IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A12-20

Apixaban (new therapeutic indication) –

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

Extract

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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
AE	adverse event
ASA	acetylsalicylic acid
$CHADS_2$ score	Sum score for categorizing stroke risk in atrial fibrillation on the basis of the following factors: chronic congestive heart failure (1 point); hypertension (1 point); age ≥ 75 years (1 point); diabetes mellitus (1 point); prior stroke or TIA (2 points)
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
HR	hazard ratio
INR	international normalized ratio
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
NVAF	non-valvular atrial fibrillation
NYHA	New York Heart Association
RCT	randomized controlled trial
SAE	serious adverse event
SE	systemic embolism
SGB	*Sozialgesetzbuch* (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TIA	transient ischaemic attack
TTR	time in therapeutic range
VKA	vitamin K antagonists

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 carry out the benefit assessment of a new therapeutic indication, approved in November 2012, of the drug apixaban. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter "the company"). The dossier was sent to IQWiG on 18.12.2012.

Research question

The present benefit assessment concerns the following new therapeutic indication of apixaban: prevention of stroke and systemic embolism (SE) in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors such as prior stroke or transient ischaemic attack (TIA), age ≥ 75 years, hypertension, diabetes mellitus, symptomatic heart failure (New York Heart Association [NYHA] Class ≥ II).

The G-BA specified the appropriate comparator therapy (ACT) separately for the following 2 populations as:

- Patients who are suitable for treatment with vitamin K antagonists (VKA) (VKA population): VKA (warfarin or phenprocoumon)
- Patients who are not suitable for treatment with VKA (ASA population): acetylsalicylic acid (ASA)

In its dossier, the company followed the specification of the G-BA. One aim of this report is therefore to assess the added benefit of apixaban in comparison with VKA (phenprocoumon or warfarin) in patients suitable for treatment with VKA, in the indication NVAF with one or more risk factors. Another aim of this report is to assess the added benefit of apixaban in comparison with ASA (at the approved dosage of 50 mg to 250 mg daily) in patients unsuitable for treatment with VKA, in the indication NVAF with one or more risk factors.

The assessment was carried out on the basis of randomized controlled trials (RCT) with a minimum duration of 6 months. The following patient-relevant outcomes were used:

- Mortality
  - all-cause mortality
- Morbidity
  - strokes (various operationalizations, including disabling strokes)
  - SE
  - myocardial infarction

- TIA

- Health-related quality of life
- Adverse events
  - bleeds
    - combination: major bleeds and clinically relevant non-major bleeds
    - major bleeds (intracranial and extracranial major bleeds)
    - clinically relevant non-major bleeds
  - overall rate of adverse events (AEs)
  - overall rate of serious adverse events (SAEs)
  - overall rate of AEs that led to treatment discontinuation
- Mortality, morbidity and AEs
  - combination: stroke, SE, major bleeds and mortality

Several operationalizations for the outcome "stroke" were used in both studies. They included strokes of ischaemic, haemorrhagic or uncertain type as well as combinations thereof. The results of all operationalizations were presented for the benefit assessment and primarily the operationalization encompassing all types was used.

Both studies also used various operationalizations regarding the complex "bleeding events". These included bleeds of differing degrees of severity (major and non-major bleeds). Since haemorrhagic strokes were also recorded under major bleeds and thus an overlap existed with the outcome "stroke", major bleeds, especially extracranial bleeds, were used to interpret the outcome.

Results VKA population

One RCT with a direct comparator was included in the assessment (ARISTOTLE). In this study apixaban was compared with warfarin. The risk of bias of the ARISTOTLE study was low, both at study level as well as for all the outcomes considered for which data from the study were available.

Nevertheless, the results of this study point to a heterogeneity of the included countries (even within Europe) regarding the quality of VKA treatment. Analysis of the ARISTOTLE study results with regard to the time a patient spent in the therapeutic range of the international normalized ratio (INR) of 2.0 to 3.0 (time in therapeutic range, TTR), showed interactions for some of the outcomes considered (e.g. $p = 0.021$ for the combined outcome "major bleeds or clinically relevant non-major bleeds"). It can be assumed that the extent of the TTR affects results. However, the TTR is not a baseline characteristic and only arose during the course of the study. It is also possible that the TTR was itself influenced by the therapeutic result (e.g. the occurrence of bleeding events), which is why the TTR is not very suitable as a subgroup-

forming characteristic. Patient characteristics (such as risk of bleeding) may also have influenced the VKA treatment and thus the TTR. Overall, it is not absolutely certain that differences caused by the quality of VKA treatment are illustrated by the TTR alone. Because of the heterogeneity in treatment results from country to country, the extent to which the results of the ARISTOTLE study adequately represent the effect of apixaban treatment in Germany remains unclear. This uncertainty means that despite its sufficient size and methodological quality, the ARISTOTLE study is not suitable for the derivation of proof of added benefit of apixaban, but merely for the derivation of indications.

All-cause mortality

Fewer patients (6.6%) died under treatment with apixaban than under treatment with warfarin (7.4%). The result was statistically significant (hazard ratio (HR) 0.89 [0.80; 1.00]; p = 0.047).

There was an indication of an effect modification (p = 0.116) caused by the characteristic "age". In patients aged < 65 years, the proportion of patients who died was not substantially different between apixaban and warfarin, but the direction of effect differed from that of the total population (HR 1.07 [0.84; 1.35]). In patients aged ≥ 65 years, deaths under warfarin (8.4%) occurred significantly more often than under treatment with apixaban (7.2%; HR 0.85 [0.72; 0.99]).

There was also an indication of an effect modification (p = 0.067) by the characteristic "weight" (≤ 60 kg versus > 60 kg). However, this effect modification did not affect the overall conclusion on the added benefit of apixaban.

Morbidity

Stroke

Statistically significantly fewer patients suffered a stroke under treatment with apixaban (2.2%) than under treatment with warfarin (2.8%; HR 0.79 [0.65; 0.95]). Consideration of the type of stroke (ischaemic, haemorrhagic, uncertain type) showed that most of the events were of the ischaemic type (276 of 449 patients with event [61%]). In addition, the difference in favour of apixaban is essentially due to the lower rate of haemorrhagic strokes (40 (0.4%) versus 78 (0.9%) patients with event; HR 0.51 [0.35; 0.75]; p < 0.001). In the case of ischaemic strokes, there was no noteworthy numerical difference between the treatment groups (1.5% versus 1.5%). The result for the combined outcome "stroke (ischaemic or uncertain type)" was not statistically significant (HR 0.92 [0.74; 1.13]; p = 0.422). The result for the outcome "disabling stroke", which can be used for assessing stroke severity, was not statistically significant (54 (0.6%) versus 64 (0.7%) patients with event; HR 0.84 [0.58; 1.20]).

For the outcome "stroke" (all types) there was an indication of an effect modification (p = 0.062) by the characteristic "age". The proportion of patients aged < 65 years with stroke did not differ substantially between apixaban and warfarin, but the direction of effect differed

from that of the total population (HR 1.22 [0.80; 1.85]). Among patients aged ≥ 65 years, strokes occurred statistically significantly more often under warfarin (3.3%) than under treatment with apixaban (2.4%; HR 0.70 [0.57; 0.87]).

SE, myocardial infarction, TIA

The result was not statistically significant for any of the other morbidity outcomes "SE", "myocardial infarction" and "TIA". For SE and myocardial infarction there were indications of effect modification by each of the characteristics "age" and "weight", but they had no influence on the conclusion regarding these outcomes.

Health-related quality of life

The outcome "quality of life" was not recorded in the ARISTOTLE study. There were therefore no evaluable data on this outcome.

Adverse events - bleeding events

Major bleeds (3.6% versus 5.1%; HR 0.69 [0.60; 0.80]) as well as clinically relevant non-major bleeds (3.5% versus 4.9%; HR 0.70 [0.60; 0.80]) occurred less often under apixaban than under warfarin. In each case, the result was statistically significant and this also applied to the combined outcome of "major and clinically relevant non-major bleeds" (6.8% versus 9.7%; HR 0.68 [0.61; 0.75]). The information about the site of major bleeds revealed that the majority of bleeding events were extracranial (615 of 789 patients with event [78%]). However, the advantage of apixaban was evident both for intracranial (HR 0.42 [0.30; 0.58]) and also for extracranial major bleeds (HR 0.79 [0.68; 0.93]).

For various outcomes regarding the complex "bleeding events", there were indications or proof of an effect modification by individual characteristics, but its relevance could not be interpreted in all cases. None of the characteristics showed a consistent effect modification over all bleeding outcomes. The only remaining effect modification relevant to the overall assessment with respect to the combined bleeding outcome was proof of an effect modification ($p = 0.029$) by the characteristic "geographical region". Such bleeding events occurred in all regions more often under treatment with warfarin than under treatment with apixaban. The result was statistically significant for all regions. The effect was strongest in Asia/Pacific and weakest in North America. The effect was somewhat less pronounced in Europe (HR 0.74 [0.62; 0.88]) than in the global population (HR 0.68 [0.61; 0.753]).

Other analyses of adverse events

A statistically significant advantage of apixaban was evident regarding the overall rate of AEs, overall rate of SAEs and treatment discontinuations due to AEs respectively. However, in each case, data on outcomes already specifically recorded (e.g. ischaemic strokes) were also incorporated. Neither in the company's dossier nor in the study reports were results available on AEs, SAEs and treatment discontinuations due to AEs, in which those events already covered by other outcomes were not included. The event rates on the specifically

recorded outcomes and the outcomes "AE", "SAE" and "treatment discontinuations due to AE", show that scenarios are conceivable for all 3 outcomes in which statistically significant effects result merely through the incorporation of these outcomes and where the effect direction might even be reversed, were such events not incorporated. In the overall assessment of the results, this could lead to a falsification of the balancing of benefit and harm. These outcomes were not considered further because the respective effect sizes cannot be estimated when patients with events regarding already recorded outcomes are not taken into account and hence only actual adverse events of the treatments are included in the effect estimates.

Mortality, morbidity and adverse events

Combined outcome "stroke, SE, major bleeds and mortality"

The combined outcome "stroke, SE, major bleeds and mortality", can support the balancing of benefit and harm, because this outcome contains those serious or fatal events that are important for the area of treatment. In line with the results in some of the individual outcomes (except SE), there was an advantage of apixaban versus warfarin also in this combined outcome (11.1% versus 12.9%; HR 0.85 [0.78; 0.92]). The result was statistically significant ($p < 0.001$).

There was proof of an effect modification by the characteristic "age" ($p = 0.042$). Among patients aged < 65 years, the proportion of patients with event did not differ substantially between apixaban and warfarin, but the direction of effect differed from that of the total population (HR 1.05 [0.87; 1.26]). Among patients aged ≥ 65 years, events of the combined outcome occurred statistically significantly more often under warfarin (15.0%) than under treatment with apixaban (12.2%; HR 0.80 [0.73; 0.88]).

Results ASA population

One RCT with a direct comparator was included in the assessment (the AVERROES study) in which apixaban was compared with ASA. ASA was given at a dose of 81 to 324 mg daily. Approx. 7% of patients were treated with an ASA dose not within the approved range (50 mg to 250 mg). The company therefore presented separate evaluations for the patients treated with the approved dosage and these were used in the present benefit assessment. The AVERROES study showed effect modifications, including for the outcomes "all-cause mortality", "major bleeds" and the combined outcome "stroke, SE, major bleeds and mortality", by the characteristic "ASA dose". However, interpretation of the results concerning this characteristic is difficult because, firstly, the ASA dose can be a characteristic for the risk of complications (e.g. for the risk of bleeding events) as the investigators potentially chose the dose depending on the risk of bleeding or subsequent complications, or also according to local customs. Secondly, the ASA dose can directly influence the treatment results of the comparator group, because in this group (and only in this group), the chosen ASA dose was also used. Since an adequate demarcation of patient groups regarding the intended ASA dose was ultimately not possible (particularly also not for future treatment decisions), results on the effect modifier "ASA dose" were not used in the present benefit

assessment. The certainty of the conclusions of the AVERROES study for the present benefit assessment is, however, reduced because it is unclear whether the results can be generally applied to ASA-treated patients with a risk of complications of any kind.

