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Ticagrelor (prevention of atherothrombotic events after myocardial infarction) –

Addendum to Commission A16-15[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ADP	adenosine diphosphate
AE	adverse event
ASA	acetylsalicylic acid
BMI	body mass index
CHD	coronary heart disease
CI	confidence interval
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)
LOCF	last observation carried forward
PT	Preferred Term
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 10 August 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-15 (Ticagrelor [prevention of atherothrombotic events after myocardial infarction] – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In the framework of the commenting procedure on the dossier assessment [2,3], the pharmaceutical company (hereinafter referred to as "the company") sent supplementary information, which went beyond the information provided in the dossier on ticagrelor [4], to prove the added benefit. To be able to decide on the added benefit, the G-BA therefore requires further analyses. The G-BA's commission comprised the assessment of the analyses presented by the company in the commenting procedure on the following outcomes: European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS), all relevant bleeding events (severe bleeding events or clinically relevant non-severe bleeding events), clinically relevant non-severe bleeding events, and discontinuation due to adverse events (AEs) excluding bleeding events. It also comprised the assessment of sensitivity analyses on subsequent events under consideration of the information provided in the dossier.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment of the data subsequently submitted for the PEGASUS-TIMI 54 study

In the framework of the commenting procedure, the company provided further analyses for the relevant subpopulation of the randomized controlled trial PEGASUS-TIMI 54 (hereinafter referred to as "PEGASUS") [5]. This study was included as relevant in the benefit assessment of ticagrelor in the therapeutic indication in adult patients with a history of myocardial infarction and a high risk of developing an atherothrombotic event [1]. A detailed description of the study, the relevant subpopulation and the relevant outcomes can be found in dossier assessment A16-15.

2.1 Data presented

In the commenting procedure, the company provided information on the median and mean treatment and observation period as well as on the observation period for the outcome "all-cause mortality". The dossier contained the corresponding information only on side effects.

In the commenting procedure, the company subsequently submitted new analyses on the following patient-relevant outcomes, which had already been presented in the dossier:

- health status (recorded with the EQ-5D VAS) over the entire course of the study; the dossier contained only analyses up to month 18
- discontinuation due to AEs (excluding bleeding events); the dossier contained only analyses including bleeding events

Furthermore, the company subsequently submitted analyses on the following outcomes, which had not been already presented in the dossier for the relevant subpopulation:

- all relevant bleeding events (severe bleeding events or clinically relevant non-severe bleeding events)
- clinically relevant non-severe bleeding events

In the commenting procedure, the company presented subgroup analyses on nearly all outcomes mentioned above. No subgroup analyses were available only for the outcome "health status", as was already the case in the dossier. Subgroup analyses for the outcome "serious AEs (SAEs)" (excluding bleeding events) were missing in the dossier and were now provided by the company in the commenting procedure. As in the dossier, there were no subgroup analyses representing the characteristic "chronic non-end-stage renal impairment" for any outcome.

Further analyses provided by the company included:

- lists of AEs and SAEs, in each case excluding bleeding events, by System Organ Class (SOC) and Preferred Term (PT)

- various sensitivity analyses:
  - SAEs excluding bleeding events and of the primary outcome events documented as SAEs as well as an analysis additionally excluding all fatal events
  - sensitivity analysis on the effect under inclusion of second and third events using incidence density ratios
  - sensitivity analyses to investigate the influence of temporary modification of the study treatment

Hereinafter, at first the information on the course of the study is provided (see Section 2.2). Then the analyses subsequently submitted on the outcomes mentioned above and subgroup analyses are assessed (see Section 2.3). Tables presenting the common AEs and SAEs (in each case excluding bleeding events) are shown in Appendix A; the sensitivity analyses can be found in Section 2.4.

2.2 Duration of treatment and follow-up

Table 1 shows the mean/median treatment duration and observation period of the patients and the follow-up period for the outcome "all-cause mortality".

