IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ticagrelor (prevention of atherothrombotic events after myocardial infarction) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Ticagrelor (Prävention atherothrombotischer Ereignisse nach Myokardinfarkt) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 2016). 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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[2] Due to legal data protection regulations, employees have the right not to be named.

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[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ACE	angiotensin converting enzyme
ADP	adenosine diphosphate
AE	adverse event
ASA	acetylsalicylic acid
AT	angiotensin
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
TIA	transient ischaemic attack
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ticagrelor (new therapeutic indication). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 21 March 2016.

Research question

The aim of the present report was to assess the added benefit of ticagrelor in combination with low-dose acetylsalicylic acid (ASA) in comparison with ASA monotherapy as appropriate comparator therapy (ACT) for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction (1 to 3 years ago) and a high risk of developing an atherothrombotic event. A high risk was assumed if at least one of the following risk factors was fulfilled: age $\geq$ 65 years, diabetes mellitus requiring medication, more than one prior myocardial infarction, multivessel coronary heart disease (multivessel CHD), or chronic non-end-stage renal impairment.

Table 2 shows the research question of the benefit assessment.

Table 2: Research question of the benefit assessment of ticagrelor

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Co-administered with ASA indicated for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction[b] and a high risk of developing an atherothrombotic event	ASA monotherapy[c, d]

a: Presentation of the respective ACT specified by the G-BA.
b: 1–3 years ago.
c: Besides ASA, further basic therapy of the myocardial infarction under consideration of possible comorbidities is assumed as part of the standard treatment, particularly the use of anticoagulants, statins, ACE inhibitors, and beta-blockers. Furthermore, an adequate lifestyle (including dietary changes, smoking cessation and physical exercise) is assumed.
d: Low-dose use (75–175 mg/day).
ACE: angiotensin converting enzyme; ACT: appropriate comparator therapy; ASA: acetylsalicylic acid; G-BA: Federal Joint Committee

The G-BA specified ASA monotherapy as ACT. The company followed this specification and further specified the use of ASA with a low dose of 75 to 175 mg/day. According to the G-BA's specification, further basic therapy of the myocardial infarction and measures for an adequate lifestyle were considered to be part of the ACT for the present benefit assessment. The company did not name these as part of the ACT.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 12 months were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Results

Study pool and study characteristics

The study PEGASUS-TIMI 54 (in the present report referred to as "PEGASUS") was included in the benefit assessment. This was a completed, randomized, double-blind study with 3 treatment arms. Patients in all treatment arms received ASA with a dosage of 75 to 150 mg/day as unblinded basic therapy. The patients were randomly assigned to 2 ticagrelor arms (90 mg: N = 7050; 60 mg: N = 7045) and one placebo arm (N = 7067). Randomization was stratified by study centres. The ticagrelor dose of 60 mg was relevant for the present research question so that hereinafter only this ticagrelor arm will be considered. The multicentre study was conducted in countries in North and Latin America, Western and Eastern Europe, Asia, as well as in Australia and in South Africa.

Patients with a minimum age of 50 years who had had a myocardial infarction 1 to 3 years before randomization were included. In addition, patients must have already received and tolerated ASA treatment before study inclusion so that the basic therapy could be administered in the study. Furthermore, patients had to meet at least one of the following criteria: age $\geq$ 65 years, diabetes mellitus requiring medication, a second prior myocardial infarction that was more than one year ago, multivessel CHD, or chronic non-end-stage renal impairment.

Based on the approval of ticagrelor, only part of the population of the PEGASUS study was relevant for the present research question. According to the approval, treatment with ticagrelor may be initiated up to 2 years from the myocardial infarction, or within one year after stopping previous adenosine diphosphate (ADP) receptor inhibitor treatment. However, the PEGASUS study also included patients whose myocardial infarction had been longer ago than 2 years and who, at the same time, had not been treated with an ADP receptor inhibitor during the last 12 months before randomization. The relevant subpopulation comprised 5388 patients in the ticagrelor arm and 5391 patients in the placebo arm. The company presented data for this subpopulation for almost all relevant outcomes.

Concomitant statin treatment was explicitly allowed during the study. Patients could also use angiotensin converting enzyme (ACE) inhibitors and beta-blockers during the study. For an adequate lifestyle, measures for diet and physical activity for patients with a history of myocardial infarction and a high atherothrombotic risk denoted as "typical" were applied in the PEGASUS study. These measures were not further explained in the study documents. It was assumed for the present benefit assessment that the aspects of adequate lifestyle were sufficiently addressed in the PEGASUS study.

The study duration was event-driven and the study was to last until 1360 events in the primary outcome, a composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke, had occurred. Furthermore, the minimum treatment duration for all patients at the end of study was 12 months.

Risk of bias

The risk of bias was rated as low at study level and for all patient-relevant outcomes for which data were available.

Outcome-specific proof could be derived from the PEGASUS study. A corresponding justification is provided for all outcomes for which this was possible.

Mortality

All-cause mortality

A statistically significant difference in favour of ticagrelor + ASA in comparison with placebo + ASA was shown for the outcome "all-cause mortality". This resulted in an indication of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy.

Morbidity

Cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke

A statistically significant difference in favour of ticagrelor + ASA in comparison with placebo + ASA was shown for the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. This resulted in an indication of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy.

Myocardial infarction (fatal/nonfatal)

A statistically significant difference in favour of ticagrelor + ASA in comparison with placebo + ASA was shown for the outcome "myocardial infarction (fatal/nonfatal)". This resulted in an indication of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy.

Unstable angina pectoris

There was no statistically significant difference between the treatment groups for the outcome "unstable angina pectoris". This resulted in no hint of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy; an added benefit is therefore not proven.

Stroke (fatal/nonfatal)

There was no statistically significant difference between the treatment groups for the outcome "stroke (fatal/nonfatal)". However, there was an indication of an effect modification by the characteristic "age". For patients < 65 years of age, there was a hint of an added benefit of

ticagrelor in combination with ASA in comparison with ASA monotherapy. For patients from 65 to 75 years of age and for patients > 75, there was no hint of an added benefit of ticagrelor in combination with ASA. Hence an added benefit of ticagrelor for patients ≥ 65 years of age is not proven.

Transient ischaemic attack

There was no statistically significant difference between the treatment groups for the outcome "transient ischaemic attack (TIA)". This resulted in no hint of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy; an added benefit is therefore not proven.

Health status

The company presented no usable data on the outcome "health status", which was recorded with the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D). This resulted in no hint of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy; an added benefit is therefore not proven.

Health-related quality of life

The outcome "health-related quality of life" was not recorded in the PEGASUS study. This resulted in no hint of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy; an added benefit is therefore not proven.

Side effects

Serious adverse events (excluding bleeding events)

There was no statistically significant difference between the treatment groups for the outcome "serious adverse events (SAEs)" (excluding bleeding events). Greater or lesser harm of ticagrelor in combination with ASA in comparison with ASA monotherapy was therefore not proven for the outcome "SAEs" (excluding bleeding events).

Discontinuation due to adverse events (excluding bleeding events)

There were no analyses excluding bleeding events for the outcome "discontinuation due to adverse events (AEs)". For the present benefit assessment, the analysis including bleeding events was considered as an approximation. A statistically significant effect to the disadvantage of ticagrelor + ASA in comparison with placebo + ASA was shown here. This resulted in an indication of greater harm of ticagrelor in combination with ASA for the outcome "discontinuation due to AEs" (including bleeding events).

All clinically relevant bleeding events

There were no analyses for the outcome "all clinically relevant bleeding events". Greater or lesser harm of ticagrelor in combination with ASA in comparison with ASA monotherapy was therefore not proven for the outcome "all clinically relevant bleeding events".

Severe bleeding events

A statistically significant effect to the disadvantage of ticagrelor + ASA in comparison with placebo + ASA was shown for the outcome "severe bleeding events". In addition, there was an indication of an effect modification by the characteristic "> 1 prior myocardial infarction" and proof of an effect modification by the characteristic "multivessel CHD". For the characteristic "> 1 prior myocardial infarction", the results in both subgroups did not differ from the result of the total relevant subpopulation of the PEGASUS study regarding direction and extent, so that the characteristic was not considered further. There was an indication of greater harm of ticagrelor in combination with ASA in comparison with ASA monotherapy both for patients with multivessel CHD and for patients without multivessel CHD. The effects in the subgroups differed in their extent, however.