The AVERROES study differentiated between patients in whom the lack of suitability for VKA treatment had been demonstrated and those in whom this was only expected. This does not raise fundamental questions regarding the informative value of the AVERROES study, but in the present benefit assessment consideration was given to the characteristic "VKA suitability" via the subgroups "unsuitable for VKA treatment (expected versus demonstrated)".

The risk of bias of the AVERROES study was low at study level as well as for all outcomes considered for which data were available from the study. Overall, the AVERROES study was suitable for deriving indications of an added benefit.

Mortality

The result for the outcome "all-cause mortality" was not statistically significant (HR 0.83 [0.65; 1.08]; p = 0.161).

There was an indication for an effect modification by the characteristic "age" (p = 0.082). The proportion of patients aged < 65 years who died did not differ substantially between apixaban and ASA, but the direction of effect differed from that of the total population (HR 1.75 [0.88; 3.48]). Among patients aged ≥ 65 years, deaths occurred statistically significantly more often under ASA (6.6%) than under treatment with apixaban (4.8%; HR 0.75 [0.57; 0.996]).

Morbidity

Stroke

Statistically significantly fewer patients suffered a stroke under treatment with apixaban than under treatment with ASA (1.9% versus 3.8%; HR 0.49 [0.35; 0.69]; p < 0.001). Consideration of the type of stroke (ischaemic, haemorrhagic, uncertain type) showed that most events were of the ischaemic type (112 von 148 patients with event [76%]). In addition, the difference in favour of apixaban was essentially due to the lower rate of ischaemic strokes (1.2% versus 3.1%; HR 0.38 [0.25; 0.58]). Although, in the case of haemorrhagic strokes, there was a numerical difference in favour of apixaban, overall only a few patients suffered an event and the result was not statistically significant (0.2% versus 0.4%; HR 0.67 [0.24; 1.88]). The result for the outcome "disabling stroke", which can be used for assessing stroke severity, likewise showed a statistically significant result in favour of apixaban (0.7% versus 2.0%; HR 0.34 [0.20; 0.58]).

With respect to the outcome "stroke" (all types) there was an indication (p = 0.151) of an effect modification by the characteristic "unsuitable for VKA treatment". In both subgroups (demonstrated and expected unsuitability for VKA therapy) strokes were statistically significantly less frequent under apixaban than under ASA. The effect was more pronounced

in patients from the subgroup “demonstrated” (HR 0.36 [0.20; 0.63]) than in patients from the subgroup “expected” (HR 0.60 [0.39; 0.93]).

SE

There was an advantage in favour of apixaban over ASA for the outcome “SE”. The result was statistically significant (2 (0.1%) versus 13 (0.5%); HR 0.15 [0.04; 0.68]; p = 0.014).

Myocardial infarction

The proportion of patients with a myocardial infarction did not differ substantially between the apixaban and ASA groups (0.9% versus 0.9%; HR 0.96 [0.54; 1.70]; p = 0.892).

TIA

The outcome TIA was not predefined as a separate outcome in the AVERROES study and was not included by the company as a patient-relevant outcome in the assessment of apixaban. Since the company’s dossier did not contain any data on the outcome “TIA” for the ASA population ≤ 250 mg, an assessment in the context of the present benefit assessment was not possible.

Health-related quality of life

The outcome “health-related quality of life” was not recorded in the AVERROES study. Accordingly, no evaluable data for this outcome were available.

Adverse events - bleeding events

Major bleeds (1.6% versus 1.0%; HR 1.54 [0.95; 2.50]; p = 0.080) as well as clinically relevant non-major bleeds (3.3% versus 2.5%; HR 1.32 [0.95; 1.82]; p = 0.095) occurred more frequently under apixaban than under ASA. The result of the individual outcomes was, however, not statistically significant in either case, whereas the result of the combined outcome “major and clinically relevant non-major bleeds” was statistically significant (4.8% versus 3.5%; HR 1.38 [1.05; 1.81]; p = 0.019). Information concerning the site of the major bleeds revealed that about two-thirds of all major bleeds were extracranial. The result for extracranial major bleeds was statistically significant to the disadvantage of apixaban (1.2% versus 0.6%; HR 1.92 [1.05; 3.51]; p = 0.034).

For 3 of the 4 outcomes concerning the complex “bleeding events”, there was an indication or a proof of an effect modification by the characteristic “severity” (measured on the $CHADS_2$ score). It was consistently shown that in patients with a maximum of one risk factor ($CHADS_2$ score ≤ 1), there was no increased risk of bleeding under apixaban. On the other hand, in patients with $CHADS_2$ score > 1, there was consistently an increased risk of bleeding under apixaban. The exception was the outcome “major bleeds”, but this also included haemorrhagic strokes.

Other analyses of adverse events

A statistically significant advantage of apixaban was evident regarding the overall rate of AEs, overall rate of SAEs and treatment discontinuations due to AEs respectively. However, in each case, data on already specifically recorded outcomes (e.g. ischaemic strokes) were also incorporated. Neither in the company‘s dossier nor in the study reports were results available on AEs, SAEs and treatment discontinuations due to AEs in which those events already covered by other outcomes were not included. The event rates on the specifically recorded outcomes show that for the two outcomes “AE” and “treatment discontinuations due to AE”, scenarios are conceivable in which statistically significant effects are caused merely through the incorporation of these outcomes. However, in contrast to the VKA population, there was no evidence that the effect direction might be reversed, were such outcomes not incorporated. For the third outcome “SAE”, the absolute risk difference of 5.2% was even markedly above the added risk difference for stroke and SE of 2.3%. When the individual system organ classes (SOC; data available only for the total population of the study) were considered, it emerged that a marked difference in favour of apixaban was only present in the area “nervous system disorders”. In turn, this was almost exclusively caused by an advantage in the preferred terms “ischaemic stroke”, “cerebrovascular accident” and “transient ischaemic attack”. The advantage of apixaban in the area SAE therefore appears adequately reliably represented by the outcome “stroke”.

Mortality, morbidity and adverse events

Combined outcome “stroke, SE, major bleeds and mortality”

The combined outcome “stroke, SE, major bleeds and mortality”, can support the balancing of benefit and harm, because this outcome contains those serious or fatal events that are important for the area of treatment. The result for the combined outcome was statistically significant in favour of apixaban (6.4% versus 8.7%; HR 0.73 [0.60; 0.89]; p = 0.002). This result is in line with the events observed in the individual outcomes since, in absolute terms, more events were prevented under apixaban (mortality, SE, stroke) than occurred (bleeds).

Extent and probability of added benefit,[4] VKA population

Age < 65 years

Overall, for patients of the VKA population aged < 65 years, there was a positive result with the certainty of result “indication” in favour of apixaban in the complex “bleeding events”. This advantage was apparent for major as well as for clinically relevant non-major bleeds.

[4] On the basis of the scientific data analyzed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analyzed, 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 1-3 cannot be drawn from the available data)), see [1]. 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), see [2].

The extent in terms of the combination bleeding outcome was "considerable", but for extracranial major bleeds it was "minor". The advantage in the complex "bleeding events" was not mirrored in the combined outcome of "stroke, SE, major bleeds and mortality". In numerical terms, more events actually occurred under apixaban for this outcome and also for the outcome "all-cause mortality" even in patients under 65 years. In addition, due to the lack of data, it is unclear whether AEs other than bleeds occurred more frequently or less frequently under apixaban.

In summary, there is no proof of added benefit of apixaban for patients of the VKA population aged < 65 years compared to warfarin.

This deviates from the conclusion of the company, which derived proof of a major added benefit for the total VKA population.

Age ≥ 65 years

Taken as a whole, for patients of the VKA population aged ≥ 65 years there were consistently positive results of the same certainty of result (indication) in favour of apixaban. The extent is "minor" for the outcome "all-cause mortality" and "minor" to "considerable" for the complex "bleeding events". For the combined outcome "stroke, SE, major bleeds and mortality", the extent is "considerable". On the other hand, informative data on AE, SAE and treatment discontinuations due to AE are missing. However, on the basis of the consistently positive results on mortality and on bleeds in this group of patients, it does not appear appropriate to therefore downgrade the extent of the added benefit of apixaban.

In summary, there is an indication of an added benefit (extent: "considerable") of apixaban versus warfarin for patients of the VKA population aged ≥ 65 years.

This deviates from the conclusion of the company, which derived proof a major added benefit for the entire VKA population.

Extent and probability of added benefit, ASA population

Overall, there remain indications of an added benefit, in each case with the extent "considerable", for the outcomes "stroke" and "SE" for the total population. This contrasts with an indication of a greater harm, with the extent "minor" (predominantly "non-major bleeds"). Since there is also an indication of a considerable added benefit in the combined outcome "stroke, SE, major bleeds and mortality", it does not appear appropriate to therefore downgrade the extent of the added benefit of apixaban from "considerable" to "minor". Overall, there is thus an indication of a considerable added benefit of apixaban over ASA in terms of the total population.

None of the identified effect modifications (characteristics "suitability for VKA treatment", "age" and "severity" [measured with the $CHADS_2$ score]) led to an overall balancing of benefit and harm that deviated from that of the total population.

In summary, for the ASA population, there is an indication of a considerable added benefit of apixaban in comparison with ASA.

This deviates from the company's conclusion, which derived proof of a major added benefit for the total ASA population.

Summary of the conclusions regarding extent and probability of the added benefit

On the basis of the results presented, the extent and probability of the added benefit are assessed as follows:

- VKA population: apixaban versus vitamin K antagonist
  - age < 65 years: no proof of added benefit
  - age ≥ 65 years: indication of an added benefit, extent "considerable"
- ASA population: apixaban versus ASA
  - Entire target population: indication of an added benefit, extent "considerable"

The overall conclusions concerning the extent of added benefit are based on the aggregation of the extents of added benefit derived at outcome level.

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

2.2 Research question

The assessment of apixaban was conducted according to the Summary of Product Characteristics (SPC) for the following therapeutic indication: "Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors such as prior stroke or transient ischaemic attack (TIA), age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II)" [3]. Within this therapeutic indication, a distinction was drawn between patients suitable for treatment with VKA (hereinafter: "VKA population"), and patients unsuitable for treatment with VKA (hereinafter: "ASA population"). The ACT was specified separately by the G-BA for these two populations and is shown in Table 2.

Table 2: Patient populations and ACT

Patient population	Appropriate comparator therapy	Comparison
VKA population[a]	VKA (phenprocoumon or warfarin)	Apixaban vs. VKA (phenprocoumon or warfarin)
ASA population[b]	ASA at the approved dosage in the indication (50 mg to 250 mg)	Apixaban vs. ASA
a: In the dossier, the company identified this population as "Patients who are suitable for treatment with vitamin K antagonists". b: In the dossier, the company identified this population as "Patients who are unsuitable for treatment with vitamin K antagonists". ASA: acetylsalicylic acid; VKA: vitamin K antagonist; vs.: versus		

The company followed this ACT.

The objective of this report is therefore to assess the added benefit of:

- Apixaban versus VKA (phenprocoumon or warfarin) in patients of the VKA population and
- Apixaban versus ASA (50 mg to 250 mg) in patients of the ASA population.

The assessment was conducted based on patient-relevant outcomes. Only RCTs with a direct comparator were included in the assessment.