Table 1: 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 [months]		
Median [Q1; Q3]	29.07 [17.73; 35.50]	30.10 [21.20; 35.80]
Mean (SD)	25.23 (12.88)	27.13 (11.53)
Observation duration		
Median [Q1; Q3]	32.4 [ND]	32.3 [ND]
Mean (SD)	31.5 (7.4)	31.3 (7.6)
All-cause mortality		
Median [Q1; Q3]	32.6 [ND]	32.4 [ND]
Mean (SD)	31.7 (7.1)	31.5 (7.3)

ASA: acetylsalicylic acid; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The mean/median treatment duration and observation period of the patients as well as the follow-up period for the outcome "all-cause mortality" did not differ substantially between the treatment groups. The corresponding information on the outcomes of morbidity is still lacking (see dossier assessment A16-15).

2.3 Results

Risk of bias

There was a high risk of bias for the outcome "health status" (recorded with the EQ-5D VAS) because more than 10% of the randomized patients were not considered in the analysis (ticagrelor + acetylsalicylic acid [ASA]: 12.9%; placebo + ASA: 12.3%).

There was a low risk of bias for each of the following outcomes: discontinuation due to AEs (excluding bleeding events), all relevant bleeding events, and clinically relevant non-severe bleeding events.

Results

Table 2 and Table 3 show the results on the comparison of ticagrelor + ASA with placebo + ASA for the relevant subpopulation of the PEGASUS study for the following outcomes: health status, discontinuation due to AEs (excluding bleeding events), all relevant bleeding events, and clinically relevant non-severe bleeding events. Where necessary, the data presented by the company were supplemented with the Institute's calculations.

Table 2: Results (morbidity) – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study **Outcome category**	**Ticagrelor + ASA**			**Placebo + ASA**			**Ticagrelor + ASA vs. placebo + ASA**
Outcome	N	**Baseline values[a] mean (SD)**	**Change at end of study mean[b] (SD)**	**N**	**Baseline values[a] mean (SD)**	**Change at end of study[b] mean (SD)**	**MD [95% CI]; p-value**
PEGASUS							
Health status (EQ-5D VAS)	4529	75.5 (17.4)	1.3 (17.3)	4570	75.8 (17.2)	1.2 (17.2)	0.0 [-0.7; 0.8]; p = 0.90

a: Presentation of the analysis of the values at the EOT time point. This corresponds to a LOCF analysis of the FAS population.
b: Higher values indicate improvement.

ASA: acetylsalicylic acid; CI: confidence interval; EOT: end of treatment; EQ-5D: European Quality of Life-5 Dimensions; FAS: full analysis set; LOCF: last observation carried forward; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Table 3: Results (side effects) – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study Outcome category Outcome	Ticagrelor + ASA		Placebo + ASA		Ticagrelor + ASA vs. placebo + ASA
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
PEGASUS					
Discontinuation due to AEs (excluding bleeding events)	5322	601 (11.3)	5331	371 (7.0)	1.62 [1.43; 1.84]; < 0.001[a]
All clinically relevant bleeding events	5322	659 (12.4)	5331	259 (4.9)	2.55 [2.22; 2.93]; < 0.001[a]
Clinically relevant non-severe bleeding events	5322	542 (10.2)	5331	204 (3.8)	2.66 [2.28; 3.11]; < 0.001[a]

a: Institute's calculation, unconditional exact test (CSZ method according to [6]).

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; 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.

Morbidity

Health status

There was no difference between the treatment groups for 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 analysis including all values recorded at the patients' end of treatment was considered for the present assessment. This approach corresponds to the last observation carried forward (LOCF) principle. The results at individual time points were not meaningfully interpretable because they considered only those patients who were examined at the respective study visits (e.g. only about 64% of the patients at month 30 and 20% of the patients at month 36).

Side effects

Discontinuation due to adverse events (excluding bleeding events)

A statistically significant effect to the disadvantage of ticagrelor + ASA in comparison with placebo + ASA was shown for the outcome "discontinuation due to AEs" (excluding bleeding events). 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 1 in Appendix C), proof could be derived from the present single study PEGASUS.

There was proof of greater harm of ticagrelor in combination with ASA for the outcome "discontinuation due to AEs".