Clinically relevant non-severe bleeding events

There were no analyses for the outcome "clinically relevant non-severe bleeding events". Greater or lesser harm of ticagrelor in combination with ASA in comparison with ASA monotherapy was therefore not proven for the outcome "clinically relevant non-severe bleeding events".

Dyspnoea

A statistically significant effect to the disadvantage of ticagrelor + ASA in comparison with placebo + ASA was shown for the outcome "dyspnoea". Since for this outcome the precision of the effect estimate was high (p-value < 0.001), and there were sufficiently homogeneous effects for subgroup analyses by region, proof could be derived from the present single study PEGASUS. For dyspnoea, there was proof of greater harm from ticagrelor in combination with ASA.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug ticagrelor in combination with ASA in comparison with the ACT are assessed as follows:

Overall, there are positive and negative effects. Positive effects were shown for mortality and for serious/severe symptoms/late complications in the outcome category "morbidity". An indication of a minor added benefit was shown for the outcome "all-cause mortality".

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

Furthermore, there was an indication of a minor added benefit both for the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke, and for the outcome "myocardial infarction (fatal/nonfatal)". In addition, there was a hint of considerable added benefit for the outcome "stroke (fatal/nonfatal)" for patients < 65 years.

These positive effects are accompanied by negative effects. In the category of serious/severe side effects, there was an indication of greater harm for the outcome "severe bleeding events" with different extent for patients with and without multivessel CHD (considerable and minor). The consideration of the underlying events in this outcome showed that the effects were mainly caused by potentially fatal/fatal events, which were partly already represented in the outcome "all-cause mortality". Further negative effects were shown for 2 outcomes in the category of non-serious/non-severe side effects with the probability "indication" for one outcome, and the probability "proof" for the other outcome; the extent was considerable in both cases.

The negative effects did not raise doubts about the positive effects, particularly in the outcome "all-cause mortality".

In summary, there is an indication of a minor added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction and a high risk of developing an atherothrombotic event.

Table 3 presents a summary of the extent and probability of the added benefit of ticagrelor.

Table 3: Ticagrelor – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
Co-administered with ASA for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction[b] and a high risk of developing an atherothrombotic event	ASA monotherapy[c, d]	Indication of minor added benefit

a: Presentation of the respective ACT specified by the G-BA.
b: 1–3 years ago.
c: Besides ASA, further basic therapy of the myocardial infarction under consideration of possible comorbidities is assumed as part of the standard treatment, particularly the use of anticoagulants, statins, ACE inhibitors, and beta-blockers. Furthermore, an adequate lifestyle (including dietary changes, smoking cessation and physical exercise) is assumed.
d: Low-dose use (75–175 mg/day).
ACE: angiotensin converting enzyme; ACT: appropriate comparator therapy; ASA: acetylsalicylic acid; G-BA: Federal Joint Committee

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of ticagrelor in combination with low-dose ASA in comparison with ASA monotherapy as ACT for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction (1 to 3 years ago) and a high risk of developing an atherothrombotic event. A high risk was assumed if at least one of the following risk factors was fulfilled: age ≥ 65 years, diabetes mellitus requiring medication, more than one prior myocardial infarction, multivessel CHD, or chronic non-end-stage renal impairment.

Table 4 shows the research question of the benefit assessment.

Table 4: Research question of the benefit assessment of ticagrelor

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	Co-administered with ASA for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction[b] and a high risk of developing an atherothrombotic event	ASA monotherapy[c, d]

a: Presentation of the respective ACT specified by the G-BA.
b: 1–3 years ago.
c: Besides ASA, further basic therapy of the myocardial infarction under consideration of possible comorbidities is assumed as part of the standard treatment, particularly the use of anticoagulants, statins, ACE inhibitors, and beta-blockers. Furthermore, an adequate lifestyle (including dietary changes, smoking cessation and physical exercise) is assumed.
d: Low-dose use (75–175 mg/day).
ACE: angiotensin converting enzyme; ACT: appropriate comparator therapy; ASA: acetylsalicylic acid; G-BA: Federal Joint Committee

The G-BA specified ASA monotherapy as ACT. The company followed this specification and further specified the use of ASA with a low dose of 75 to 175 mg/day. According to the G-BA's specification, further basic therapy of the myocardial infarction and measures for an adequate lifestyle were considered to be part of the ACT for the present benefit assessment. The company did not name these as part of the ACT.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. RCTs with a minimum duration of 12 months were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on ticagrelor (status: 2 February 2016)
- bibliographical literature search on ticagrelor (last search on 12 January 2016)
- search in trial registries for studies on ticagrelor (last search on 13 January 2016)

To check the completeness of the study pool:

- search in trial registries for studies on ticagrelor (last search on 5 April 2016)

No additional relevant study was identified from the check.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
PEGASUS-TIMI 54 (PEGASUS[b])	Yes	Yes	No
a: Study for which the company was sponsor. b: In the following tables, the study is referred to with this abbreviated form. ASA: acetylsalicylic acid; RCT: randomized controlled trial; vs.: versus			

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PEGASUS	RCT, double-blind, parallel	Patients ≥ 50 years with myocardial infarction 1–3 years before randomization with currently well-tolerated ASA treatment and ≥ 1 of the following atherothrombotic risk factors: ▪ age ≥ 65 years ▪ diabetes mellitus requiring medication ▪ second myocardial infarction that was more than one year ago ▪ multivessel CHD ▪ chronic non-end-stage renal impairment	▪ ticagrelor 90 mg + ASA (N = 7050)[b] ▪ ticagrelor 60 mg + ASA (N = 7045) ▪ placebo + ASA (N = 7067) Relevant subpopulation thereof[c]: ▪ ticagrelor 60 mg + ASA (n = 5388) ▪ placebo + ASA (n = 5391)	▪ Study inclusion: up to 14 days before randomization ▪ Event-driven study duration: after 1360 events in the primary outcome and when all patients had been treated for ≥ 12 months (until about 38 months) ▪ Follow up: 14–28 days after the end of study	1161 centres in 31 countries worldwide[d]: North and Latin America, Western and Eastern Europe, Asia, Australia, South Africa 10/2010–12/2014	Primary: ▪ composite outcome of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke Secondary: ▪ all-cause mortality ▪ myocardial infarction, unstable angina pectoris, stroke, TIA ▪ bleeding events ▪ AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: The study arm is not relevant for the assessment and is not shown in the next tables.
c: In patients in the relevant subpopulation, the myocardial infarction was ≤ 2 years ago or the previous treatment with ADP receptor inhibitors was ≤ 1 year ago.
d: Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, China, Czech Republic, Columbia, France, Germany, Hungary, Italy, Japan, Netherlands, Norway, Peru, Philippines, Poland, Romania, Russia, Slovak Republic, South Africa, South Korea, Spain, Sweden, Turkey, Ukraine, United Kingdom, USA

ADP: adenosine diphosphate; AE: adverse event; ASA: acetylsalicylic acid; CHD: coronary heart disease; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; TIA: transient ischaemic attack; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA

Study	Intervention	Comparison
PEGASUS	Ticagrelor 60 mg, twice/day + ASA 75–150 mg, once/day	Placebo for ticagrelor 60 mg, twice/day + ASA 75–150 mg, once/day
	Basic ASA therapy ▪ stable dose during the study (75–150 mg), temporary increase (> 150 mg/day) possible if medically indicated (e.g. ACS or PCI)	
	Allowed prior and concomitant treatment ▪ statins (simvastatin and lovastatin ≤ 40 mg/day, other statins without restrictions) ▪ parenteral anticoagulants for short-term therapeutic treatment (< 7 days) ▪ GpIIb/IIIa inhibitors ▪ ACE inhibitors, beta-blockers[a] ▪ diet and physical activity: typical measures for diet and physical activity for patients with a history of myocardial infarction and a high atherothrombotic risk[b] **Non-permitted concomitant treatment** ▪ planned use of ADP receptor inhibitors (clopidogrel[c], ticlopidine, prasugrel), dipyridamole, cilostazol ▪ strong CYP3A4 inhibitors, CYP3A substrates with narrow therapeutic index, strong CYP3A4 inducers ▪ oral anticoagulants ▪ fibrinolytic agents ▪ CYP2C19 inhibitors with use of clopidogrel during modification of the study medication ▪ major surgery within 5 days after the end of treatment	
	Treatment discontinuations possible in case of non-permitted concomitant treatments **Modification of the study medication** Investigator decided on the indication for treatment with ADP receptor inhibitor clopidogrel: study medication, while maintaining blinding, was modified according to the following schedule for the duration of the indication for clopidogrel	
	ticagrelor 90 mg, twice/day[d] + placebo for clopidogrel, once/day + ASA 75–150 mg, once/day[f]	placebo for ticagrelor, twice/day + clopidogrel 75 mg, once/day[e] + ASA 75–150 mg, once/day[f]