Further information on the research question can be found in Module 3, Section 3.1 and in Modules 4B and 4C, in each case Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

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:

- List of studies on apixaban (studies completed up to 20.11.2012)
- Searches in trial registries for studies on apixaban (last search on 21.11.2012)

Searches by the Institute:

- Searches in trial registries for studies on apixaban to check the search results of the company (last search on 02.01.2013).

The check produced no deviations from the study pool presented in the company's dossier.

Further information on the inclusion criteria for studies in the present benefit assessment and the methods of information retrieval can be found in Modules 4B and 4C, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 3: Study pool – RCT, direct comparison – apixaban versus warfarin (VKA population) and apixaban versus ASA (ASA population)

Research question Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
VKA population			
ARISTOTLE (CV185030)	yes	yes	no
ASA population			
AVERROES (CV185048)	yes	yes	no
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. ASA: acetylsalicylic acid; VKA: vitamin K antagonists			

The study pool corresponded to that of the company.

A further RCT identified by the company, B0661003 (CV185067) [4], was excluded from the assessment, because its treatment duration of 12 weeks did not meet the inclusion criteria concerning study duration in the therapeutic indication under consideration (for explanation, see Section 2.7.2.1 of the full dossier assessment). This study was also excluded by the company for the same reason.

A long-term open-label extension (LTOLE) study in which all suitable patients received open-label apixaban, followed the double-blind, Phase III AVERROES study. Since participation in the LTOLE study was voluntary and approx. one-third of the patients did not take part, it was not considered further during the assessment of the added benefit of apixaban. This also corresponds to the company's approach.

Section 2.6 contains a list of data sources cited by the company for the studies included by the Institute.

Further information about the results of the information retrieval and the resulting study pool can be found in Module 4B, Sections 4.3.1.1 and 4.3.2.1.1 and in Module 4C, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Table 4 and Table 5 describe the studies used for the benefit assessment. The two included studies were active-controlled approval studies of the company, in which the efficacy and safety of apixaban were investigated in comparison with warfarin (ARISTOTLE) or ASA

(AVERROES). Both studies were randomized and double-blind. In the ARISTOTLE study, a total of 18,201 patients and in the AVERROES study a total of 5598 patients were randomized.

The total duration of the ARISTOTLE study covered a treatment period and a follow-up period. The treatment period comprised the period up to the discontinuation of treatment of a patient or until accrual of about 448 primary outcome events (depending on which criterion was met first). The follow-up period covered the period up to 30 days after the treatment discontinuation of a patient or until accrual of about 448 primary outcome events (depending on which criterion was met first). The average duration of the ARISTOTLE study was 1.7 years (1 day to 4.1 years).

Patients in the ARISTOTLE study received 5 mg apixaban twice daily (or 2.5 mg apixaban twice daily in a subgroup of patients who met 2 of the following criteria at randomization: age ≥ 80 years, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dl) or received warfarin (dosage to target INR range 2.0 to 3.0). In addition to apixaban, warfarin-placebo or in addition to warfarin, apixaban-placebo was administered as appropriate.

The total duration of the AVERROES study likewise comprised a treatment period and a follow-up period and/or optional participation in the open-label extension study LTOLE. The treatment period of the AVERROES study covered the period up to the discontinuation of treatment of a patient or until accrual of about 226 events of the primary benefit outcome (depending on which criterion was met first). However, this study was discontinued prematurely after the first planned interim analysis, because of superior efficacy of apixaban based on predefined criteria. The follow-up observation period for patients who did not participate in the open-label extension study (LTOLE) lasted for up to 30 days after ingestion of the last dose of the double-blind study medication. The average duration of the AVERROES study was 1.1 years (1 day to 2.9 years).

Patients in the AVERROES study received apixaban (dosage corresponding to the ARISTOTLE study) or treatment with ASA (81-324 mg once daily) and the respective placebo medication. Furthermore, in the double-blind phase of the AVERROES study, patients received ASA doses of 81 mg to 324 mg daily. In accordance with the specified ACT (ASA at the dosage approved for this indication of 50 mg to 250 mg once daily) [5-7], the company excluded those patients from the assessment who were to receive an ASA dose higher than 250 mg once daily (a total of 395 patients, corresponding to 7.06% of the total population). This approach of the company is accepted and therefore, only those patients of the AVERROES study, who were to receive ASA in the dosage approved for this indication of 50 mg to 250 mg once daily were considered in this assessment (see Section 2.7.1 of the full dossier assessment).

Table 4: Characteristics of the studies included – RCT, direct comparison – apixaban versus warfarin (VKA population) and apixaban versus ASA (ASA population)

Research question **Study**	**Study design**	**Population**	**Interventions (number of randomized patients)**	**Study duration**	**Location and period of study**	**Primary outcome; secondary outcomes**[a]
VKA population						
ARISTOTLE (CV185030)	RCT, double-blind, double-dummy, parallel, multicentre	Adults (men and women ≥ 18 years) with documented non-valvular atrial fibrillation (with or without prior warfarin/VKA treatment) and with at least one additional risk factor for stroke	Apixaban (N = 9120) Warfarin (N = 9081)	Treatment: until earlier event: ▪ Treatment discontinuation of the patient or ▪ Accrual of 448 primary outcome events (cut-off date) Average: 1.7 years (1 day – 4.1 years) Follow-up: until later event: ▪ Up to 30 days after treatment discontinuation of the patient or ▪ Accrual of 448 primary outcome events	40 countries world-wide with a total of 1053 study centres, of which: Asia/Pacific (176), Europe (424), Latin America (137), North America (316) 12/2006 – 05/2011	Primary: combined outcome (stroke or SE) Secondary: all-cause mortality, stroke, SE, myocardial infarction, TIA, bleeds, adverse events

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Table 4: Characteristics of the studies included – RCT, direct comparison – apixaban versus warfarin (VKA population) and apixaban versus ASA (ASA population) (continued)

Research question Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ASA population						
AVERROES (CV185048)	RCT, double-blind, double-dummy, parallel, multicentre	Adults (men and women ≥ 50 years) with documented non-valvular atrial fibrillation and at least one additional risk factor for stroke, who at the time of screening were receiving no VKA treatment for one of the following reasons: ▪ Previous VKA treatment was demonstrated as unsuitable and was therefore terminated. ▪ No previous VKA treatment had taken place, but was expected to be unsuitable.	Apixaban (N = 2807) ASA (N = 2791) of which subpopulation: ASA population ≤ 250 mg[b]: Apixaban (n = 2607) ASA (n = 2596)	Treatment: until earlier event: ▪ Treatment discontinuation of the patient or ▪ Accrual of 226 primary outcome events. Because of superior efficacy of apixaban, the study was prematurely ended after the first planned interim analysis on the basis of predefined criteria. Cut-off date for primary outcome events was 28.05.2010. Average: 1.1 years (1 day – 2.9 years) double-blind phase Follow-up: ▪ Up to 30 days after the last dose of the double-blind study medication	36 countries worldwide with a total of 526 study centres, of which: Asia/Pacific (95), Europe (233), Latin America (98), North America (100)	Primary: combined outcome (stroke and SE) Secondary: all-cause mortality, stroke, SE, myocardial infarction, TIA, bleeds, adverse events

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Table 4: Characteristics of the studies included – RCT, direct comparison – apixaban versus warfarin (VKA population) and apixaban versus ASA (ASA population) (continued)

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for the present benefit assessment.
b: This subpopulation is the relevant population for the benefit assessment.
ASA: acetylsalicylic acid; N: number of randomized patients; n: relevant subpopulation; SE: systemic embolism; TIA: transient ischaemic attack; VKA: vitamin K antagonist

Table 5: Characteristics of the interventions – RCT, direct comparison – apixaban versus warfarin (VKA population) and apixaban versus ASA (ASA population)

Research question Study	Apixaban	Warfarin
VKA population		
ARISTOTLE	Apixaban tablet 5 mg twice daily orally (or 2.5 mg twice daily orally in selected patients[a]) + Warfarin placebo tablet 2 mg 1, 2 or 3 tablets daily[b] orally	Warfarin tablet 2 mg 1, 2 or 3 tablets daily[b] orally + Apixaban placebo tablet 5 mg twice daily orally (or 2.5 mg twice daily orally in selected patients[a])
ASA population		
AVERROES	Apixaban tablet 5 mg twice daily orally (or 2.5 mg twice daily orally in selected patients[a]) + ASA placebo tablet 81 mg 1, 2, or 3 tablets once daily[c] orally	ASA tablet 81 mg 1, 2, or 3 tablets once daily[c] orally + Apixaban placebo tablet 5 mg twice daily orally (or 2.5 mg twice daily orally in selected patients[a])

a: If 2 of the following 3 criteria were met at randomization: age ≥ 80 years, bodyweight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dl.
b: Warfarin/warfarin-placebo was titrated to an INR target range of 2.0 to 3.0.
c: The ASA dosage was left to the investigator's discretion and was specified for each patient at screening before randomization. The dosage was kept constant during the double-blind study, provided an alteration was not clinically indicated.
ASA: acetylsalicylic acid; INR: International Normalized Ratio; VKA: vitamin K antagonist

Table 6 shows the characteristics of the patients in the studies included. In neither study were there were any substantial deviations between the treatment groups for the characteristics considered.

Table 6: Characteristics of the study populations – RCT, direct comparison – apixaban versus warfarin (VKA population) and apixaban versus ASA (ASA population)

Research question Study Group	N	Age [years] mean (SD)	Sex f/m %	Previous VKA treatment [yes / no] n (%)	Unsuitable for VKA treatment [demonstrated/ expected] n (%)	Geographical region			
						North America n (%)	Latin America n (%)	Europe n (%)	Asia/ Pacific n (%)
VKA population									
ARISTOTLE									
Apixaban	9120	69 (10)	36 / 64	5208 (57) / 3912 (43)	-[a]	2249 (25)	1743 (19)	3672 (40)	1456 (16)
Warfarin	9081	69 (10)	35 / 65	5193 (57) / 3888 (43)	-[a]	2225 (25)	1725 (19)	3671 (40)	1460 (16)
ASA-population									
AVERROES									
Apixaban	2607	70 (9)	42 / 58	-[a]	999 (38) / 1608 (62)	285 (11)	575 (22)	1205 (46)	542 (21)
ASA	2596	70 (10)	42 / 58	-[a]	1008 (39) / 1588 (61)	290 (11)	582 (22)	1181 (46)	543 (21)

a: Characteristic not recorded
ASA: acetylsalicylic acid; f: female, m: male; N: number of randomized patients; n: number of patients; SD: standard deviation; VKA: vitamin K antagonist

Table 7 shows the risk of bias at study level.

Table 7: Risk of bias at study level – RCT, direct comparison – apixaban vs. warfarin (VKA population) and apixaban vs. ASA (ASA population)

Research question Study	Adequate randomization sequence generation	Allocation concealment	Blinding		No indications of selective reporting	No other sources of bias	Risk of bias at study level
			Patient	Treating staff			
VKA population							
ARISTOTLE	yes	yes	yes	yes	yes	yes	low
ASA population							
AVERROES	yes	yes	yes	yes	yes	no[a]	low

a: The adjusted effect estimates and confidence intervals planned in the case of premature study discontinuation were not reported

ASA: acetylsalicylic acid; VKA: vitamin K antagonist

The risk of bias at study level was rated as low for both studies. This concurs with the company's assessment.

