “myocardial infarction”, and “stroke”, as well as the combination of cardiovascular mortality, myocardial infarction and stroke, were all not statistically significant. The result for the combined outcome will not be further considered, as none of its individual components showed an advantage. An added benefit is not proven for the other 4 outcomes.

Health-related quality of life

The PC dossier contained no evaluable data on health-related quality of life. An added benefit for the outcome “health-related quality of life” is not proven.

Adverse effects

The results of the indirect comparison for adverse events, serious adverse events and study discontinuations due to adverse events were all not statistically significant. Greater harm for these 3 outcomes is not proven. For other adverse events, data were limited. In particular, there were no adequate data for bleeding events – severe bleeding, potentially fatal and fatal bleeding.

STEMI (CABG)

The PC submitted no data for the comparison ticagrelor + ASA vs. ASA for the therapeutic indication “STEMI (CABG)”. An added benefit is not proven

Probability and extent of the added benefit

On the basis of the above results and after consideration of outcome categories and effect sizes, the extent and probability of the added benefit of ticagrelor were assessed as follows:

There is proof of considerable added benefit of ticagrelor + ASA in comparison with clopidogrel + ASA for the therapeutic indication “unstable angina/NSTEMI”. This overall conclusion on the extent of the added benefit is based on the aggregation of the extent of the added benefit derived at the outcome level.

An added benefit is not proven in the therapeutic indications “STEMI (drug treatment)”, “STEMI (PCI)” or “STEMI (CABG)” in comparison with the appropriate comparator therapy clopidogrel + ASA, prasugrel + ASA or ASA monotherapy, respectively.

This procedure for deriving an overall conclusion on added benefit represents a suggestion by IQWiG. The G-BA decides on the added benefit.

Keywords: ticagrelor, acute coronary syndrome, benefit assessment

The full dossier assessment (German version) is published under www.iqwig.de