a: Not explicitly mentioned as allowed medication, but it can be inferred from the study documents that there was use during the study (ACE inhibitors about 59% and beta-blockers about 72% of the patients in the total population, no data on the use during the study was available for the relevant subpopulation).
b: It is not clear from the study documents what was understood by "typically".
c: Allowed at the investigator's discretion.
d: The initial dose could be increased to 180 mg at the investigator's discretion.
e: The initial dose could be increased to 300 mg or 600 mg at the investigator's discretion; furthermore, increase to 75 mg twice/day could be conducted within the first week.
f: Increase of the ASA dose possible at the investigator's discretion for the duration of the modification.
ACE: angiotensin converting enzyme; ACS: acute coronary syndrome; ADP: adenosine diphosphate; ASA: acetylsalicylic acid; CYP: cytochrome P450; Gp: glycoprotein; PCI: percutaneous coronary intervention; RCT: randomized controlled trial; vs.: versus

Study design and study population

The included PEGASUS study was a completed, randomized, double-blind study with 3 treatment arms. Patients in all treatment arms received ASA with a dosage of 75 to 150 mg/day as unblinded basic therapy. In 2 treatment arms, ticagrelor was administered in different dosages (60 mg or 90 mg), and in the third treatment arm, the patients received placebo instead of ticagrelor. The multicentre study was conducted in countries in North and Latin America, Western and Eastern Europe, Asia, as well as in Australia and in South Africa.

Patients with a minimum age of 50 years who had had a myocardial infarction 1 to 3 years before randomization were included. In addition, patients must have already received and tolerated ASA treatment before study inclusion so that the basic therapy could be administered in the study. Furthermore, patients had to meet at least one of the following criteria: age $\geq$ 65 years, diabetes mellitus requiring medication, a second prior myocardial infarction that was more than one year ago, multivessel CHD, or chronic non-end-stage renal impairment.

The patients were randomly assigned in a ratio of 1:1:1 to 2 ticagrelor arms (90 mg: N = 7050; 60 mg: N = 7045) and one placebo arm (N = 7067). Randomization was stratified by study centres. The ticagrelor dose of 60 mg was relevant for the present research question so that hereinafter only this ticagrelor arm will be considered.

The study duration was event-driven and the study was to last until 1360 events in the primary outcome, a composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke, had occurred. Furthermore, the minimum treatment duration for all patients at the end of study was 12 months. The secondary outcomes included all-cause mortality, myocardial infarction (fatal/nonfatal), unstable angina pectoris, stroke (fatal/nonfatal), TIA, health status, bleeding with different severity grades, and further AEs, among others.

Relevant subpopulation

Based on the approval of ticagrelor, only part of the population of the PEGASUS study was relevant for the present research question.

According to the approval, treatment with ticagrelor may be initiated up to 2 years from the myocardial infarction, or within one year after stopping previous ADP receptor inhibitor treatment. However, the PEGASUS study also included patients whose myocardial infarction had been longer ago than 2 years and who, at the same time, had not been treated with an ADP receptor inhibitor during the last 12 months before randomization.

The relevant subpopulation comprised 5388 patients in the ticagrelor arm and 5391 patients in the placebo arm. The company presented data for this subpopulation for almost all relevant outcomes (see Section 2.4.1 for details).

Modification of the study medication/concomitant treatment

If treatment with the ADP receptor inhibitor clopidogrel was indicated, temporary modification of the study medication, while maintaining blinding, was allowed in the course of the study in both study arms. In this case, patients in the ticagrelor arm received a dosage of 90 mg instead of 60 mg ticagrelor, and patients in the placebo arm received clopidogrel.

In addition, certain concomitant treatments were restricted or prohibited during participation in the study, e.g. treatment with other anticoagulants or major surgery. Such treatments could only be conducted if the study medication was temporarily discontinued.

Concomitant statin treatment was explicitly allowed during the study. Patients could also use ACE inhibitors and beta-blockers during the study.

For an adequate lifestyle, measures for diet and physical activity for patients with a history of myocardial infarction and a high atherothrombotic risk denoted as “typical” were applied in the PEGASUS study. These measures were not further explained in the study documents. It was assumed for the present benefit assessment that the aspects of adequate lifestyle were sufficiently addressed in the PEGASUS study.

Planned duration of follow-up

Table 8 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 8: Planned duration of follow up – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA

Study **Outcome category** **Outcome**	**Planned follow-up**
PEGASUS	
Mortality	
All-cause mortality	▪ up to 14–28 days after the last treatment (end-of-study visit) ▪ in case of premature treatment discontinuation until the end of study if possible
Morbidity	
Composite outcome of cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke, myocardial infarction (fatal/nonfatal), stroke (fatal/nonfatal)	▪ up to 14–28 days after the last treatment (end-of-study visit) ▪ in case of premature treatment discontinuation until the end of study if possible
Unstable angina pectoris, TIA	▪ up to 14–28 days after the last treatment (end-of-study visit)
Health status (EQ-5D VAS)	▪ Recording times: month 8, 12, 18, 24, 30, and 36 (± 10 days), and at premature discontinuation of treatment (end-of-study visit) ▪ no follow-up planned
Health-related quality of life	
	▪ not recorded
Side effects	
AEs, discontinuation due to AEs, bleeding events, dyspnoea	▪ up to 14–28 days after the last treatment (end-of-study visit) ▪ after premature treatment discontinuation: recording of AEs 14–28 days after the end of treatment and at the next subsequent examination
SAEs	▪ up to 14–28 days after the last treatment (end-of-study visit) ▪ after premature treatment discontinuation: recording of SAEs in all subsequent examinations until the end of study
AE: adverse event; ASA: acetylsalicylic acid; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; SAE: serious adverse event; TIA: transient ischaemic attack; VAS: visual analogue scale; vs.: versus	

Follow-up until 14 to 28 days after the last treatment of the patients was planned for all outcomes, except the outcome “health status”. In case of premature treatment discontinuation, if possible, data on the following outcomes were recorded for all patients until the end of the study, and considered in the analysis: all-cause mortality, composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke, myocardial infarction (fatal/nonfatal), stroke (fatal/nonfatal), SAEs. In case of withdrawal of consent, public sources were also used for the follow-up of all-cause mortality.

The patients’ health status was to be recorded with the EQ-5D VAS at several time points up to and including month 36. No follow-up was planned.

Characteristics of the study population

Table 9 shows the characteristics of the patients in the studies included.

Table 9: Characteristics of the study population – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study **Characteristics** **Category**	**Ticagrelor + ASA**	**Placebo + ASA**
PEGASUS	N = 5388	N = 5391
Age [years], mean (SD)	65 (9)	65 (8)
Sex [F/M], %	24/76	24/76
BMI [kg/m²], mean (SD)	28.5 (5.0)	28.4 (5.0)
Time from diagnosis of the myocardial infarction until randomization, n (%)		
< 1 year	54 (1.0)	47 (0.9)
≥ 1 year–< 2 years	4277 (79.4)	4286 (79.5)
≥ 2 years–≤ 3 years	1034 (19.2)	1037 (19.2)
> 3 years	17 (0.3)	14 (0.3)
Unknown	1 (0.0)	0 (0)
No history of myocardial infarction	5 (0.1)	7 (0.1)
Time interval between the last treatment with ADP receptor inhibitors and randomization, n (%)		
< 30 days[a]	2391 (44.4)	2403 (44.6)
30 days–12 months	2231 (41.4)	2230 (41.4)
> 12 months	366 (6.8)	343 (6.4)
Unknown	2 (0.0)	5 (0.1)
Type of myocardial infarction, n (%)		
STEMI	2872 (53.3)	2928 (54.3)
NSTEMI	2209 (41.0)	2177 (40.4)
Unknown	302 (5.6)	279 (5.2)
History of angina pectoris, n (%)	1695 (31.5)	1602 (29.7)
History of coronary stent implantation, n (%)		
Yes	4409 (81.8)	4399 (81.6)
No	958 (17.8)	977 (18.1)
Unknown	21 (0.4)	15 (0.3)