All relevant bleeding events and clinically relevant non-severe bleeding events

A statistically significant effect to the disadvantage of ticagrelor + ASA versus placebo + ASA was shown for the 2 outcomes "all relevant bleeding events" (severe bleeding events or clinically relevant non-severe bleeding events) and "clinically relevant non-severe bleeding events". Since for each of these outcomes the precision of the effect estimate was high (p-value < 0.001), and in each case there were sufficiently homogeneous effects for subgroup analyses by region (see Figure 2 and Figure 3 in Appendix C), proof for both outcomes could be derived from the present single study PEGASUS. There was proof of greater harm of ticagrelor in combination with ASA both for the outcome "all relevant bleeding events" and for the outcome "clinically relevant non-severe bleeding events".

Subgroups and other effect modifiers

The effect modifiers considered for the research question are described in dossier assessment A16-15. Prerequisites for proof or indication of an interaction as well as for the presentation of subgroup results are also described in dossier assessment A16-15.

The company also provided subgroup analyses for all outcomes subsequently submitted except for the outcome "health status". For the outcome "SAEs" (excluding bleeding events), the dossier contained results for the relevant subpopulation, but there were no subgroup analyses. These were presented by the company in the commenting procedure.

Table 4 summarizes the subgroup results on the comparison of ticagrelor + ASA with placebo + ASA for the relevant subpopulation of the PEGASUS study. Where necessary, the data subsequently submitted by the company were supplemented with the Institute's calculations.

Table 4: Subgroups (side effects) – 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						
SAEs (excluding bleeding events)						
Sex						
Male	4073	755 (18.5)	4030	824 (20.4)	0.91 [0.83; 0.99]	0.030[a]
Female	1249	289 (23.1)	1301	287 (22.1)	1.05 [0.91; 1.21]	0.533[a]
					Interaction:	0.091[b]
All relevant bleeding events						
Sex						
Male	4073	480 (11.8)	4030	206 (5.1)	2.31 [1.97; 2.70]	< 0.001[a]
Female	1249	179 (14.3)	1301	53 (4.1)	3.52 [2.62; 4.73]	< 0.001[a]
					Interaction:	0.014[b]
Age (years)						
< 65	2533	246 (9.7)	2401	109 (4.5)	2.14 [1.72; 2.66]	< 0.001[a]
65-75	2138	297 (13.9)	2301	112 (4.9)	2.85 [2.32; 3.52]	< 0.001[a]
> 75	651	116 (1.8)	629	38 (6.0)	2.95 [2.08; 4.18]	< 0.001[a]
					Interaction:	0.119[b]
Clinically relevant non-severe bleeding events						
Sex						
Male	4073	397 (9.7)	4030	164 (4.1)	2.40 [2.01; 2.86]	< 0.001[a]
Female	1249	145 (11.6)	1301	40 (3.1)	3.78 [2.68; 5.31]	< 0.001[a]
					Interaction:	0.020[b]
Age (years)						
< 65	2533	207 (8.2)	2401	88 (3.7)	2.23 [1.75; 2.84]	< 0.001[a]
65-75	2138	244 (11.4)	2301	87 (3.8)	3.02 [2.38, 3.83]	< 0.001[a]
> 75	651	91 (14.0)	629	29 (4.6)	3.03 [2.03; 4.54]	< 0.001[a]
					Interaction:	0.172[b]
Multivessel CHD						
Yes	3278	327 (10.0)	3256	136 (4.2)	2.39 [1.97; 2.90]	< 0.001[a]
No	2043	214 (10.5)	2075	68 (3.3)	3.20 [2.45; 4.17]	< 0.001[a]
					Interaction:	0.083[b]
BMI (kg/m^2)						
< 30	3552	380 (10.7)	3642	136 (3.7)	2.86 [2.37; 3.47]	< 0.001[a]
≥ 30	1763	162 (9.2)	1681	68 (4.0)	2.27 [1.73; 2.99]	< 0.001[a]
					Interaction:	0.174[b]

(continued)

Table 4: Subgroups (side effects) – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation) (continued)

a: Institute's calculation, unconditional exact test (CSZ method according to [6]).
b: Institute's calculation, Cochran's Q test.
ASA: acetylsalicylic acid; BMI: body mass index; 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

Side effects

Serious adverse events (excluding bleeding events)