Further information on study design, study populations and the risk of bias at study level can be found in Module 4B and Module 4C, Sections 4.3.1.2.1. 4.3.1.2.2 as well as in Appendix 4-G of the dossier and in Sections 2.7.2.2, 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

The following patient-relevant outcomes were considered in the present assessment (for reasons, see Sections 2.7.2.2 and 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - strokes (various operationalizations, including disabling strokes)
  - SE
  - myocardial infarction
  - TIA
- Health-related quality of life

- Adverse events
  - bleeding events
    - combination: major bleeds and clinically relevant non-major bleeds
    - major bleeds (intracranial and extracranial major bleeds)
    - clinically relevant non-major bleeds
  - overall rate of AEs
  - overall rate of SAEs
  - overall rate of AEs that led to treatment discontinuation
- Mortality, morbidity and adverse events
  - combination: stroke, SE, major bleeds and mortality

Several operationalizations for the outcome “stroke” were used in both studies. They included strokes of ischaemic, haemorrhagic or uncertain type as well as combinations thereof. The results of all operationalizations were presented for the benefit assessment and primarily the operationalization encompassing all types was used.

Both studies also used various operationalizations regarding the complex “bleeding events”. These included bleeds of varying degrees of severity (major and non-major bleeds). Since haemorrhagic strokes were also recorded under major bleeds and thus an overlap existed with the outcome “stroke”, major bleeds, especially extracranial bleeds, were used for the interpretation of the outcome.

The choice of patient-relevant outcomes deviated from that of the company, who used other outcomes (especially combined) in the dossier (Module 4B and Module 4C). In addition the following outcomes not considered by the company were included: “health-related quality of life” and “TIA” (see also Sections 2.7.2.2 and 2.7.2.4.3 of the full dossier assessment for the explanation of the choice of outcomes).

Table 8 shows for which outcomes data were available from the studies included. Table 9 describes the risk of bias for these outcomes.

Table 8: Matrix of outcomes – RCT, direct comparison – apixaban versus warfarin (VKA population) and apixaban versus ASA (ASA population)

Research question / **Study**	**All-cause mortality**	**Stroke (all operationalizations)**	**SE**	**Myocardial infarction**	**TIA**	**Health-related quality of life**	**Bleeding events (all operationalizations)**	**Overall rate of AEs**	**Overall rate of SAEs**	**Overall rate of treatment discontinuations due to AE**	**Stroke, SE, major bleeds or mortality**
VKA population											
ARISTOTLE	yes	yes	yes	yes	yes[a]	-[b]	yes	(yes)[c]	(yes)[c]	(yes)[c]	yes
ASA population											
AVERROES	yes	yes	yes	yes	-[d]	-[b]	yes	(yes)[c]	(yes)[c]	(yes)[c]	yes

a: Institute's calculation, TIA event rates were taken from the "List of supplemental tables - Final Clinical Study Report" of the ARISTOTLE study report.
b: Outcome was not recorded.
c: Data on AE, SAE and treatment discontinuations due to AE usable to only a limited extent because, in each case, specifically recorded outcomes (such as ischaemic strokes) were also incorporated; see also Sections 2.4.1.1 and 2.4.2.1.
d: No data available for the population of interest

AE: adverse event; ASA: acetylsalicylic acid; SAE: serious adverse event; SE: systemic embolism; TIA: transient ischaemic attack; VKA: vitamin K antagonist

Table 9: Risk of bias at study and outcome level – RCT, direct comparison – apixaban versus warfarin (VKA population) and apixaban versus ASA (ASA population)

Research question / **Study**		**Outcomes**										
	Study level	**All-cause mortality**	**Stroke (all operationalizations)**	**SE**	**Myocardial infarction**	**TIA**	**Health-related quality of life**	**Bleeding events (all operationalizations)**	**Overall rate of AEs**	**Overall rate of SAEs**	**Overall rate of treatment discontinuations due to AE**	**Stroke, SE, major bleeds or mortality**
VKA population												
ARISTOTLE	n	n	n	n	n	n	-[a]	n	(n)[b]	(n)[b]	(n)[b]	n
ASA population												
AVERROES	n	n	n	n	n	-[c]	-[a]	n	(n)[b]	(n)[b]	(n)[b]	n

a: Outcome was not recorded.
b: Data on AE, SAE and treatment discontinuations due to AE usable to only a limited extent because, in each case, specifically recorded outcomes elsewhere (such as ischaemic strokes) were also incorporated; see also Sections 2.4.1.1 and 2.4.2.1.
c: No data available for the population of interest
AE: adverse event; ASA: acetylsalicylic acid; SAE: serious adverse event; SE: systemic embolism; TIA: transient ischaemic attack; VKA: vitamin K antagonist

Apart from the data not available on the outcomes "TIA" (ASA population) and the non-recorded data on "health-related quality of life" (both populations), all relevant outcomes were reported (see Table 8). For proper observance of the ITT principle, the "intended" treatment period instead of the "actual" treatment period should, however, have been evaluated also for adverse events (for explanation, see Section 2.7.2.4.1 of the full dossier assessment).

The risk of bias for all outcomes was rated as low. The results on overall rates of AE, SAE and treatment discontinuations due to AE were not used for the benefit assessment because, in each case, events relating to specifically recorded outcomes (such as ischaemic strokes) were also incorporated (see Sections 2.4.1.1 and 2.4.2.1).

The assessment of risk of bias concurs with that of the company, provided the outcomes were also used by the company.

Further information about the choice of outcomes and risk of bias at outcome level can be found in Modules 4B and 4C, in each case Sections 4.3.1.2.2, 4.3.1.3 of the dossiers and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.4.1 Results for the VKA population

The results for the VKA population are shown in the following sections. Based on the ARISTOTLE study, due to the questionable applicability of the results to Germany, at most indications of an added benefit can be derived (for reasons, see Section 2.7.2.4.1 of the full dossier assessment). The results of the total population of the ARISTOTLE study are shown in Section 2.4.1.1. Conclusions regarding the added benefit at outcome level are reached in Section 2.4.1.2 (subgroup analyses), since indications or proof of effect modifications arose for some outcomes for some subgroups.

2.4.1.1 Overall results for the VKA population

Table 10 summarizes the results from the comparison of apixaban versus warfarin in patients of the VKA population. Where necessary, the data from the company's dossier were supplemented by the Institute's own calculations.

Table 10: VKA population: results – RCT, direct comparison, apixaban versus warfarin

Study Outcome category Outcome	Apixaban N	Apixaban Patients with events n (%)	Warfarin N	Warfarin Patients with events n (%)	Apixaban vs. warfarin HR [95% CI]; p-value
ARISTOTLE					
Mortality[a]					
All-cause mortality	9120	603 (6.6)	9081	669 (7.4)	0.89 [0.80; 1.00]; 0.047
Morbidity[a]					
Stroke (ischaemic,[b] haemorrhagic or uncertain type)	9120	199 (2.2)	9081	250 (2.8)	0.79 [0.65; 0.95]; 0.012
Stroke (ischaemic[b] or uncertain type)	9120	162 (1.8)	9081	175(1.9)	0.92 [0.74; 1.13]; 0.422
Stroke (ischaemic[c])	9120	140 (1.5)	9081	136 (1.5)	1.02 [0.81; 1.29]; 0.871
Stroke (haemorrhagic)	9120	40 (0.4)	9081	78 (0.9)	0.51 [0.35; 0.75]; < 0.001
Stroke (uncertain type)	9120	14 (0.2)	9081	21 (0.2)	0.65 [0.33; 1.28]; 0.212
Disabling stroke	9120	54 (0.6)	9081	64 (0.7)	0.84 [0.58; 1.20]; 0.338
Systemic embolism	9120	15 (0.2)	9081	17 (0.2)	0.87 [0.44; 1.75]; 0.702
Myocardial infarction	9120	90 (1.0)	9081	102 (1.1)	0.88 [0.66; 1.17]; 0.372
TIA	9120	70 (0.8)	9081	54 (0.6)	1.29[d] [0.91; 1.84]; 0.176[e]
Health-related quality of life					
Outcome not recorded					

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Table 10: VKA population: results – RCT, direct comparison, apixaban versus warfarin (continued)

Study Outcome category Outcome	Apixaban		Warfarin		Apixaban vs. warfarin
	N	Patients with events n (%)	N	Patients with events n (%)	HR [95% CI]; P-value
Adverse events[f]					
Major bleeds[g] or clinically relevant non-major bleeds[h]	9088	613 (6.8)	9052	877 (9.7)	0.68 [0.61; 0.753]; < 0.001
Major bleeds[g]	9088	327 (3.6)	9052	462 (5.1)	0.69 [0.60; 0.80]; < 0.001
Intracranial major bleeds[g]	9088	52 (0.6)	9052	122 (1.4)	0.42 [0.30; 0.58]; < 0.001
Major bleeds[g] other site (extracranial, including gastrointestinal)	9088	275 (3.0)[i]	9052	340 (3.8)[i]	0.79 [0.68; 0.93]; 0.004
Clinically relevant non-major bleeds[h]	9088	318 (3.5)	9052	444 (4.9)	0.70 [0.60; 0.804]; < 0.001
Overall rate AE	9088	7406 (81.5)	9052	7521 (83.1)	0.93 [0.90; 0.96]; < 0.001
Overall rate SAE	9088	3182 (35.0)	9052	3302 (36.5)	0.94 [0.89; 0.99]; 0.010
Treatment discontinuations due to AE	9088	688 (7.6)	9052	758 (8.4)	0.89 [0.81; 0.99]; 0.031
Mortality[a], morbidity[a] and adverse events[f]					
Stroke (ischaemic,[b] haemorrhagic or uncertain type), SE, major bleeds[g] or mortality	9120	1009 (11.1)	9081	1168 (12.9)	0.85 [0.78; 0.92]; < 0.001

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Table 10: VKA population: results – RCT, direct comparison, apixaban versus warfarin (continued)

a: Analysis period: intended treatment period. Period that starts on the day of randomization and ends with the efficacy cut-off date. The efficacy cut-off date was specified and documented before the study was unblinded.
b: With or without haemorrhagic transformation
c: Without haemorrhagic transformation
d: Relative risk, point estimate and confidence interval Institute's calculation, asymptotic
e: P-value, Institute's calculation, Fisher's exact test
f: Analysis period: Treatment period. Period in which measured values or events from the start of the first dose of the blinded study medication to 2 days after the last dose for bleeding outcomes, bleeding-related serious or non-serious adverse events and 30 days after the last dose for deaths as serious adverse event and all serious adverse events were summarized.
g: At least one of the following criteria: decrease in haemoglobin level ≥ 2 g/dl over a 24-hour period, transfusion of 2 or more units of packed red cells, bleeding in at least one critical body region (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal), fatal bleeding
h: Clinically overt bleeding that does not correspond to the additional criteria of major bleeds and which meets at least one of the following criteria: led to hospitalization, medical or surgical treatment by a doctor, modification of the antithrombotic treatment
i: Percentages calculated by Institute

AE: adverse event; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; SAE: serious adverse event; TIA: transient ischaemic attack

Mortality

All-cause mortality

Fewer patients died under treatment with apixaban than under treatment with warfarin. The result was statistically significant.

Morbidity

Stroke

Statistically significantly fewer patients suffered a stroke under treatment with apixaban than under treatment with warfarin. Consideration of the type of stroke (ischaemic, haemorrhagic, uncertain type) showed that most of the events were of the ischaemic type (276 of 449 patients with event [61%]). In addition, the difference in favour of apixaban is essentially due to the lower rate of haemorrhagic strokes (40 (0.4%) versus 78 (0.9%) patients with event; HR 0.51 [0.35; 0.75]; $p < 0.001$). In the case of ischaemic strokes, there was no noteworthy numerical difference between the treatment groups.

The result for the outcome "disabling stroke", which can be used for assessing stroke severity, was not statistically significant.

SE, myocardial infarction, TIA

For none of the other morbidity outcomes "SE", "myocardial infarction" or "TIA", was the result statistically significant.

Health-related quality of life

The outcome "health-related quality of life" was not recorded in the ARISTOTLE study. There are therefore no evaluable data on this outcome.