(continued)

Table 9: Characteristics of the study population – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation) (continued)

Study Characteristics Category	**Ticagrelor + ASA**	**Placebo + ASA**
PEGASUS	N = 5388	N = 5391
Type of stent, n (%)[b]		
BMS	2240 (41.6)	2213 (41.0)
DES	2307 (42.8)	2331 (43.2)
Unknown	211 (3.9)	214 (4.0)
Smoker at the time point of randomization, n (%)		
Never smoker	1856 (34.4)	1938 (35.9)
Ex-smoker	2592 (48.1)	2583 (47.9)
Current smoker	939 (17.4)	865 (16.0)
Unknown	1 (0.0)	5 (0.1)
Hypertension requiring medication, n (%)	4183 (77.6)	4175 (77.4)
Atherothrombotic risk factors for study inclusion, n (%)[b]		
Age ≥ 65 years	2825 (52.4)	2956 (54.8)
Diabetes mellitus[c]	1774 (32.9)	1710 (31.7)
> 1 prior myocardial infarction	884 (16.4)	900 (16.7)
Multivessel CHD	3313 (61.5)	3300 (61.2)
Chronic non-end-stage renal impairment (creatinine clearance according to Cockcroft Gault < 60 mL/min)[d]	306 (5.7)	340 (6.3)
Number of atherothrombotic risk factors[e] for study inclusion, n (%)		
0	34 (0.6)	31 (0.6)
1	2790 (51.8)	2700 (50.1)
2	1765 (32.8)	1852 (34.4)
≥ 3	799 (14.8)	808 (15.0)
ASA dose at randomization, n (%)[f]		
≤ 75 mg	1021 (18.9)	1036 (19.2)
> 75 mg	4354 (80.8)	4339 (80.5)
No ASA	13 (0.2)	16 (0.3)
Beta-blockers at randomization, n (%)	4477 (83.1)	4531 (84.0)
Statins at randomization, n (%)	4933 (91.6)	4999 (92.7)
ACE inhibitors/AT1 antagonists at randomization, n (%)	4326 (80.3)	4360 (80.9)
Ethnicity, n (%)		
Caucasian	4592 (85.2)	4606 (85.4)
Black	106 (2.0)	98 (1.8)
Asian	639 (11.9)	637 (11.8)
Other	51 (0.9)	50 (0.9)

(continued)

Table 9: Characteristics of the study population – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation) (continued)

Study Characteristics Category	**Ticagrelor + ASA**	**Placebo + ASA**
PEGASUS	N = 5388	N = 5391
Region, n (%)		
Asia and Australia	665 (12.3)	661 (12.3)
Europe and South Africa	3042 (56.5)	3037 (56.3)
North America	1096 (20.3)	1094 (20.3)
South America	585 (10.9)	599 (11.1)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a: Including patients in whom the unblinded treatment with ADP receptor blockers was continued on the day of the randomization or after randomization.
b: Double counting possible.
c: Of which "requiring medication" are defined as type 1 or type 2 diabetes treated with oral antidiabetics or insulin: n (%) for ticagrelor + ASA: 1549 (28.7) and for placebo + ASA: 1519 (28.2).
d: No further operationalization of the chronic non-end-stage renal impairment reported (see Section 2.7.2.4.1 of the full dossier assessment).
e: Comprises the following risk factors for the development of an atherothrombotic event: age ≥ 65 years, diabetes mellitus requiring medication, > 1 prior myocardial infarction, multivessel CHD, chronic non-end-stage renal impairment (creatinine clearance according to Cockcroft Gault < 60 mL/min).
f: At most 0.4% of the patients in the total population received an ASA dose of < 75 mg or > 150 mg after randomization. There is no information for the relevant subpopulation.
ACE: angiotensin converting enzyme; ADP: adenosine diphosphate; ASA: acetylsalicylic acid; AT: angiotensin; BMI: body mass index; BMS: bare metal stent; CHD: coronary heart disease; DES: drug-eluting stent; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; NSTEMI: myocardial infarction without ST-segment elevation; RCT: randomized controlled trial; SD: standard deviation; STEMI: myocardial infarction with ST-segment elevation; vs.: versus

The mean age of the patients in the PEGASUS study was 65 years. About one fourth of the patients were women. The mean body mass index (BMI) of the patients was about 28.5 kg/m².

In most patients (about 80%), the prior myocardial infarction was less than 2 years ago. Most patients (about 86%) had received treatment with ADP receptor inhibitors within 12 months before randomization.

About 50% of the patients had exactly one of the following risk factors: age ≥ 65 years, diabetes mellitus requiring medication, > 1 prior myocardial infarction that was more than one year ago, multivessel CHD, or chronic non-end-stage renal impairment. About 48% of the patients had 2 or more of these characteristics.

Irrespective of the need for medication, about 32% of the patients had diabetes mellitus (the diabetes mellitus did not require medication in about 28.5%). About 16% of the patients had more than one prior myocardial infarction, and about 61% had multivessel coronary CHD.

About 6% of the patients had chronic non-end-stage renal impairment (for the comment, see Section 2.7.2.4.1 of the full dossier assessment).

At the time point of randomization, the proportion of current smokers was below 20%; hence the decisive proportion of the patients were non-smokers at this time point. About 77% of the patients had hypertension requiring medication.

No data on the implementation of the basic ASA therapy during the study were available for the relevant subpopulation. However, only at most 0.4% of the patients in the total population were treated outside the dose range under 75 mg or above 150 mg.

At randomization, more than 91% of the patients in the relevant subpopulation were receiving concomitant treatment with statins, and more than 80% each were treated with beta-blockers or ACE inhibitors/angiotensin (AT)1 antagonists. No data on the concomitant treatment in the course of the study were available for the relevant subpopulation. However, it could be inferred from study documents that there was no important difference between the concomitant treatment at randomization for the total population and the treatment after randomization.

The vast majority of patients (about 85%) were Caucasian with most patients being from Europe and South Africa (about 56%) and North America (about 20%). For the proportion of patients from South Africa, no data were available for the relevant subpopulation; the proportion for the total population was about 2.2%.

No data were available on the proportion of patients who discontinued the study or the treatment for the relevant subpopulation in the present benefit assessment.

Duration of treatment and follow-up

Table 10 shows the mean/median treatment duration of the patients and the follow-up period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study **Duration of the study phase** **Outcome category**	**Ticagrelor + ASA**	**Placebo + ASA**
PEGASUS	N = 5388	N = 5391
Treatment duration		
Median/mean	ND	ND
Observation duration		
Median/mean	ND	ND
All-cause mortality		
Median/mean	ND	ND
Morbidity		
Median/mean	ND	ND
Health-related quality of life	Not recorded	
Adverse events[a]		
Median/mean	ND	ND
Patient years	11191.11	12051.74

a: Analysis includes data from the start of treatment until 7 days after the end of treatment, with N = 5322 for ticagrelor + ASA and N = 5331 for placebo + ASA. According to the study protocol, follow-up was planned until 14–28 days after the end of treatment.

ASA: acetylsalicylic acid; N: number of analysed patients: ND: no data; RCT: randomized controlled trial; vs.: versus

Apart from the information on the course of the study for the outcomes on side effects, no information on observation periods was available for the relevant subpopulation. The observation periods for side effects did not differ substantially between the treatment groups. Due to the same planned follow-up durations for the other relevant outcomes (see Table 8), it can be assumed that the actual observation periods of these outcomes also did not differ substantially between the treatment groups. This was also shown by the mean (median) observation periods of the total population of the PEGASUS study, which also did not differ substantially between ticagrelor + ASA with 31.8 (33.3) months and placebo + ASA with 31.7 (33.1) months. The same applied to the mean (median) treatment duration of the total population with 25.3 (29.4) months for ticagrelor + ASA and 27.3 (30.4) months for placebo + ASA.

During participation in the study, it was possible to temporarily switch or discontinue treatment with the study medication. There was no information on the relevant subpopulation as to how many patients in the treatment arms this applied to. In the total population, about 4% in each treatment arm received switching of the study medication while blinding was maintained. In the total population, treatment was temporarily discontinued in 25.4% of the patients in the ticagrelor arm and in 22.7% of the patients in the placebo arm.

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
PEGASUS	Yes	Yes	Yes	Yes	Yes	Yes	Low
ASA: acetylsalicylic acid; RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low. This is in accordance with the assessment of the company.