There was an indication of an effect modification by the characteristic "sex" for the outcome "SAEs" (excluding bleeding events). A statistically significant difference in favour of ticagrelor + ASA was shown for men. Since there was only an indication of an effect modification and, in contrast to the result of the total relevant subpopulation, the subgroup result was statistically significant, there is a hint of lesser harm of ticagrelor in combination with ASA in comparison with ASA monotherapy for men. The relative risk [95% confidence interval (CI)] in the total relevant subpopulation was 0.94 [0.87; 1.02] (see dossier assessment A16-15, Table 15). For women, there was no statistically significant difference between the treatment groups. For women, there was therefore no hint of greater or lesser harm of ticagrelor in combination with ASA in comparison with ASA monotherapy regarding SAEs (excluding bleeding events); greater or lesser harm is therefore not proven.

All relevant bleeding events (severe bleeding events or clinically relevant non-severe bleeding events) and clinically relevant non-severe bleeding events

There was proof and there were indications of effect modifications for the outcomes "all relevant bleeding events" and "clinically relevant non-severe bleeding events".

There was proof of an effect modification by the characteristic "sex" and an indication of an effect modification by the characteristic "age" for the outcome "all relevant bleeding events".

For the outcome "clinically relevant non-severe bleeding events", there was proof of an effect modification by the characteristic "sex" and an indication of an effect modification by each of the characteristics "age", "multivessel coronary heart disease (multivessel CHD)" and "body mass index (BMI)".

For both outcomes, these were only quantitative interactions. The results in the respective subgroups did not differ in the direction of the effect or in the extent of the corresponding result in the total relevant subpopulation. The added benefit was therefore derived on the basis of the total relevant subpopulation of the PEGASUS study both for the outcome "all relevant bleeding events" and for the outcome "clinically relevant non-severe bleeding events".

2.4 Sensitivity analyses subsequently submitted

Serious adverse events

The company provided an analysis of SAEs excluding bleeding events and of the primary outcome events documented as SAEs. It also provided an analysis that excluded all fatal events in addition to the events mentioned above.

The results of the sensitivity analyses are presented in Appendix B (Table 9). A low risk of bias was assumed. In each case, the results showed no statistically significant effect between the treatment arms. They were therefore consistent with the result on the outcome "SAEs" (excluding bleeding events) included in dossier assessment A16-15.

Second and third events using incidence density ratio

The company provided a sensitivity analysis on the occurrence of second and third events using incidence density ratio for the composite outcome of cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke. The result of this sensitivity analysis is presented in Appendix B (Table 10). The sensitivity analysis showed a statistically significant difference in favour of ticagrelor + ASA versus placebo + ASA. This concurs with the result from the primary analysis (hazard ratio [95% CI]: 0.80 [0.67; 0.96]; p-value = 0.018) (see dossier assessment A16-15, Table 14).

Overall, the sensitivity analysis using the incidence density ratio did not raise doubts about the result of the primary analysis.

Influence of temporary modification of the study treatment

As described in dossier assessment A16-15, the PEGASUS study allowed temporary modification of the study medication, with blinding maintained, in both study arms during the course of the study if treatment with the adenosine diphosphate (ADP) receptor inhibitor clopidogrel was indicated. 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. See dossier assessment A16-15 for details.

The company provided sensitivity analyses for the outcome "all-cause mortality" and the composite outcome (and its individual components) to investigate the influence of the temporary modification of the study treatment on the effect. In these analyses, patients were censored at the time point of treatment adjustment. The study documents showed that only about 4% of the patients in the total population had temporary treatment adjustment (ticagrelor + ASA: 3.6% vs. placebo + ASA: 4.3%). The number of patients who were censored and the time points of their censoring remained unclear for the analyses of the company. Since the results were nearly identical with the primary analysis (see dossier assessment A16-15), no bias due to censoring was assumed. The results of the sensitivity analyses are presented in Appendix B (Table 11).

Mortality – all-cause mortality

The sensitivity analysis on the outcome "all-cause mortality" showed a statistically significant result in favour of ticagrelor + ASA versus placebo + ASA. The result was therefore consistent with the analysis included in dossier assessment A16-15.