Adverse events

Bleeding events

Major bleeds as well as clinically relevant non-major bleeds occurred less frequently under apixaban. In each case, the result was statistically significant and this also applied to the combined outcome of “major and clinically relevant non-major bleeds”.

The information about the site of major bleeds revealed that the majority of bleeds were extracranial (615 of 789 patients with event [78%]). However, the advantage of apixaban was evident both for intracranial (in line with the results on haemorrhagic strokes shown under “strokes”) and also for extracranial bleeds.

There was a statistically significant advantage of apixaban regarding the overall rate of AEs, overall rate of SAEs and treatment discontinuations due to AEs respectively. However, in each case, data on already specifically recorded outcomes (e.g. ischaemic strokes) were also incorporated. Neither in the company‘s dossier nor in the study reports were results available on AEs, SAEs and treatment discontinuations due to AEs, in which those events already covered by other outcomes were not included. The event rates on the specifically recorded outcomes and the outcomes “AE”, “SAE” and “treatment discontinuations due to AE”, show that scenarios are conceivable for all 3 outcomes, in which statistically significant effects result merely through the incorporation of these outcomes and in which the effect direction might even be reversed, were such events not incorporated. In the overall assessment of the results, this could lead to a falsification of the balancing of benefit and harm. Since the respective effect sizes cannot be estimated when patients with events regarding already recorded outcomes are not taken into account and therefore only actual adverse events of the treatments are included in the effect estimates, these outcomes were not considered further.

Mortality, morbidity and adverse events

Stroke, SE, major bleeds and mortality

The combined outcome “stroke, SE, major bleeds and mortality”, can support the balancing of benefit and harm, because this outcome contains those serious or fatal events that are important for the area of treatment.

In line with the results the individual outcomes (except SE), there was also an advantage of apixaban in this combined outcome. The result was statistically significant.

2.4.1.2 Subgroup analyses on the VKA population

To identify possible effect modifiers, certain subgroups were investigated in detail to determine whether heterogeneous treatment effects were present. In the company’s dossier,

interaction tests between the treatment and grouping variable were conducted using the chi-squared test according to Wald in the Cox proportional hazards model, into which the covariables for treatment group, grouping variable and interaction of treatment and grouping variable were entered.

Corresponding investigations were carried for the following (subgroup) characteristics (for explanation of the selection, see Section 2.7.2.2 of the full dossier assessment):

- Geographical region (North America/Latin America/Europe/Asia and Pacific region)
- Age (< 65/≥ 65 – < 75/≥ 75 years)
- Sex (male/female)
- Weight (≤ 60 kg/> 60 kg)
- Renal dysfunction (severe or moderate [≤ 50 ml/min]/mild [> 50-80 ml/min]/none [> 80 ml/min])
- $CHADS_2$ sum score for classifying the risk of stroke (≤ 1/2/≥ 3)

The investigation was performed for the outcomes:

- All-cause mortality
- Stroke (ischaemic, haemorrhagic or uncertain type)
- SE
- Myocardial infarction
- Complex of bleeding events
  - Combination outcome: major bleeds and clinically relevant non-major bleeds
  - major bleeds
  - major bleeds extracranial
  - clinically relevant non-major bleeds
- Combination outcome: “stroke, SE, major bleeds or all-cause mortality”

All subgroup characteristics, as well as their intensity or thresholds, were predefined in the ARISTOTLE study.

The company submitted the corresponding analyses for all the outcomes that it classed as relevant. Its dossier also contained subgroup analyses of other characteristics that are not considered further here (see Section 2.7.2.2 of the full dossier assessment).

Only the results for subgroups and outcomes that gave at least indications of an interaction between treatment effect and subgroup are presented below. The condition for proof of

different subgroup effects was a statistically significant interaction ($p < 0.05$). A p-value of ≥ 0.05 and < 0.2 provided an indication of an effect modification.

All-cause mortality

With the outcome "all-cause mortality", there were indications of effect modification by the characteristics "age" and "weight". Table 11 shows the relevant results.

Table 11: VKA population: subgroups – outcome "all-cause mortality" according to age and weight, RCT, direct comparison, apixaban versus warfarin

Study Characteristic Subgroup	Apixaban		Warfarin		Apixaban vs. warfarin	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	HR [95% CI]	P-value[b]
ARISTOTLE						
Age (years)						0.116
< 65	2731	143 (5.2)	2740	134 (4.9)	1.07 [0.84; 1.35]	
≥ 65[c]	6389	460 (7.2)	6341	535 (8.4)	0.85 [0.72; 0.99]	
≥ 65 - < 75	*3539*	*179 (5.1)*	*3513*	*229 (6.5)*	*0.77 [0.64; 0.94]*	
≥ 75	*2850*	*281 (9.9)*	*2828*	*306 (10.8)*	*0.91 [0.78; 1.07]*	
Weight (kg)						0.067
≤ 60	1018	122 (12.0)	967	107 (11.1)	1.11 [0.86; 1.44]	
> 60	8070	479 (5.9)	8084	560 (6.9)	0.85 [0.75; 0.96]	

Numbers in italics: subgroups (from primary subgroup analyses), that were combined; see also text below
a: All percentages: Institute's calculation
b: Interaction test (relative to original subgroups)
c: Combination of the subgroups ≥ 65 – < 75 and ≥ 75, because paired comparison showed no heterogeneity, see also text below; all values Institute's calculation
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event

Age

The investigation across all 3 age groups showed an indication ($p = 0.116$) of an effect modification. The paired comparison of adjacent subgroups revealed that the subgroup < 65 years was statistically significantly different (at level 0.2) from the subgroup aged ≥ 65 – < 75 years ($p = 0.041$) and the latter subgroup was comparable with the subgroup ≥ 75 years ($p = 0.208$). The effects of age groups ≥ 65 – < 75 years and ≥ 75 years were therefore combined to a joint effect.

In patients aged < 65 years, the proportions of patients who died did not differ substantially between apixaban and warfarin, but the direction of effect differed from that of the total population (HR 1.07 [0.84; 1.35]). In patients aged ≥ 65 years, deaths occurred statistically significantly more frequently under warfarin (8.4%) than under treatment with apixaban (7.2%; HR 0.85 [0.72; 0.99]).

Weight

There was also an indication of an effect modification by the characteristic "weight" (p = 0.067).

In patients weighing ≤ 60 kg, the proportion of patients who died did not differ substantially between apixaban and warfarin, but the direction of effect differed from that of the total population (HR 1.11 [0.86; 1.44]). In patients weighing > 60 kg, deaths occurred statistically significantly more frequently under warfarin (6.94%) than under treatment with apixaban (5.9%; HR 0.85 [0.75; 0.96]).

Stroke

With respect to the outcome "stroke" (ischaemic, haemorrhagic or uncertain type), there was an indication of an effect modification by the characteristic "age". Table 12 shows the relevant results.

Table 12: VKA population: subgroups – outcome "stroke" (ischaemic, haemorrhagic, or uncertain type) according to age, RCT, direct comparison, apixaban versus warfarin

Study Characteristic Subgroup	Apixaban		Warfarin		Apixaban vs. warfarin	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	HR [95% CI]	P-value[b]
ARISTOTLE						
Age (years)						0.062
< 65	2731	49 (1.8)	2740	40 (1.5)	1.22 [0.80; 1.85]	
≥ 65[c]	6389	150 (2.4)	6341	210 (3.3)	0.70 [0.57; 0.87]	
≥ 65 – < 75	*3539*	*74 (2.1)*	*3513*	*109 (3.1)*	*0.67 [0.50; 0.90]*	
≥ 75	*2850*	*76 (2.7)*	*2828*	*101 (3.6)*	*0.74 [0.55; 0.997]*	

Numbers in italics: subgroups (from primary subgroup analyses), that were combined; see also text below
a: All percentages: Institute's calculation
b: Interaction test (relative to original subgroups)
c: Combination of the subgroups ≥ 65 – < 75 and ≥ 75, because paired comparison showed no heterogeneity, see also text below; all values Institute's calculation
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event

The investigation across all 3 age groups showed an indication (p = 0.062) of an effect modification. The paired comparison of adjacent subgroups revealed that the subgroup < 65 years was statistically significantly different (at level 0.2) from the subgroup aged ≥ 65 – < 75 years (p = 0.022) and the latter subgroup was comparable with the subgroup ≥ 75 years (p = 0.642). The effects of age groups ≥ 65 – < 75 years and ≥ 75 years were therefore combined to a joint effect.

In patients aged < 65 years, the proportions of patients with stroke did not differ substantially between apixaban and warfarin, but the direction of effect differed from that of the total

population (HR 1.22 [0.80; 1.85]). In patients aged ≥ 65 years, strokes occurred statistically significantly more frequently under warfarin (3.3%) than under treatment with apixaban (2.4%; HR 0.70 [0.57; 0.87]).

SE

With respect to the outcome "SE", there were indications of effect modification by the characteristics "age" and "weight". Table 13 shows the relevant results.

Table 13: VKA population: subgroups – outcome "systemic embolism" according to age and weight, RCT, direct comparison, apixaban versus warfarin

Study Characteristic Subgroup	Apixaban		Warfarin		Apixaban vs. warfarin	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	HR [95% CI]	P-value[b]
ARISTOTLE						
Age (years)						0.128
< 65	2731	2 (0.1)	2740	4 (0.1)	0.51 [0.09; 2.81]	
≥ 65 – < 75	3539	9 (0.3)	3513	4 (0.1)	2.23 [0.69; 7.25]	
≥ 75	2850	4 (0.1)	2828	9 (0.3)	0.44 [0.14; 1.43]	
Weight (kg)						0.155
≤ 60	1018	2 (0.2)	967	6 (0.6)	0.32 [0.07; 1.60]	
> 60	8070	13 (0.2)	8084	11 (0.1)	1.18 [0.53; 2.64]	

a: All percentages: Institute's calculation
b: Interaction test
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event

Age

The investigation across all 3 age groups showed an indication (p = 0.128) of an effect modification. The results of the adjacent subgroups, each with a low event rate and imprecise estimation, were not similar and therefore no paired interaction tests were conducted.

In the individual age groups and also in the total population, the proportions of patients with SE did not differ substantially between apixaban and warfarin. Overall, there were therefore no further consequences from this indication of effect modification.

Weight

There was also an indication (p = 0.155) of an effect modification by the characteristic "weight".

In neither of the two weight groups nor in the total population did the proportions of patients with SE differ substantially between apixaban and warfarin. Overall, there were therefore no further consequences from this indication of effect modification.

Myocardial infarction

With respect to the outcome "myocardial infarction", there were indications of effect modification by the characteristics "age" and "weight". Table 14 shows the relevant results.

Table 14: VKA population: subgroups – outcome "myocardial infarction" according to age and weight, RCT, direct comparison, apixaban versus warfarin

Study Characteristic Subgroup	Apixaban		Warfarin		Apixaban vs. warfarin	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	HR [95% CI]	P-value[b]
ARISTOTLE						
Age (years)						0.185
< 65	2731	15 (0.5)	2740	27 (1.0)	0.56 [0.30; 1.06]	
≥ 65 – < 75	3539	34 (1.0)	3513	40 (1.1)	0.84 [0.53; 1.32]	
≥ 75	2850	41 (1.4)	2828	35 (1.2)	1.16 [0.74; 1.82]	
Weight (kg)						0.150
≤ 60	1018	11 (1.1)	967	6 (0.6)	1.73 [0.64; 4.69]	
> 60	8070	79 (1.0)	8084	96 (1.2)	0.82 [0.61; 1.10]	

a: All percentages: Institute's calculation
b: Interaction test
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event

Age

The investigation across all 3 age groups showed an indication (p = 0.185) of an effect modification. The results of the adjacent subgroups, each with imprecise estimation, were similar and therefore no paired interaction tests were conducted.