Overall assessment of the certainty of conclusions

Outcome-specific proof could be derived from the PEGASUS study (see also Section 2.7.2.8.1 of the full dossier assessment).

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke (composite outcome)
  - myocardial infarction (fatal/nonfatal)
  - unstable angina pectoris
  - stroke (fatal/nonfatal)
  - TIA
  - health status (EQ-5D VAS)
- Health-related quality of life

- Side effects
  - SAEs
  - discontinuation due to AEs
  - all clinically relevant bleeding events
    - severe bleeding events
    - clinically relevant non-severe bleeding events
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment). In addition, deviating from the company, the outcome “all clinically relevant bleeding events” was considered to be patient-relevant for the assessment. For all other outcomes on side effects, analyses excluding bleeding events were considered to be relevant.

Table 12 shows for which outcomes data were available in the studies included.

Table 12: Matrix of outcomes – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study	Outcomes														
	All-cause mortality	Cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke	Myocardial infarction (fatal/nonfatal)	Unstable angina pectoris	Stroke (fatal/nonfatal)	TIA	Health status (EQ-5D VAS)	Health-related quality of life	SAEs (excluding bleeding events)	Discontinuation due to AEs (excluding bleeding events)	Discontinuation due to AEs (including bleeding events)	All clinically relevant bleeding events (according to PLATO definition)	Severe bleeding events (according to PLATO definition)	Clinically relevant non-severe bleeding events (according to PLATO definition)	Dyspnoea[a]
PEGA-SUS	Yes	Yes	Yes	Yes	Yes	Yes	No[b]	No[c]	Yes	No[d]	Yes[e]	No[d]	Yes	No[d]	Yes

a: Composed of the following events (MedDRA coding): dyspnoea (PT), exertional dyspnoea (PT), dyspnoea at rest (PT), nocturnal dyspnoea (PT), dyspnoea paroxysmal nocturnal (PT).
b: No usable data available; for reasons, see Section 2.7.2.4.3 of the full dossier assessment.
c: Outcome not recorded.
d: No data available for the relevant subpopulation.
e: Used as an approximation for the outcome "discontinuation due to AEs" (excluding bleeding events); for reasons, see Section 2.7.2.4.3 of the full dossier assessment).

AE: adverse event; ASA: acetylsalicylic acid; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PLATO: Platelet Inhibition and Patient Outcomes; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; TIA: transient ischaemic attack; VAS: visual analogue scale; vs.: versus

Differing from all other outcomes, only data until 18 months after start of treatment were available for the outcome "health status" (recorded using the EQ-5D VAS). Data on the time point 36 months were only available for the total population. Hence no usable data were available for the outcome "health status".

The outcome "health-related quality of life" was not recorded in the PEGASUS study.

The company presented no data on the relevant subpopulation for the following outcomes: discontinuation due to AEs (excluding bleeding events), all clinically relevant bleeding events, and clinically relevant non-severe bleeding events. The outcome "discontinuation due to AEs" (including bleeding events) was used as an approximation for the outcome "discontinuation due to AEs" (excluding bleeding events) (for reasons, see Section 2.7.2.4.3 of the full dossier assessment).

2.4.2 Risk of bias

Table 13 shows the risk of bias for the relevant outcomes.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study		Outcomes														
	Study level	All-cause mortality	Cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke	Myocardial infarction (fatal/nonfatal)	Unstable angina pectoris	Stroke (fatal/nonfatal)	TIA	Health status (EQ-5D VAS)	Health-related quality of life	SAEs (excluding bleeding events)	Discontinuation due to AEs (excluding bleeding events)	Discontinuation due to AEs (including bleeding events)	All clinically relevant bleeding events	Severe bleeding events	Clinically relevant non-severe bleeding events	Dyspnoea
PEGA-SUS	L	L	L	L	L	L	L	–[a]	–[b]	L	–[c]	L	–[c]	L	–[c]	L

a: No usable data available.
b: Outcome not recorded.
c: No data available for the relevant subpopulation.
AE: adverse event; ASA: acetylsalicylic acid; EQ-5D: European Quality of Life-5 Dimensions; L: low; RCT: randomized controlled trial; SAE: serious adverse event; TIA: transient ischaemic attack; VAS: visual analogue scale; vs.: versus

The outcome-specific risk of bias was rated as low for all outcomes for which data were available. This is in accordance with the assessment of the company.

2.4.3 Results

Table 14 and Table 15 summarize the results on the comparison of ticagrelor + ASA with placebo + ASA for the relevant subpopulation. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. Kaplan-Meier curves on the survival time analyses can be found in Appendix A.

Table 14: Results (time to event and continuous outcomes) – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study **Outcome category** **Outcome**	**Ticagrelor + ASA**		**Placebo + ASA**		**Ticagrelor + ASA vs. placebo + ASA**
	N	**Median survival time in months [95% CI]** **Patients with event n (%[a])**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%[a])**	**HR [95% CI]; p-value**
PEGASUS					
Mortality (time to event)					
All-cause mortality	5388	NA 206 (4.4)	5391	NA 256 (5.4)	0.80 [0.67; 0.96]; 0.018
Cardiovascular mortality	5388	NA 119 (2.6)	5391	NA 167 (3.6)	0.71 [0.56; 0.90]; 0.004
Morbidity (time to event)					
Cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke	5388	NA 373 (7.9)	5391	NA 463 (9.6)	0.80 [0.70; 0.91]; 0.001
Myocardial infarction (fatal/nonfatal)	5388	NA 230 (4.8)	5391	NA 274 (5.6)	0.83 [0.70; 0.99]; 0.041
Unstable angina pectoris[b]	5388	NA 32 (0.7)	5391	NA 29 (0.6)	1.10 [0.66; 1.82]; 0.714
Stroke (fatal/nonfatal)	5388	NA 71 (1.5)	5391	NA 95 (2.0)	0.74 [0.55; 1.01]; 0.058
TIA[c]	5388	NA 10 (0.2)	5391	NA 15 (0.3)	0.66 [0.30; 1.48]; 0.315
Morbidity (continuous outcomes)					
Health status (EQ-5D VAS)	No usable data available[d]				
Health-related quality of life					
Outcome not recorded					

a: Probabilities from Kaplan-Meier analysis.
b: Includes events that resulted in hospitalization of the patients within 24 hours after onset of the last symptoms.
c: Includes events that resulted in hospitalization of the patients within 48 hours after onset of the last symptoms.
d: No data available for the relevant time point, 36 months (see Section 2.7.2.4.3 of the full dossier assessment).

ASA: acetylsalicylic acid; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial; TIA: transient ischaemic attack; VAS: visual analogue scale; vs.: versus

Table 15: Results (dichotomous outcomes) – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study Outcome category Outcome	Ticagrelor + ASA N	Ticagrelor + ASA Patients with event n (%)	Placebo + ASA N	Placebo + ASA Patients with event n (%)	Ticagrelor + ASA vs. placebo + ASA RR [95% CI]; p-value
PEGASUS					
Side effects					
Adverse events (excluding bleeding events, supplementary information)	5322	ND	5331	ND	–
SAEs (excluding bleeding events)[a]	5322	1044 (19.6)	5331	1111 (20.8)	0.94 [0.87; 1.02]; 0.130[b]
Discontinuation due to AEs	5322	ND	5331	ND	–
▪ excluding bleeding events					
▪ including bleeding events	5322	829 (15.6)	5331	429 (8.0)	1.94 [1.73; 2.16]; < 0.001[b]
All clinically relevant bleeding events	5322	ND	5331	ND	–
Severe bleeding events	5322	145 (2.7)	5331	59 (1.1)	2.46 [1.82; 3.32]; < 0.001[b]
Fatal or potentially fatal bleeding events	5322	100 (1.9)	5331	44 (0.8)	2.28 [1.60; 3.24]; < 0.001[b]
Intracranial bleeding events	5322	23 (0.4)	5331	18 (0.3)	1.28 [0.69; 2.37]; 0.529[b]
Other severe bleeding events	5322	48 (0.9)	5331	15 (0.3)	3.21 [1.80; 5.72]; < 0.001[b]
Clinically relevant non-severe bleeding events	5322	ND	5331	ND	–
Dyspnoea	5322	738 (13.9)	5331	306 (5.7)	2.42 [2.13; 2.75]; < 0.001[b]

a: Includes events leading to death.
b: Institute's calculation, unconditional exact test (CSZ method according to [3]).
AE: adverse event; ASA: acetylsalicylic acid; CI: confidence interval; CSZ: convexity, symmetry, z score; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Outcome-specific proof could be derived from the PEGASUS study. A corresponding justification is provided for all outcomes for which this was possible.