Morbidity – cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke (and corresponding individual components)

The sensitivity analysis on the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke showed a statistically significant difference in favour of ticagrelor + ASA in comparison with placebo + ASA. Within the individual components, a statistically significant difference in favour of ticagrelor + ASA was also shown for the outcomes "cardiovascular mortality" and "myocardial infarction". There was no statistically significant difference between the treatment groups for the outcome "stroke". Overall, the results were therefore consistent with those included in dossier assessment A16-15.

Summary

Overall, the sensitivity analyses presented by the company did not result in an assessment deviating from dossier assessment A16-15.

3 Extent and probability of added benefit

Hereinafter, the derivation of extent and probability of the added benefit is presented at outcome level under consideration of the present addendum and dossier assessment A16-15, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [7].

3.1 Assessment of the added benefit at outcome level

Table 5 shows the results of the PEGASUS study relevant for the derivation of the added benefit.

Table 5: 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
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)		Change mean: 1.3 vs. 1.2 MD: 0.0 [-0.7; 0.8] p = 0.90	Lesser benefit/added benefit not proven

(continued)

Table 5: 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]
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
Sex	Male	18.5% vs. 20.4% RR: 0.91 [0.83; 0.99] p = 0.03 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
	Female	23.1% vs. 22.1% RR: 1.05 [0.91; 1.21] p = 0.533	Greater/lesser harm not proven
Discontinuation due to AEs (excluding bleeding events)		11.3% vs. 7.0% RR: 1.62 [1.43; 1.84] RR: 0.62 [0.54; 0.70][e] p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
All clinically relevant bleeding events		12.4% vs. 4.9% RR: 2.55 [2.22; 2.93] RR: 0.39 [0.34; 0.45][e] p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
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"
	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"

(continued)

Table 5: 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]
Clinically relevant non-severe bleeding events	10.2% vs. 3.8% RR: 2.66 [2.28; 3.11] RR: 0.38 [0.32; 0.44][e] p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
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; MD: mean difference; RR: relative risk; SAE: serious adverse event; TIA: transient ischaemic attack; VAS: visual analogue scale; vs.: versus

3.2 Overall conclusion on added benefit

Table 6 summarizes the results included in the overall conclusion on the extent of added benefit of ticagrelor in the therapeutic indication in adult patients with a history of myocardial infarction and a high risk of developing an atherothrombotic event.

Table 6: 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 (excluding bleeding events) proof of greater harm; extent: “considerable” ▪ dyspnoea proof of greater harm; extent: “considerable” ▪ clinically relevant non-severe bleeding events proof of greater harm; extent: “considerable”
Serious/severe side effects ▪ SAEs (excluding bleeding events) ▫ men: hint of lesser harm; extent: “minor”	
▪ Health-related quality of life: outcome not recorded	
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 for the composite outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. Within the individual components of this outcome, there was an indication of a minor added benefit for the outcome “myocardial infarction” (fatal/nonfatal) and, for patients < 65 years, a hint of considerable added benefit for the outcome “stroke” (fatal/nonfatal). There was a hint of lesser harm for the outcome “SAEs” in men in the category “serious/severe side effects”.

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 3 outcomes in the category “non-serious/non-severe side effects”, each with the probability “proof” and the extent “considerable”. The outcomes “discontinuation due to AEs” and “dyspnoea” were not independent from each other because the effect for the outcome “discontinuation due to AEs” was partly based on discontinuation due to dyspnoea.

In comparison with dossier assessment A16-15, there is additionally a hint of lesser harm for the outcome “SAEs” in men (extent: “minor”) as well as proof of greater harm for the outcome “clinically relevant non-severe bleeding events” in all patients (extent: “considerable”) in the balancing of the overall conclusion on the added benefit of ticagrelor + ASA. As discussed in the oral hearing, no data were available on health-related quality of life [8]. Against the background that the data subsequently submitted by the company proved the greater harm from ticagrelor + ASA in comparison with the appropriate comparator therapy with a further outcome and due to the importance of health-related quality of life in the present therapeutic indication, the negative effects called into question the positive effects.

In summary, there is no proof of 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.

This deviates from dossier assessment A16-15, which resulted in an indication of a minor added benefit of ticagrelor + ASA in comparison with the appropriate comparator therapy [1].