Neither in the individual age groups nor in the total population did the proportions of patients with myocardial infarction differ substantially between apixaban and warfarin. Overall, there were therefore no further consequences from this indication of effect modification.

Weight

There was also an indication (p = 0.150) of an effect modification by the characteristic "weight".

In neither of the two weight groups nor in the total population did the proportions of patients with myocardial infarction differ substantially between apixaban and warfarin. Overall there were therefore once again no further consequences from this indication of effect modification.

Bleeding events

With respect to the various bleeding outcomes there were indications or proof of effect modifications by individual characteristics. These are shown below. The conclusions about

the importance of the observed effect modifications for the complex "bleeding events" are summarized after the description of the various outcomes.

Combination: major bleeds and clinically relevant non-major bleeds

For the combined outcome "major bleeds or clinically relevant non-major bleeds" there was proof for the characteristic "region", and an indication for the characteristic "weight" of an effect modification. Table 15 shows the relevant results.

Table 15: VKA population: subgroups – outcome "major bleeds or clinically relevant non-major bleeds" according to geographical region and weight, RCT, direct comparison, apixaban versus warfarin

Study Characteristic Subgroup	Apixaban		Warfarin		Apixaban vs. warfarin	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	HR [95% CI]	P-value[b]
ARISTOTLE						
Geographical region						0.029
North America	2244	193 (8.6)	2219	247 (11.1)	0.78 [0.64; 0.94]	
Latin America	1739	115 (6.6)	1721	171 (9.9)	0.64 [0.50; 0.81]	
Europe	3657	217 (5.9)	3656	286 (7.8)	0.74 [0.62; 0.88]	
Asia/Pacific	1448	88 (6.1)	1456	173 (11.9)	0.49 [0.38; 0.63]	
Weight (kg)						0.071
≤ 60	1013	55 (5.4)	965	101 (10.5)	0.51 [0.37; 0.71]	
> 60	8043	555 (6.9)	8059	773 (9.6)	0.70 [0.63; 0.78]	

a: All percentages: Institute's calculation
b: Interaction test
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event

Geographical region

The investigation across all 4 regions showed proof (p = 0.029) of an effect modification.

In all regions, bleeding events occurred more frequently under treatment with warfarin than under treatment with apixaban. The result was statistically significant for all regions, with the effect most pronounced in Asia/Pacific and least in North America. The effect was a little less pronounced in Europe (HR 0.74 [0.62; 0.88]) than in the total population (HR 0.68 [0.61; 0.753]).

Weight

There was an indication (p = 0.071) of an effect modification by the characteristic "weight".

The result was statistically significant for both weight groups and the direction of effect corresponded to that of the total population. Since there was an effect modification in terms of the characteristic "geographical region" and the effect observed in Europe was less

pronounced than that in the total population, analyses stratified for Europe would be necessary to enable a conclusive interpretation of the effect sizes of the respective weight groups. Since no such analyses were available, they are not considered further.

Major bleeds

With respect to the outcome "major bleeds" there was proof of an effect modification by the characteristic "renal dysfunction" and there was an indication of an effect modification by the characteristics "region" and "sex". Table 16 shows the relevant results.

Table 16: VKA population: subgroups – outcome "major bleeds" according to geographical region, sex and renal dysfunction, RCT, direct comparison, apixaban versus warfarin

Study Characteristic Subgroup	Apixaban		Warfarin		Apixaban vs. warfarin	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	HR [95% CI]	P-value[b]
ARISTOTLE						
Geographical region						0.164
North America	*2244*	*106 (4.7)*	*2219*	*137 (6.2)*	*0.77 [0.60; 0.997]*	
Latin America	*1739*	*60 (3.5)*	*1721*	*94 (5.5)*	*0.60 [0.44; 0.84]*	
Europe	*3657*	*110 (3.0)*	*3656*	*135 (3.7)*	*0.80 [0.62; 1.02]*	
Asia/Pacific	*1448*	*51 (3.5)*	*1456*	*96 (6.6)*	*0.52 [0.37; 0.74]*	
North America/ Europe[c]	5901	216 (3.7)	5875	272 (4.6)	0.79 [0.66; 0.94]	
Latin America/ Asia/Pacific[c]	3187	111 (3.5)	3177	190 (6.0)	0.57 [0.45; 0.71]	
Sex						0.082
Male	5868	225 (3.8)	5879	294 (4.2)	0.76 [0.64; 0.90]	
Female	3220	102 (3.2)	3173	168 (5.3)	0.58 [0.45; 0.74]	
Renal dysfunction (calculated creatinine clearance in ml/min)						0.028
severe or moderate (≤ 50)	1493	73 (4.9)	1512	142 (9.4)	0.50 [0.38; 0.67]	
mild / none[d]	7557	253 (3.3)	7504	318 (4.2)	0.78 [0.66; 0.92]	
mild (> 50-80)	*3807*	*157 (4.1)*	*3758*	*199 (5.3)*	*0.77 [0.62; 0.94]*	
none (> 80)	*3750*	*96 (2.6)*	*3746*	*119 (3.2)*	*0.79 [0.61; 1.04]*	

Numbers in italics: subgroups (from primary subgroup analyses), that were combined; see also text below

a: All percentages: Institute's calculation

b:Interaction test (relative to original subgroups)

c: Combination of the groups North America/Europe and Latin America/Asia-Pacific, since no heterogeneity was demonstrable in the paired comparison, see also text below; all values Institute's calculation

d: Combination of the groups "mild" and "none", since no heterogeneity was demonstrable on paired comparison, see also text below; all values Institute's calculation

CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event

Geographical region

The investigation across all 4 regions showed an indication ($p = 0.164$) of an effect modification. The paired comparisons between North America and Europe and Latin America and Asia/Pacific each showed no heterogeneity ($p = 0.878$ and $p = 0.579$ respectively). Although no formal heterogeneity ($p = 0.241$) could be shown between the combination of the results of North America and Latin America, in view of the observed effects and p-values of the paired comparisons, it appeared reasonable to combine the regions North America/Europe on the one hand and Latin America/Asia-Pacific on the other.

More bleeding events occurred under warfarin than under apixaban both in North America/Europe and also in Latin America/Asia-Pacific. The result was statistically significant in each case, though the effect was less pronounced in North America/Europe.

Sex and renal dysfunction

There was an indication ($p = 0.082$) of an effect modification by the characteristic “sex” and proof ($p = 0.028$) of an effect modification by the characteristic “renal dysfunction”. For both characteristics, the result for the resulting subgroups was in each case statistically significant in favour of apixaban and the direction of effect corresponded to that of the total population. Since there was an effect modification in relation to the characteristic “geographical region” and the effect observed in North America/Europe was less pronounced than in the total population, analyses stratified for Europe would be necessary for conclusive interpretation of the effect sizes for the respective subgroups. Since no such analyses were available, they are not considered further.

Major bleeds extracranial

With respect to the outcome “major bleeding extracranial” there was an indication of an effect modification by each of the characteristics “sex” and “renal dysfunction”. Table 17 shows the relevant results.

Table 17: VKA population: subgroups – outcome "major bleeds extracranial according to sex and renal dysfunction, RCT, direct comparison, apixaban versus warfarin

Study Characteristic Subgroup	Apixaban		Warfarin		Apixaban vs. warfarin	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	HR [95% CI]	P-value[b]
ARISTOTLE						
Sex						0.057
Male	5868	191 (3.3)	5879	214 (3.6)	0.88 [0.73; 1.07]	
Female	3220	84 (2.6)	3173	126 (4.0)	0.64 [0.48; 0.84]	
Renal dysfunction (calculated creatinine clearance in ml/min)						0.178
severe or moderate (≤ 50)	1493	65 (4.4)	1512	102 (6.7)	0.62 [0.46; 0.85]	
mild/none[c]	7557	210 (2.8)	7504	236 (3.1)	0.87 [0.75; 0.999]	
mild (> 50-80)	*3807*	*132 (3.5)*	*3758*	*147 (3.9)*	*0.87 [0.69; 1.10]*	
none (> 80)	*3750*	*78 (2.1)*	*3746*	*89 (2.4)*	*0.86 [0.64; 1.17]*	

Numbers in italics: subgroups (from primary subgroup analyses). that were combined; see also text below
a: All percentages: Institute's calculation
b: Interaction test (relative to original subgroups)
c: Combination of the groups "mild" and "none". since no heterogeneity was demonstrable in the paired comparison, see also text below; all values Institute's calculation
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event

Sex

There was an indication (p = 0.057) of an effect modification by the characteristic "sex".

In men, there was no substantial difference in the proportions of patients with extracranial bleeding between apixaban and warfarin; the direction of effect corresponded, however, to that of the total population (HR 0.88 [0.73; 1.07]). In women, events relating this outcome occurred statistically significantly more often under warfarin (4.0%) than under treatment with apixaban (2.6%; HR 0.64 [0.48; 0.84]).

Renal dysfunction

The investigation across all 3 categories of severity of renal dysfunction formed in the study showed an indication (p = 0.178) of an effect modification. The paired comparison of adjacent subgroups showed that the subgroup "severe-moderate" differed statistically significantly (at level 0.2) from the subgroup "mild" (p = 0.092) and the latter subgroup was comparable to the subgroup with no renal dysfunction (p = 0.963). The effects of the groups "mild" and "no renal dysfunction" were therefore combined to a common effect.

In both severity groups, fewer extracranial major bleeds occurred under apixaban than under warfarin. In each case, the result was statistically significant. The effect was less pronounced in patients with not more than mild renal dysfunction.

Clinically relevant non-major bleeds

There was an indication of an effect modification by the characteristic "weight" with respect to the outcome "clinically relevant non-major bleeds". Table 18 shows the relevant results.

Table 18: VKA population: subgroups – outcome "clinically relevant non-major bleeds" according to weight, RCT, direct comparison, apixaban versus warfarin

Study Characteristic Subgroup	Apixaban		Warfarin		Apixaban vs. warfarin	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	HR [95% CI]	P-value[b]
ARISTOTLE						
Weight (kg)						0.159
≤ 60	1013	21 (2.1)	965	41 (4.3)	0.49 [0.29; 0.82]	
> 60	8043	294 (3.7)	8059	402 (5.0)	0.72 [0.62; 0.83]	

a: All percentages: Institute's calculation
b: Interaction test
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event

In patients of both weight groups, clinically relevant non-major bleeds occurred more frequently under treatment with warfarin than under treatment with apixaban. The result was statistically significant in both cases. The effect was admittedly greater for patients weighing ≤ 60 kg, but the estimation was imprecise.

Summary of the subgroup results on the complex "bleeding events"

For the various outcomes regarding the complex "bleeding events", there were indications or proof of an effect modification by individual characteristics, but its significance could not be interpreted in all cases. None of the characteristics showed a consistent effect modification over all bleeding outcomes. To avoid false conclusions regarding subgroups, it therefore appears logical to draw separate conclusions only for those events for which proof, but not merely indications, of effect modification have arisen and which remain interpretable.

Taking these considerations into account, the following conclusion arises concerning effect modifications for the complex "bleeding events":

- In terms of the combined bleeding events outcome, there is proof that the effect in favour of apixaban is less pronounced in Europe than in the total population. For the overall conclusion on the extent of added benefit, it was therefore examined whether the conclusion would change if this weaker effect was taken into account.

Combination outcome "stroke, SE, major bleeds or all-cause mortality"

There was proof of an effect modification by the characteristic "age" with respect to the combination outcome "stroke, SE, major bleeds and mortality". Table 19 shows the relevant results.