Mortality

All-cause mortality

A statistically significant difference in favour of ticagrelor + ASA in comparison with placebo + ASA was shown for the outcome "all-cause mortality". This resulted in an

indication of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy.

This deviates from the assessment of the company, which derived proof of an added benefit of ticagrelor together with ASA for the combination of all outcomes on mortality it included.

Morbidity

Cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke

A statistically significant difference in favour of ticagrelor + ASA in comparison with placebo + ASA was shown for the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. This resulted in an indication of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy.

This deviates from the assessment of the company, which derived proof of an added benefit of ticagrelor in combination with ASA for the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke.

Myocardial infarction (fatal/nonfatal)

A statistically significant difference in favour of ticagrelor + ASA in comparison with placebo + ASA was shown for the outcome "myocardial infarction (fatal/nonfatal)". This resulted in an indication of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy.

This deviates from the assessment of the company, which derived proof of an added benefit of ticagrelor in combination with ASA for the outcome "myocardial infarction (fatal/nonfatal)".

Unstable angina pectoris

There was no statistically significant difference between the treatment groups for the outcome "unstable angina pectoris". This resulted in no hint of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy; an added benefit is therefore not proven.

This is in accordance with the assessment of the company.

Stroke (fatal/nonfatal)

There was no statistically significant difference between the treatment groups for the outcome "stroke (fatal/nonfatal)". However, there was an indication of an effect modification by the characteristic "age". For patients < 65 years of age, there was a hint of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy. For patients from 65 to 75 years of age and for patients > 75, there was no hint of an added benefit of ticagrelor in combination with ASA. Hence an added benefit of ticagrelor for patients ≥ 65 years of age is not proven.

This deviates from the assessment of the company, which considered no subgroup results, and concluded for the total relevant subpopulation of the PEGASUS study for the outcome "stroke (fatal/nonfatal)" that an added benefit of ticagrelor in combination with ASA is not proven.

Transient ischaemic attack

There was no statistically significant difference between the treatment groups for the outcome "TIA". This resulted in no hint of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy; an added benefit is therefore not proven.

This is in accordance with the assessment of the company.

Health status (EQ-5D VAS)

The company presented no usable data on the outcome "health status" recorded with the EQ-5D VAS. This resulted in no hint of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy; an added benefit is therefore not proven.

The company did not consider the outcome "health status" (EQ-5D VAS) in the derivation of the added benefit.

Health-related quality of life

The outcome "health-related quality of life" was not recorded in the PEGASUS study. This resulted in no hint of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy; an added benefit is therefore not proven.

Side effects

Serious adverse events (excluding bleeding events)

There was no statistically significant difference between the treatment groups for the outcome "SAEs" (excluding bleeding events). Greater or lesser harm of ticagrelor in combination with ASA in comparison with ASA monotherapy was therefore not proven for the outcome "SAEs" (excluding bleeding events).

This is in accordance with the assessment of the company.

Discontinuation due to adverse events (excluding bleeding events)

There were no analyses excluding bleeding events for the outcome "discontinuation due to AEs".

For the present benefit assessment, the analysis including bleeding events was considered as an approximation (for a detailed justification, see Section 2.7.2.4.3 of the full dossier assessment). A statistically significant effect to the disadvantage of ticagrelor + ASA in comparison with placebo + ASA was shown here. This resulted in an indication of greater

harm of ticagrelor in combination with ASA for the outcome "discontinuation due to AEs" (including bleeding events).

This deviates from the company's assessment, which derived proof of higher risk for the outcome "discontinuation due to AEs" (including bleeding events).

All clinically relevant bleeding events

There were no analyses for the outcome "all clinically relevant bleeding events". Greater or lesser harm of ticagrelor in combination with ASA in comparison with ASA monotherapy was therefore not proven for the outcome "all clinically relevant bleeding events".

Severe bleeding events

A statistically significant effect to the disadvantage of ticagrelor + ASA in comparison with placebo + ASA was shown for the outcome "severe bleeding events". In addition, there was an indication of an effect modification by the characteristic "> 1 prior myocardial infarction" and proof of an effect modification by the characteristic "multivessel CHD".

For the characteristic "> 1 prior myocardial infarction", the results in both subgroups did not differ from the result of the total relevant subpopulation of the PEGASUS study regarding direction and extent, so that the characteristic was not considered further.

There was an indication of greater harm of ticagrelor in combination with ASA in comparison with ASA monotherapy both for patients with multivessel CHD and for patients without multivessel CHD. The effects in the subgroups differed in their extent, however.

This deviates from the assessment of the company, which considered no subgroup results, and additionally used a different operationalization for the outcome "bleeding events". On the basis of its outcome on bleeding events, the company derived proof of higher risk for the total relevant subpopulation of the PEGASUS study.

Clinically relevant non-severe bleeding events

There were no analyses for the outcome "clinically relevant non-severe bleeding events". Greater or lesser harm of ticagrelor in combination with ASA in comparison with ASA monotherapy was therefore not proven for the outcome "clinically relevant non-severe bleeding events".

Dyspnoea

A statistically significant effect to the disadvantage of ticagrelor + ASA in comparison with placebo + ASA was shown for the outcome "dyspnoea". Since for this outcome the precision of the effect estimate was high (p-value < 0.001), and there were sufficiently homogeneous effects for subgroup analyses by region (see Figure 7 in Appendix C of the full dossier assessment), proof could be derived from the present single study PEGASUS. For dyspnoea, there was proof of greater harm from ticagrelor in combination with ASA.

This assessment concurs with that of the company.

2.4.4 Subgroups and other effect modifiers

The following effect modifiers were considered in the present benefit assessment:

- age (< 65 years/65 years to 75 years/> 75 years)
- sex (male/female)
- diabetes mellitus (yes/no)
- > 1 prior myocardial infarction (yes/no)
- multivessel CHD (yes/no)
- current smoker at study inclusion
- BMI at baseline (< 30 kg/m²/≥ 30 kg/m²)

In the present assessment, only the results on subgroups and outcomes are presented in which there was at least an indication of an interaction between treatment effect and subgroup characteristic. Subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification.

In the present benefit assessment, subgroup analyses are reported irrespective of the sample size and the number of events. This deviates from the company's approach, which only presented subgroup results if more than 15 events were observed in at least one subgroup (for the comment, see Section 2.7.2.2 of the full dossier assessment).

Table 16 and Table 17 summarize the subgroup results on the comparison of ticagrelor + ASA with placebo + ASA for the relevant subpopulation of the PEGASUS study. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 16: Subgroups (time to event) – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study Outcome category	Ticagrelor + ASA		Placebo + ASA		Ticagrelor + ASA vs. placebo + ASA	
Outcome **Characteristic** **Subgroup**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%[a])**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%[a])**	**HR [95% CI]**	**p-value**
PEGASUS						
Mortality						
All-cause mortality						
BMI (kg/m^2)						
< 30	3588	NA 149 (4.9)	3686	NA 162 (4.9)	0.95 [0.76; 1.19]	0.651
≥ 30	1787	NA 56 (3.4)	1693	NA 93 (6.5)	0.56 [0.40; 0.78]	< 0.001
					Interaction:	0.009
Morbidity						
Cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke						
Age (years)						
< 65	2556	NA 145 (6.5)	2429	NA 191 (8.9)	0.71 [0.57; 0.88]	0.002
65-75	2168	NA 162 (8.3)	2324	NA 181 (8.7)	0.96 [0.77; 1.18]	0.685
> 75	664	NA 66 (11.6)	638	NA 91 (15.5)	0.70 [0.51; 0.96]	0.028
					Interaction:	0.096
Sex						
Male	4121	NA 263 (7.2)	4077	NA 347 (9.5)	0.74 [0.63; 0.87]	< 0.001
Female	1267	NA 110 (9.8)	1314	NA 116 (9.7)	0.98 [0.76; 1.27]	0.883
					Interaction:	0.070
BMI (kg/m^2)						
< 30	3588	NA 225 (7.1)	3686	NA 309 (9.1)	0.74 [0.62; 0.88]	< 0.001
≥ 30	1787	NA 146 (9.2)	1693	NA 153 (10.5)	0.90 [0.71; 1.12]	0.346
					Interaction:	0.189