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

4 References

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Appendix A – Results on side effects

Table 7: Common AEs (in the SOC and in the PT ≥ 5% in at least one study arm) – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study	Patients with event n (%)	
SOC[a] **PT[a]**	**Ticagrelor + ASA** **N = 5322**	**Placebo + ASA** **N = 5331**
PEGASUS		
Overall rate of adverse events	3762 (70.7)	3606 (67.6)
Infections and infestations	1169 (22.0)	1233 (23.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	240 (4.5)	271 (5.1)
Metabolism and nutrition disorders	456 (8.6)	419 (7.9)
Psychiatric disorders	264 (5.0)	244 (4.6)
Nervous system disorders	701 (13.2)	667 (12.5)
Cardiac disorders	598 (11.2)	656 (12.3)
Vascular disorders	470 (8.8)	483 (9.1)
Respiratory, thoracic and mediastinal disorders	1078 (20.3)	670 (12.6)
Dyspnoea	648 (12.2)	245 (4.6)
Gastrointestinal disorders	1018 (19.1)	942 (17.7)
Skin and subcutaneous tissue disorders	344 (6.5)	361 (6.8)
Musculoskeletal and connective tissue disorders	970 (18.2)	1054 (19.8)
Renal and urinary disorders	267 (5.0)	268 (5.0)
General disorders and administration site conditions	695 (13.1)	775 (14.5)
Non-cardiac chest pain	268 (5.0)	302 (5.7)
Investigations	328 (6.2)	322 (6.0)
Injury, poisoning and procedural complications	428 (8.0)	399 (7.5)

a: MedDRA version 17.0.

AE: adverse event; ASA: acetylsalicylic acid; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 8: Common SAEs (in the SOC and in the PT ≥ 1% in at least one study arm) – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Ticagrelor + ASA N = 5322**	**Placebo + ASA N = 5331**
PEGASUS		
Overall rate of SAEs	1044 (19.6)	1111 (20.8)
Infections and infestations	165 (3.1)	197 (3.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	133 (2.5)	151 (2.8)
Nervous system disorders	69 (1.3)	65 (1.2)
Cardiac disorders	230 (4.3)	224 (4.2)
Atrial fibrillation	54 (1.0)	39 (0.7)
Vascular disorders	67 (1.3)	91 (1.7)
Respiratory, thoracic and mediastinal disorders	85 (1.6)	82 (1.5)
Gastrointestinal disorders	90 (1.7)	91 (1.7)
Musculoskeletal and connective tissue disorders	97 (1.8)	112 (2.1)
Renal and urinary disorders	53 (1.0)	50 (0.9)
General disorders and administration site conditions	118 (2.2)	135 (2.5)
Non-cardiac chest pain	71 (1.3)	79 (1.5)
Injury, poisoning and procedural complications	91 (1.7)	71 (1.3)

a: MedDRA version 17.0.

ASA: acetylsalicylic acid; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Appendix B – Results on sensitivity analyses

Results on the outcome "SAEs" (excluding bleeding events, events of the primary outcome) and on the outcome "SAEs" (excluding bleeding events, events of the primary outcome, all fatal events)

Table 9: Sensitivity analyses (side effects) – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study Outcome category Outcome	Ticagrelor + ASA		Placebo + ASA		Ticagrelor + ASA vs. placebo + ASA
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
PEGASUS					
SAEs (excluding bleeding events, events of the primary outcome)	5322	999 (18.8)	5331	1039 (19.5)	0.96 [0.89; 1.04]; 0.522[a]
SAEs (excluding bleeding events, events of the primary outcome, all fatal events)	5322	974 (18.3)	5331	1016 (19.1)	0.96 [0.89; 1.04]; 0.324[a]

a: Institute's calculation, unconditional exact test (CSZ method according to [6]).