Table 19: VKA population: subgroups – combination outcome "stroke, SE, major bleeds or all-cause mortality" according to age, RCT, direct comparison, apixaban versus warfarin

Study Characteristic Subgroup	Apixaban		Warfarin		Apixaban vs. warfarin	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	HR [95% CI]	P-value[b]
ARISTOTLE						
Age (years)						0.042
< 65	2731	228 (8.3)	2740	218 (8.0)	1.05 [0.87; 1.26]	
≥ 65[c]	6389	781 (12.2)	6341	750 (15.0)	0.80 [0.73; 0.88]	
≥ 65 – < 75	*3539*	*340 (9.6)*	*3513*	*426 (12.1)*	*0.79 [0.68; 0.91]*	
≥ 75	*2850*	*441 (15.5)*	*2828*	*524 (18.5)*	*0.82 [0.72; 0.93]*	

Numbers in italics: subgroups (from primary subgroup analyses), that were combined; see also text below
a: All percentages: Institute's calculation
b: Interaction test (relative to original subgroups)
c: Combination of the groups ≥ 65 – < 75 and ≥ 75, since no heterogeneity was demonstrable in the paired comparison, see also text below; all values Institute's calculation
CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event

The investigation across all 3 age groups showed proof (p = 0.042) of an effect modification. Paired comparisons of adjacent subgroups showed that the subgroup < 65 years was statistically significantly different from the subgroup aged ≥ 65 – < 75 years (p = 0.017) and the latter subgroup was comparable with the subgroup ≥ 75 years (p = 0.691). The effects of the age groups ≥ 65 – < 75 years and ≥ 75 years were therefore combined to a common effect.

In patients aged < 65 years, the proportions of patients with an event did not differ substantially between apixaban and warfarin, but the direction of effect differed from that of the total population (HR 1.07 [0.87; 1.26]). In patients aged ≥ 65 years, events of the combined outcome occurred statistically significantly more often under warfarin (15.0%) than under treatment with apixaban (12.2%; HR 0.80 [0.73; 0.88]).

2.4.2 Results for the ASA population

The results on the ASA population are presented in the sections below. On the basis of the AVERROES study, at most "indications" of an added benefit were derived (for further reasons, see Section 2.7.2.4.1 of the full dossier assessment). The overall results of the AVERROES study (only patients for whom treatment with a maximum of 250 mg ASA daily was intended) are shown in Section 2.4.2.1. Conclusions concerning the added benefit at outcome level are reached in Section 2.4.2.2 (subgroup analyses) because, with respect to some outcomes for some subgroups, there were indications or proof of effect modifications.

2.4.2.1 Overall results for the ASA population

Table 20 summarizes the results on the comparison of apixaban versus ASA in patients of the ASA population.

Table 20: ASA population: results – RCT, direct comparison, apixaban versus ASA

Study Outcome category Outcome	Apixaban N	Apixaban Patients with events n (%)	ASA N	ASA Patients with events n (%)	Apixaban vs. ASA HR [95% CI]; P-value
AVERROES					
Mortality[a]					
All-cause mortality	2607	109 (4.2)	2596	131 (5.1)	0.83 [0.65; 1.08]; 0.161
Morbidity[a]					
Stroke (ischaemic,[b] haemorrhagic or uncertain type)	2607	49 (1.9)	2596	99 (3.8)	0.49 [0.35; 0.69]; < 0.001
Stroke (ischaemic[b] or uncertain type)	2607	43 (1.6)	2596	91 (3.5)	0.47 [0.33; 0.67]; < 0.001
Stroke (ischaemic [c])	2607	31 (1.2)	2596	81 (3.1)	0.38 [0.25; 0.58]; < 0.001
Stroke (haemorrhagic)	2607	6 (0.2)	2596	9 (0.4)	0.67 [0.24; 1.88]; 0.448
Stroke (uncertain type)	2607	9 (0.3)	2596	4 (0.2)	2.12 [0.68; 7.18]; 0.187
Disabling stroke	2607	18 (0.7)	2596	53 (2.0)	0.34 [0.20; 0.58]; < 0.001
Systemic embolism	2607	2 (0.1)	2596	13 (0.5)	0.15 [0.04; 0.68]; 0.014
Myocardial infarction	2607	23 (0.9)	2596	24 (0.9)	0.96 [0.54; 1.70]; 0.892
TIA	No relevant data available				
Health-related quality of life					
Outcome not recorded					

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Table 20: ASA population: results – RCT, direct comparison, apixaban versus ASA (continued)

Study Outcome category Outcome	Apixaban N	Apixaban Patients with events n (%)	ASA N	ASA Patients with events n (%)	Apixaban vs. ASA HR [95% CI]; P-value
Adverse events[d]					
Major bleeds[e] or clinically relevant non-major bleeds[f]					
	2605	125 (4.8)	2596	90 (3.5)	1.38 [1.05; 1.81]; 0.019
Major bleeds[e]					
	2605	42 (1.6)	2596	27 (1.0)	1.54 [0.95; 2.50]; 0.080
intracranial major bleeds[e]					
	2605	11 (0.4)	2596	11 (0.4)	0.99 [0.43; 2.28]; 0.979
major bleeds[e] other site (extracranial, including gastrointestinal)					
	2605	31 (1.2)	2596	16 (0.6)	1.92 [1.05; 3.51]; 0.034
Clinically relevant non-major bleeds[f]					
	2605	86 (3.3)	2596	65 (2.5)	1.32 [0.95; 1.82]; 0.095
Overall rate AEs					
	2605	1691 (64.9)	2596	1781 (68.6)	0.90 [0.85; 0.97]; 0.003
Overall rate SAEs					
	2605	612 (23.5)	2596	746 (28.7)	0.80 [0.72; 0.89]; < 0.001
Treatment discontinuations due to AEs					
	2605	245 (9.4)	2596	340 (13.1)	0.71 [0.60; 0.83]; < 0.001
Mortality[a], morbidity[a] and adverse events[d]					
Stroke (ischaemic,[b] haemorrhagic or uncertain type), SE, major bleeds[e] or mortality					
	2607	167 (6.4)	2596	227 (8.7)	0.73 [0.60; 0.89]; 0.002

(continued on next page)

Table 20: ASA population: results – RCT, direct comparison, apixaban versus ASA (continued)

a: Analysis period: intended treatment period. Period that starts on the day of randomization and ends with the efficacy cut-off date. The efficacy cut-off date was specified to ensure that at least 226 unrefuted primary efficacy events had occurred and was documented before unblinding or before the start of the open-label extension of the study, whichever occurred first.
b: With or without haemorrhagic transformation
c: Without haemorrhagic transformation
d: Analysis period: Treatment period. Period in which measured values or events from the start of the first dose of the blinded study medication to 2 days after the last dose for bleeding outcomes, bleeding-related serious or non-serious adverse events and 30 days after the last dose for deaths as serious adverse event and all serious adverse events were summarized.
e: At least one of the following criteria: decrease in haemoglobin level ≥ 2 g/dl over a 24-hour period, transfusion of 2 or more units of packed red cells, bleeding at least one a critical body region (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal), fatal bleeding
f: Clinically overt bleeding that did not correspond to the additional criteria of major bleeds and which met at least one of the following criteria: led to hospitalization, medical or surgical treatment by a doctor, modification of the antithrombotic treatment
AE: adverse event; ASA: acetylsalicylic acid; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; SE: systemic embolism; TIA: transient ischaemic attack

Mortality

All-cause mortality

The result regarding the outcome “all-cause mortality” was not statistically significant.

Morbidity

Stroke

Under treatment with apixaban, statistically significantly fewer patients suffered a stroke than under treatment with ASA. Consideration of the types (ischaemic, haemorrhagic, uncertain type) showed that the majority of events were ischaemic (112 of 148 patients with event [76%]). In addition, the difference in favour of apixaban was essentially due to the lower rate of ischaemic strokes (1.2% versus 3.1%; HR 0.38 [0.25; 0.58]). Although, in the case of haemorrhagic strokes, there was a numerical difference in favour of apixaban, overall only few events occurred and the result was not statistically significant.

The result concerning the outcome “disabling stroke”, which can be used to assess stroke severity, was also statistically significantly in favour of apixaban.

SE

There was an advantage of apixaban over ASA for the outcome “SE”. The result was statistically significant. Overall, only a few SE occurred.

Myocardial infarction

The proportion of patients with a myocardial infarction did not differ substantially between the apixaban and the ASA group. The result was not statistically significant.

TIA

The outcome “TIA” was not pre-defined as a separate outcome in the AVERROES study and was not included by the company as a patient-relevant outcome in the assessment of apixaban. Since no data on the outcome “TIA” were presented for the ASA population ≤ 250 mg, an assessment was not possible in the context of this benefit assessment. An added benefit of apixaban for the outcome “TIA” is not proven.

Health-related quality of life

Since the outcome "quality of life" was not recorded in the AVERROES study, no evaluable data on this outcome were available. An added benefit of apixaban for health-related quality of life is not proven.

Adverse events

Bleeding events

Major bleeds as well as clinically relevant non-major bleeds occurred more frequently under apixaban. The result of the individual outcomes was, however, not statistically significant in either case, whereas the result of the combined outcome “major and clinically relevant non-major bleeds” was statistically significant.

The information about the site of major bleeds revealed that about two-thirds of all bleeding events occurred extracranially. The result for extracranial major bleeds was statistically significantly to the disadvantage of apixaban.

Other analyses of adverse events

There was a statistically significant advantage of apixaban for each of the outcomes “overall rate of AE”, “overall rate of SAE” and “treatment discontinuations due to AE”. However in each case, data on specifically recorded outcomes (e.g. ischaemic stroke) were also incorporated. Neither in the company‘s dossier nor in the study reports were results available on AEs, SAEs and treatment discontinuations due to AEs, in which those events already covered by other outcomes were not included. The event rates on the specifically recorded outcomes show that for the two outcomes “AE” and “treatment discontinuations due to AE” scenarios are conceivable, in which statistically significant effects result merely through the incorporation of these outcomes. However, in contrast to the VKA population, there is no evidence that the direction of effect could be reversed, were such outcomes not included. For the third outcome, “SAE”, the absolute risk difference of 5.2% was even markedly above the added risk difference for strokes and SE of 2.3%. When the individual system organ classes (SOC; data available only for the total population of the study) were considered, however, it emerged that a marked difference in favour of apixaban was only present in the area “nervous system disorders”. In turn, this was almost exclusively caused by an advantage in the preferred terms “ischaemic stroke”, “cerebrovascular accident” and “transient ischaemic attack”. The advantage of apixaban in the area SAE therefore appears adequately reliably represented by the outcome “strokes”.

In summary, the results on the outcomes "AE", "SAE" and "treatment discontinuations due to AE" were not additionally used for the derivation of the overall conclusion on added benefit.

Mortality, morbidity and adverse events

Stroke, SE, major bleeds or mortality

The balancing of benefit and harm can be supported with the combined outcome "stroke, SE, major bleeds and mortality", because this outcome contains those serious or fatal events that are important for the area of treatment.

The result for the combined outcome was statistically significantly in favour of apixaban. This result is in line with the results observed in the individual outcomes, since for these, more events in absolute terms were prevented under apixaban (mortality, SE, stroke) than occurred (bleeding events).

2.4.2.2 Subgroups analyses on the ASA population

To identify possible effect modifiers, certain subgroups were investigated in detail to determine whether heterogeneous treatment effects were present. In the company's dossier, interaction tests between the treatment and the grouping variable were conducted using the chi-squared test according to Wald in the Cox proportional hazards model, into which the covariables for treatment group, grouping variable and interaction of treatment and grouping variable were entered.