(continued)

Table 16: Subgroups (time to event) – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation) (continued)

Study Outcome category	Ticagrelor + ASA		Placebo + ASA		Ticagrelor + ASA vs. placebo + ASA	
Outcome Characteristic Subgroup	N	Median survival time in months [95% CI] Patients with event n (%[a])	N	Median survival time in months [95% CI] Patients with event n (%[a])	HR [95% CI]	p-value
PEGASUS						
Morbidity						
Myocardial infarction (fatal/nonfatal)						
Sex						
Male	4121	NA 161 (4.4)	4077	NA 209 (5.6)	0.75 [0.61; 0.93]	0.007
Female	1267	NA 69 (6.1)	1314	NA 65 (5.5)	1.10 [0.78; 1.54]	0.578
					Interaction:	0.059
BMI (kg/m^2)						
< 30	3588	NA 123 (3.9)	3686	NA 184 (5.4)	0.68 [0.54; 0.86]	0.001
≥ 30	1787	NA 106 (6.6)	1693	NA 90 (6.1)	1.11 [0.84; 1.47]	0.465
					Interaction:	0.008
Stroke (fatal/nonfatal)						
Age (years)						
< 65	2556	NA 21 (1.0)	2429	NA 41 (1.9)	0.48 [0.28; 0.81]	0.006
65–75	2168	NA 35 (1.8)	2324	NA 33 (1.7)	1.14 [0.71; 1.84]	0.579
> 75	664	NA 15 (2.6)	638	NA 21 (4.0)	0.69 [0.35; 1.34]	0.269
					Interaction:	0.055

a: Probabilities from Kaplan-Meier analysis.

ASA: acetylsalicylic acid; BMI: body mass index; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Table 17: Subgroups (dichotomous outcomes) – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study Outcome category	Ticagrelor + ASA		Placebo + ASA		Ticagrelor + ASA vs. placebo + ASA	
Outcome Characteristic Subgroup	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
PEGASUS						
Side effects						
Severe bleeding events						
> 1 prior myocardial infarction[a]						
Yes	869	31 (3.6)	893	6 (0.7)	5.31 [2.23; 12.66][b]	< 0.001[c]
No	4453	114 (2.6)	4438	53 (1.2)	2.14 [1.55; 2.96][b]	< 0.001[c]
					Interaction:	0.055[d]
Multivessel CHD						
Yes	3278	103 (3.1)	3256	33 (1.0)	3.10 [2.10; 4.57][b]	< 0.001[c]
No	2043	42 (2.1)	2075	26 (1.3)	1.64 [1.01; 2.67][b]	0.044[c]
					Interaction:	0.045[d]

a: ≥ one year before randomization.
b: Institute's calculation, asymptotic.
c: Institute's calculation, unconditional exact test (CSZ method according to [3]).
d: Institute's calculation, Cochran's Q test.
ASA: acetylsalicylic acid; CI: confidence interval; CHD: coronary heart disease; CSZ: convexity, symmetry, z score; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Mortality

All-cause mortality

There was proof of an effect modification by the characteristic "BMI" for the outcome "all-cause mortality". No statistically significant difference between the treatment groups was shown for patients with a BMI < 30 kg/m², whereas a statistically significant difference in favour of ticagrelor + ASA was shown for patients with a BMI ≥ 30 kg/m².

Handling of the result on the characteristic "BMI"

On the characteristic "BMI", results in the opposite direction of the result on all-cause mortality were shown both for the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke, and for the outcome "myocardial infarction (fatal/nonfatal)". A statistically significant difference in favour of ticagrelor + ASA was shown for patients with a BMI < 30 kg/m², whereas no statistically significant difference between the treatment groups was shown for patients with a BMI ≥ 30 kg/m². The opposing subgroup results for the characteristic "BMI" across different outcomes, which were not

independent from one another, cannot be meaningfully interpreted with regard to content, and were therefore not considered further in the overall consideration for the benefit assessment. The added benefit for the outcome "all-cause mortality" was therefore derived for the total relevant subpopulation of the PEGASUS study (see Section 2.4.3).

This assessment concurs with that of the company except for the justification why no subgroup results were considered. The company stated that it considered the subgroup results as a whole not to be interpretable and therefore did not consider subgroups in general.

Morbidity

Cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke

There was an indication of an effect modification for the characteristics "age", "sex", and "BMI" for the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke.

The subgroup results could not be meaningfully interpreted because no data were available for the investigation of possible dependencies between the subgroup characteristics. The added benefit was therefore derived for the total relevant subpopulation of the PEGASUS study (see Section 2.4.3).

This assessment concurs with that of the company except for the justification why no subgroup results were considered.

Myocardial infarction (fatal/nonfatal)

There was an indication of an effect modification by the characteristic "sex" and proof of an effect modification by the characteristic "BMI" for the outcome "myocardial infarction (fatal/nonfatal)".

The subgroup results could not be meaningfully interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. The added benefit was therefore derived for the total relevant subpopulation of the PEGASUS study (see Section 2.4.3).

This assessment concurs with that of the company except for the justification why no subgroup results were considered.

Stroke (fatal/nonfatal)

There was an indication of an effect modification by the characteristic "age" for the outcome "stroke (fatal/nonfatal)". A statistically significant difference in favour of ticagrelor + ASA was shown for patients < 65 years. Since there was only an indication of an effect modification and, in contrast to the result of the total population, the subgroup result was statistically significant (see Table 14), there is a hint of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy for the age group < 65 years.

For patients between 65 and 75 years of age and for patients > 75 years, there was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy for both subgroups. Hence an added benefit of ticagrelor in combination with ASA is not proven for the age groups 65 to 75 years and > 75 years.

This deviates from the company's assessment, which considered no subgroup results.

Side effects

Severe bleeding events

For the outcome "severe bleeding events", there was an indication of an effect modification by the characteristic "> 1 prior myocardial infarction" and proof of an effect modification by the characteristic "multivessel CHD".

A statistically significant difference to the disadvantage of ticagrelor + ASA in comparison with placebo + ASA was shown for the characteristic "> 1 prior myocardial infarction". The direction of effect and the extent for both subgroups concurred with the result of the total relevant subpopulation of the PEGASUS study. Hence this characteristic was not further considered in the derivation of the added benefit.

Statistically significant differences to the disadvantage of ticagrelor + ASA in comparison with placebo + ASA were shown both for patients with multivessel CHD and for patients without multivessel CHD. This resulted in an indication of greater harm of ticagrelor in combination with ASA both for patients with multivessel CHD and for patients without multivessel CHD. The effects in both subgroups differed in their extent (see Section 2.5.1).

This deviates from the assessment of the company, which considered no subgroup results, and derived proof of higher risk of ticagrelor in combination with ASA in comparison with ASA monotherapy for the total relevant subpopulation of the PEGASUS study for a different operationalization of the outcome on bleeding events.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in indications of an added benefit for the outcomes "all-cause mortality", "myocardial infarction (fatal/nonfatal)", and for the composite outcome

of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. Furthermore, there was a hint of an added benefit for the outcome "stroke (fatal/nonfatal)". There were indications of greater harm for the outcomes "discontinuation due to AEs" (including bleeding events) and "severe bleeding events". Furthermore, there was proof of greater harm for the outcome "dyspnoea". There was proof of an effect modification for the subgroup characteristic "multivessel CHD". Furthermore, there was an indication of an effect modification for the characteristic "age". The extent of the respective added benefit at outcome level was estimated from these results (see Table 18).