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; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Second and third events using incidence density ratio

Table 10: Sensitivity analyses (morbidity) – RCT, direct comparison: ticagrelor + ASA vs. placebo + ASA (relevant subpopulation)

Study Outcome category Outcome	Ticagrelor + ASA		Placebo + ASA		Ticagrelor + ASA vs. placebo + ASA
	N	Number of recurrent events n	N	Number of recurrent events n	IDR [95% CI]; p-value
PEGASUS					
Cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke	ND	477	ND	589	0.80 [0.68; 0.94]; 0.007

ASA: acetylsalicylic acid; CI: confidence interval; IDR: incidence density ratio; n: number of recurrent events; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; vs.: versus

Influence of temporary modification of the study treatment

Table 11: Sensitivity analyses on the influence of temporary modification of the study treatment (mortality, morbidity) – 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	ND 193 (3.6)	5391	ND 241 (4.5)	0.79 [0.66; 0.96]; 0.016
Cardiovascular mortality	5388	ND 112 (2.1)	5391	ND 158 (2.9)	0.70 [0.55; 0.89]; 0.004
Morbidity (time to event)					
Cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke	5388	ND 361 (6.7)	5391	ND 456 (8.5)	0.78 [0.68; 0.90]; < 0.001
Myocardial infarction (fatal/nonfatal)	5388	ND 220 (4.1)	5391	ND 270 (5.0)	0.81 [0.67; 0.96]; 0.017
Stroke (fatal/nonfatal)	5388	ND 69 (1.3)	5391	ND 92 (1.7)	0.74 [0.54; 1.01]; 0.060

a: Probabilities from Kaplan-Meier analysis.

ASA: acetylsalicylic acid; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: patients with event; ND: no data; RCT: randomized controlled trial; vs.: versus

Appendix C – Subgroup analyses by geographical region to check the consistency of the result

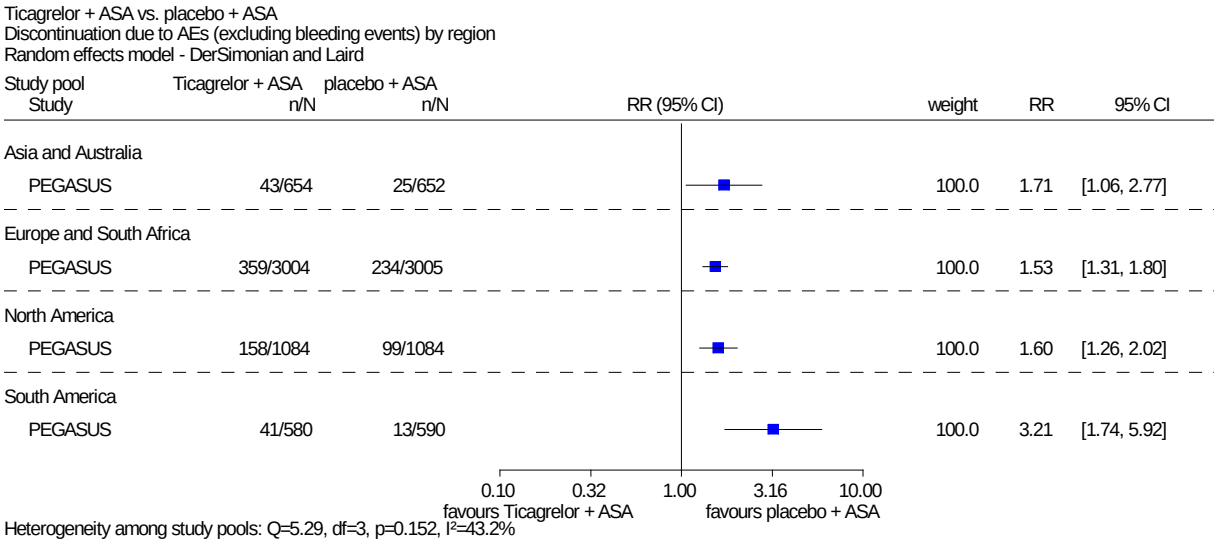

Figure 1: Discontinuation due to AEs (excluding bleeding events) – subgroup analyses by geographical region

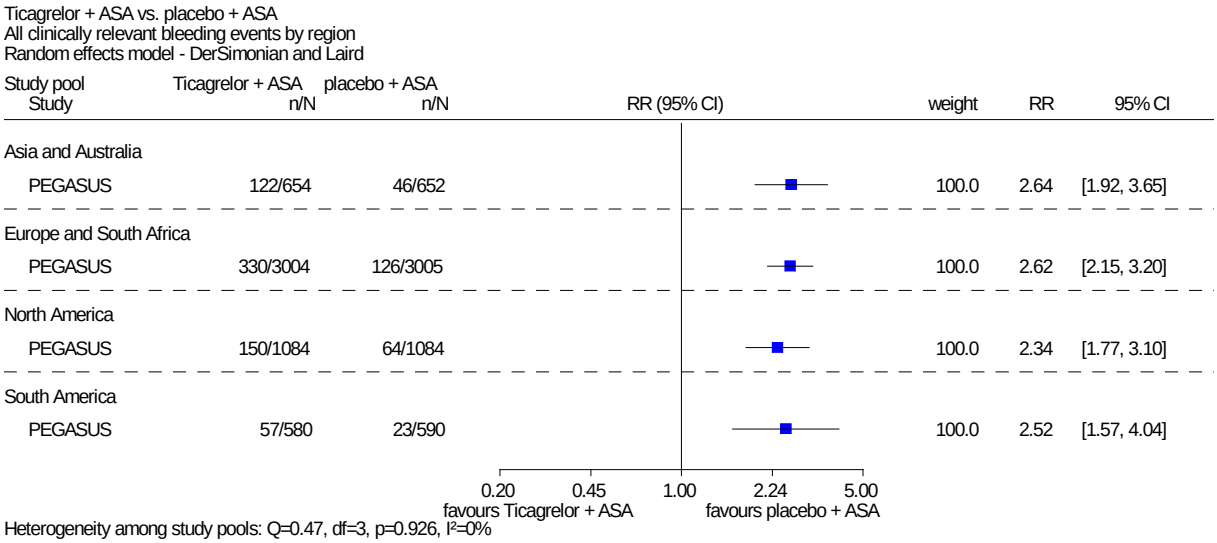

Figure 2: All relevant bleeding events – subgroup analyses by geographical region

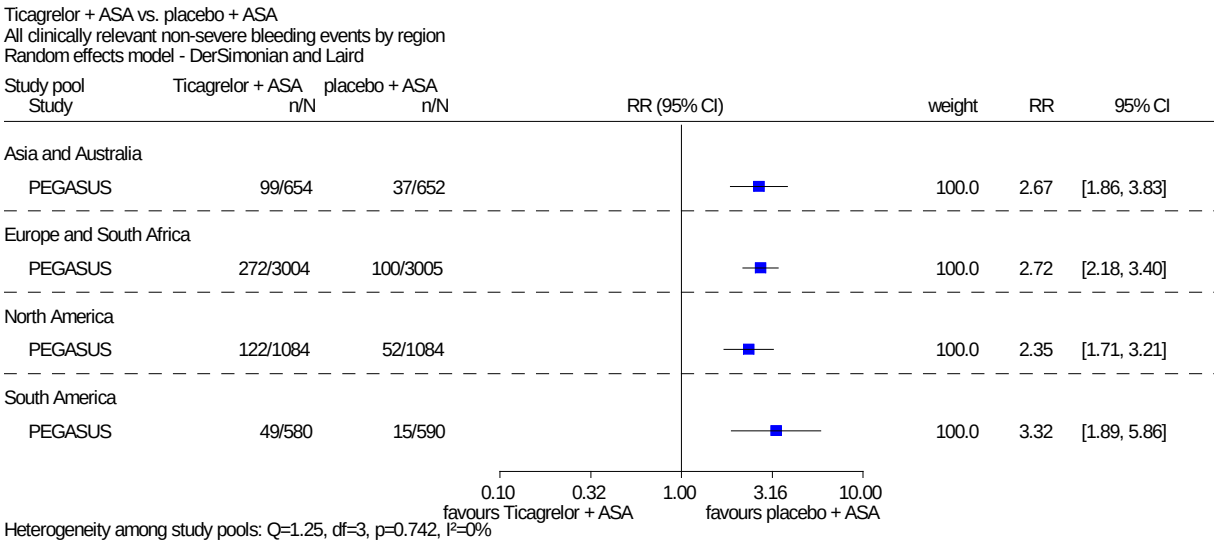

Figure 3: All relevant non-severe bleeding events – subgroup analyses by geographical region