Table 18: Extent of added benefit at outcome level: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ticagrelor + ASA vs. placebo + ASA** **Proportion of events** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	4.4%[c] vs. 5.4%[c] HR: 0.80 [0.67; 0.96] p = 0.018 probability: "indication"	Outcome category: mortality $0.95 \leq CI_u < 1.00$ added benefit, extent: "minor"
Morbidity		
Cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke	7.9%[c] vs. 9.6%[c] HR: 0.80 [0.70; 0.91] p = 0.001 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Myocardial infarction (fatal/nonfatal)	4.8%[c] vs. 5.6%[c] HR: 0.83 [0.70; 0.99] p = 0.041 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Unstable angina pectoris	0.7%[c] vs. 0.6%[c] HR: 1.10 [0.66; 1.82] p = 0.714	Lesser benefit/added benefit not proven

(continued)

Table 18: Extent of added benefit at outcome level: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation) (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**		**Ticagrelor + ASA vs. placebo + ASA** **Proportion of events** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Morbidity			
Stroke (fatal/nonfatal)		1.5%[c] vs. 2.0%[c] HR: 0.74 [0.55; 1.01] p = 0.058	
Age (years)	< 65	1.0%[c] vs. 1.9%[c] HR: 0.48 [0.28; 0.81] p = 0.006 probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
	65-75	1.8%[c] vs. 1.7%[c] HR: 1.14 [0.71; 1.84] p = 0.579	Lesser benefit/added benefit not proven
	> 75	2.6%[c] vs. 4.0%[c] HR: 0.69 [0.35; 1.34] p = 0.269	Lesser benefit/added benefit not proven
TIA		0.2%[c] vs. 0.3%[c] HR: 0.66 [0.30; 1.48] p = 0.315	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)		No usable data available	
Health-related quality of life			
		Outcome not recorded	
Side effects			
SAEs (excluding bleeding events)[d]		19.6% vs. 20.8% RR: 0.94 [0.87; 1.02] p = 0.130	Greater/lesser harm not proven
Discontinuation due to AEs ▪ excluding bleeding events		No data available	
▪ including bleeding events		15.6% vs. 8.0% RR: 1.94 [1.73; 2.16] RR: 0.52 [0.46; 0.58][e] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

(continued)

Table 18: Extent of added benefit at outcome level: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation) (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ticagrelor + ASA vs. placebo + ASA** **Proportion of events** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
All clinically relevant bleeding events	No data available	
Severe bleeding events		
Multivessel CHD – Yes	3.1% vs. 1.0% RR: 3.10 [2.10; 4.57] RR: 0.32 [0.22; 0.48][e] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$ greater harm, extent: "considerable"
Multivessel CHD – No	2.1% vs. 1.3% RR: 1.64 [1.01; 2.67] RR: 0.61 [0.38; 0.99][e] p = 0.044 probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Clinically relevant non-severe bleeding events	No data available	
Dyspnoea	13.9% vs. 5.7% RR: 2.42 [2.13; 2.75] RR: 0.41 [0.36; 0.47][e] p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Probabilities from Kaplan-Meier analysis.
d: Includes events leading to death.
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; ASA: acetylsalicylic acid; CI: confidence interval; CI_u: upper limit of CI; CHD: coronary heart disease; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; RR: relative risk; SAE: serious adverse event; TIA: transient ischaemic attack; VAS: visual analogue scale; vs.: versus

The outcomes "discontinuation due to AEs" (including bleeding events) and "dyspnoea" were allocated to the category of non-serious/non-severe side effects. For the outcome "discontinuation due to AEs", there was no indication that discontinuations in the PEGASUS study were mainly caused by SAEs. For the outcome "dyspnoea", the company cited the proportion of serious dyspnoea in both study arms with less than 3% of all episodes of dyspnoea.

The outcome “severe bleeding events” was allocated to the category of serious/severe side effects. All outcomes of the category “morbidity” were considered as serious/severe symptoms/late complications.

The assessments on the categorization of the outcomes concurred with the company’s approach.

2.5.2 Overall conclusion on the added benefit

Table 19 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of ticagrelor in combination with ASA in comparison with ASA monotherapy

Positive effects	**Negative effects**
Mortality ▪ all-cause mortality indication of added benefit; extent: “minor”	Serious/severe side effects: ▪ severe bleeding events ▫ multivessel CHD: indication of greater harm; extent “considerable” ▫ no multivessel CHD: indication of greater harm; extent “minor”
Morbidity – serious/severe symptoms/late complications ▪ cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke (composite outcome) indication of added benefit; extent: “minor” ▪ myocardial infarction (fatal/nonfatal) indication of added benefit; extent: “minor” ▪ stroke (fatal/nonfatal) ▫ age < 65 years hint of added benefit; extent: “considerable”	Non-serious/non-severe side effects: ▪ discontinuation due to AEs (including bleeding events) indication of greater harm; extent “considerable” ▪ dyspnoea proof of greater harm; extent: “considerable”
AE: adverse event; ASA: acetylsalicylic acid; CHD: coronary heart disease	

Overall, there are positive and negative effects. Positive effects were shown for mortality and for serious/severe symptoms/late complications in the outcome category “morbidity”. An indication of a minor added benefit was shown for the outcome “all-cause mortality”. Furthermore, there was an indication of a minor added benefit both for the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke, and for the outcome “myocardial infarction (fatal/nonfatal)”. In addition, there was a hint of considerable added benefit for the outcome “stroke (fatal/nonfatal)” for patients < 65 years.

These positive effects are accompanied by negative effects. In the category of serious/severe side effects, there was an indication of greater harm for the outcome "severe bleeding events" with different extent for patients with and without multivessel CHD (considerable and minor). The consideration of the underlying events in this outcome showed that the effects were mainly caused by potentially fatal/fatal events, which were partly already represented in the outcome "all-cause mortality". Further negative effects were shown for 2 outcomes in the category of non-serious/non-severe side effects with the probability "indication" for one outcome, and the probability "proof" for the other outcome; the extent was considerable in both cases.

The negative effects did not raise doubts about the positive effects, particularly in the outcome "all-cause mortality".

In summary, there is an indication of a minor added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction and a high risk of developing an atherothrombotic event.

Summary

The result of the assessment of the added benefit of ticagrelor in comparison with the ACT is summarized in Table 20.

Table 20: Ticagrelor – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
Co-administered with ASA for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction[b] and a high risk of developing an atherothrombotic event	ASA monotherapy[c, d]	Indication of minor added benefit

a: Presentation of the respective ACT specified by the G-BA.
b: 1–3 years ago.
c: Besides ASA, further basic therapy of the myocardial infarction under consideration of possible comorbidities is assumed as part of the standard treatment, particularly the use of anticoagulants, statins, ACE inhibitors, and beta-blockers. Furthermore, an adequate lifestyle (including dietary changes, smoking cessation and physical exercise) is assumed.
d: Low-dose use (75–175 mg/day).
ACE: angiotensin converting enzyme; ACT: appropriate comparator therapy; ASA: acetylsalicylic acid; G-BA: Federal Joint Committee

This deviates from the company's approach, which derived proof of considerable added benefit of ticagrelor in combination with ASA in comparison with ASA monotherapy.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6 List of included studies

PEGASUS-TIMI 54

AstraZeneca. A randomised, double-blind, placebo controlled, parallel group, multinational trial, to assess the prevention of thrombotic events with ticagrelor compared to placebo on a background of acetyl salicylic acid (ASA) therapy in patients with history of myocardial infarction; [PEGASUS: PrEvention with ticaGrelor of secondAry thrombotic events in high-riSk patients with prior acUte coronary Syndrome; thrombolysis in myocardial infarction study group]; study D5132C00001; clinical study report [unpublished]. 2015.

AstraZeneca. A randomised, double-blind, placebo controlled, parallel group, multinational trial, to assess the prevention of thrombotic events with ticagrelor compared to placebo on a background of acetyl salicylic acid (ASA) therapy in patients with history of myocardial infarction; [PEGASUS: PrEvention with ticaGrelor of secondAry thrombotic events in high-riSk patients with prior acUte coronary Syndrome; thrombolysis in myocardial infarction study group]; study D5132C00001; Zusatzanalysen [unpublished]. 2016.

AstraZeneca. A randomized, double-blind, placebo controlled, parallel group, multinational trial, to assess the prevention of thrombotic events with ticagrelor compared to placebo on a background of acetyl salicylic acid (ASA) therapy in patients with history of myocardial infarction [online]. In: EU Clinical Trials Register. [Accessed: 05.04.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-017242-30.

AstraZeneca. Prevention of cardiovascular events (eg, death from heart or vascular disease, heart attack, or stroke) in patients with prior heart attack using ticagrelor compared to placebo on a background of aspirin: full text view [online]. In: ClinicalTrials.gov. 18.12.2015 [Accessed: 05.04.2016]. URL: https://clinicaltrials.gov/ct2/show/study/NCT01225562.

AstraZeneca. Prevention of cardiovascular events (eg, death from heart or vascular disease, heart attack, or stroke) in patients with prior heart attack using ticagrelor compared to placebo on a background of aspirin: study results [online]. In: ClinicalTrials.gov. 18.12.2015 [Accessed: 05.04.2016]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01225562.

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a16-15-ticagrelor-new-therapeutic-indication-benefit-assessment-according-to-35a-social-code-book-v.7313.html.