Corresponding investigations were carried for the following (subgroup) characteristics (for explanation of the selection, see Section 2.7.2.2 of the full dossier assessment):

- Age (< 65/≥ 65 – < 75/≥ 75 years)
- Sex (male/female)
- Weight (≤ 60 kg/> 60 kg)
- $CHADS_2$ sum score for classifying the risk of stroke (≤ 1/2/≥ 3)
- Renal dysfunction (severe or moderate [≤ 50 ml/min]/mild [> 50-80 ml/min]/none [> 80 ml/min])
- Unsuitable for VKA treatment (demonstrated/expected)

The investigation was performed for the following outcomes:

- All-cause mortality
- Stroke (ischaemic, haemorrhagic or uncertain type)
- SE
- Myocardial infarction

- Complex of bleeding events
  - combination outcome "major bleeds and clinically relevant non-major bleeds"
  - major bleeds
  - major bleeds extracranial
  - clinically relevant non-major bleeds
- Combination outcome "stroke, SE, major bleeds or all-cause mortality"

All subgroup characteristics and their intensity and/or thresholds were predefined in the AVERROES study.

The company submitted the corresponding analyses for all the outcomes that it classed as relevant. Its dossier also contained subgroup analyses of other characteristics that are not considered further here (see Section 2.7.2.2 of the full dossier assessment).

Only the results for subgroups and outcomes that gave at least indications of an interaction between treatment effect and subgroup are presented below. The condition for proof of different subgroup effects was a statistically significant interaction ($p < 0.05$). A p-value of ≥ 0.05 and < 0.2 provided an indication of an effect modification.

All-cause mortality

With the outcome "all-cause mortality", there were indications of effect modification by the characteristic "age". Table 21 shows the relevant results.

Table 21: ASA population: subgroups – outcome all-cause mortality according to age, RCT, direct comparison, apixaban versus ASA

Study Characteristic Subgroup	Apixaban		ASA		Apixaban vs. ASA	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	HR [95% CI]	P-value[b]
AVERROES						
Age (years)						0.082
< 65	797	22 (2.8)	804	13 (1.6)	1.75 [0.88; 3.48]	
≥ 65[c]	1810	87 (4.8)	1792	118 (6.6)	0.75 [0.57; 0.996]	
≥ 65 – < 75	*974*	*32 (3.3)*	*876*	*36 (4.1)*	*0.79 [0.49; 1.28]*	
≥ 75	*836*	*55 (6.6)*	*916*	*82 (9.0)*	*0.74 [0.52; 1.04]*	

Numbers in italics: subgroups (from primary subgroup analyses), that were combined; see also text below
a: All percentages: Institute's calculation
b: Interaction test (relative to original subgroups)
c: Combination of the subgroups ≥ 65 – < 75 and ≥ 75, because paired comparison showed no heterogeneity, see also text below; all values Institute's calculation
ASA: acetylsalicylic acid; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event

The investigation across all 3 age groups showed an indication (p = 0.082) of an effect modification. The paired comparison of adjacent groups revealed that the subgroup < 65 years was statistically significantly different (at level 0.2) from the subgroup aged ≥ 65 – < 75 years (p = 0.063) and the latter subgroup was comparable with the subgroup ≥ 75 years (p = 0.796). Therefore the effects of age groups ≥ 65 – < 75 years and ≥ 75 years were combined to a joint effect.

In patients aged < 65 years, the proportions of patients who died did not differ substantially between apixaban and ASA, but the direction of effect differed from that of the total population (HR 1.75 [0.88; 3.48]). In patients aged ≥ 65 years, deaths occurred statistically significantly more frequently under ASA (6.6%) than under treatment with apixaban (4.8%; HR 0.75 [0.57; 0.996]).

Stroke

With respect to the outcome “stroke” (ischaemic, haemorrhagic or uncertain type) there was an indication of an effect modification by the characteristics “unsuitable for VKA therapy” and also for “age”. There was proof of an effect modification by the characteristic “weight”. Table 22 shows the relevant results.

Table 22: ASA population: subgroups – outcome "stroke" (ischaemic, haemorrhagic or uncertain type) according to suitability for VKA therapy, age and weight, RCT, direct comparison, apixaban versus ASA

Study Characteristic Subgroup	Apixaban		ASA		Apixaban vs. ASA	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	HR [95% CI]	P-value[b]
AVERROES						
Unsuitable for VKA treatment						0.151
demonstrated	999	16 (1.6)	1008	45 (4.5)	0.36 [0.20; 0.63]	
expected	1608	33 (2.1)	1588	54 (3.5)	0.60 [0.39; 0.93]	
Age (years)						0.102
< 75[c]	1771	30 (1.7)	1680	41 (2.4)	0.67 [0.38; 1.17]	
< 65	*797*	*7 (0.9)*	*804*	*16 (2.0)*	*0.45 [0.18; 1.08]*	
≥ 65 – < 75	*974*	*23 (2.4)*	*876*	*25 (2.9)*	*0.82 [0.47; 1.44]*	
≥ 75	836	19 (2.3)	916	58 (6.3)	0.36 [0.21; 0.60]	
Weight (kg)						0.011
≤ 60	446	18 (4.0)	404	16 (4.0)	1.04 [0.53; 2.04]	
> 60	2161	31 (1.4)	2191	83 (3.8)	0.38 [0.25; 0.57]	

Numbers in italics: subgroups (from primary subgroup analyses), that were combined; see also text below
a: All percentages: Institute's calculation
b: Interaction test (relative to original subgroups)
c: Combination of the subgroups ≥ 65 – < 75 and ≥ 75, because paired comparison showed no heterogeneity, see also text below; all values Institute's calculation
ASA: acetylsalicylic acid; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event

Unsuitable for VKA therapy

There was an indication (p = 0.151) of an effect modification by the characteristic "unsuitable for VKA therapy".

In both subgroups (demonstrated or expected unsuitability for VKA therapy) there were statistically significantly fewer strokes under apixaban than under ASA. The effect was more pronounced in the patients of the subgroup "demonstrated" (HR 0.36 [0.20; 0.63]) than in those of the subgroup "expected" (HR 0.60 [0.39; 0.93]).

Age, weight

There was an indication (p = 0.102) of an effect modification by the characteristic "age" and proof (p = 0.011) of an effect modification by the characteristic "weight".

Since there was an effect modification by the characteristic "suitability for VKA therapy" and the effect in patients in whom the lack of suitability was demonstrated was far more pronounced, stratified analyses would be required on the population with demonstrated

unsuitability for a conclusive interpretation of the effect sizes of the respective subgroups. Since no such analyses were available, they are not considered further.

Bleeding events

There were indications or proof for effect modifications with respect to some of the various bleeding outcomes by the individual characteristics. These are shown below. Conclusions about the importance of the observed effect modifications for the complex "bleeding events" are summarized after the description of the various outcomes.

Major bleeds or clinically relevant non-major bleeds

For the combined outcome "major bleeds or clinically relevant non-major bleeds" there was an indication of an effect modification by the characteristic "severity" (measured using the $CHADS_2$ score). Table 23 shows the relevant results.

Table 23: ASA population: subgroups – outcome "major bleeds or clinically relevant non-major bleeds" according to $CHADS_2$ score, RCT, direct comparison, apixaban versus ASA

Study Characteristic Subgroup	Apixaban		ASA		Apixaban vs. ASA	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	HR [95% CI]	P-value[b]
AVERROES						
$CHADS_2$-Score						0.181
≤ 1	973	32 (3.3)	987	34 (3.4)	0.95 [0.59; 1.55]	
> 1[c]	1632	93 (5.7)	1609	56 (3.5)	1.65 [1.18; 2.29]	
= 2	*961*	*52 (5.4)*	*867*	*30 (3.5)*	*1.57 [1.00; 2.46]*	
≥ 3	*671*	*41 (6.1)*	*742*	*26 (3.5)*	*1.75 [1.07; 2.85]*	

Numbers in italics: subgroups (from primary subgroup analyses), that were combined; see also text below
a: All percentages: Institute's calculation
b: Interaction test (relative to original subgroups)
c: Combination of the groups =2 and ≥ 3, because paired comparison showed no heterogeneity, see also text below; all values Institute's calculation
ASA: acetylsalicylic acid; $CHADS_2$:sum score for categorizing stroke risk in atrial fibrillation on the basis of the following factors: chronic congestive heart failure (1 point); hypertension (1 point) ; age ≥75 years (1 point); diabetes mellitus (1 point); prior stroke or TIA (2 points); CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; TIA: transient ischaemic attack

The investigation across all 3 groups of severity showed an indication ($p = 0.181$) of an effect modification. The paired comparisons of adjacent groups showed that the subgroup $CHADS_2$ score ≤ 1 was statistically significantly different (at level 0.2) from the subgroup $CHADS_2$ score = 2 ($p = 0.140$) and the latter subgroup was comparable with the subgroup $CHADS_2$ score ≥ 3 ($p = 0.753$). The effects of the groups $CHADS_2$ score = 2 and ≥ 3 were therefore combined to a common effect.

Among patients with $CHADS_2$ score ≤ 1, the proportions of patients with bleeding events did not differ substantially between apixaban and ASA, however the direction of effect differed from that of the total population (HR 0.95 [0.59; 1.55]). In patients with $CHADS_2$ score > 1, bleeding events under ASA (3.5%) occurred statistically significantly less often than under treatment with apixaban (5.7%; HR 1.65 [1.18; 2.29]).

Major bleeds extracranial

There was proof of an effect modification with respect to the outcome "major bleeds other site" (extracranial, including gastrointestinal) by the characteristic "severity" (measured using the $CHADS_2$ score). Table 24 shows the relevant results.

Table 24: ASA population: subgroups – outcome "major bleeds extracranial" according to $CHADS_2$ score, RCT, direct comparison, apixaban versus ASA

Study Characteristic Subgroup	Apixaban		ASA		Apixaban vs. ASA	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	HR [95% CI]	P-value[b]
AVERROES						
$CHADS_2$-Score						0.041
≤ 2[c]	1934	14 (0.7)	1854	13 (0.7)	1.00 [0.47; 2.12]	
≤ 1	*973*	*4 (0.4)*	*987*	*3 (0.3)*	*1.36 [0.30; 6.07]*	
= 2	*961*	*10 (1.0)*	*867*	*10 (1.2)*	*0.90 [0.37; 2.15]*	
≥ 3	671	17 (2.5)	742	3 (0.4)	6.19 [1.82; 21.13]	

Numbers in italics: subgroups (from primary subgroup analyses), that were combined; see also text below
a: All percentages: Institute's calculation
b: Interaction test (relative to original subgroups)
c: Combination of the groups ≤ 1 und = 2, because paired comparison showed no heterogeneity, see also text below; all values Institute's calculation
ASA: acetylsalicylic acid; $CHADS_2$:sum score for categorizing stroke risk in atrial fibrillation on the basis of the following factors: chronic congestive heart failure (1 point); hypertension (1 point) ; age ≥75 years (1 point); diabetes mellitus (1 point); prior stroke or TIA (2 points); CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; TIA: transient ischaemic attack

The investigation across all 3 severity groups showed proof (p = 0.041) of an effect modification. The paired comparison of adjacent subgroups revealed that the subgroup $CHADS_2$ score = 2 was comparable with subgroup $CHADS_2$ score ≤ 1 (p = 0.637), but differed statistically significantly (at level 0.2) from subgroup $CHADS_2$ score ≥ 3 (p = 0.012). The effects of the groups $CHADS_2$ score ≤ 1 and $CHADS_2$ score = 2 were therefore combined to a common effect ($CHADS_2$ score ≤ 2).

Among patients with $CHADS_2$ score ≤ 2, the proportions of patients with major extracranial bleeds did not differ substantially between apixaban and ASA. In patients with $CHADS_2$ score ≥ 3, major extracranial bleeds occurred statistically significantly more frequently under apixaban (2.5%) than under treatment with ASA (0.4%; HR 6.19 [1.82; 21.13]).

Clinically relevant non-major bleeds

There was an indication of an effect modification with respect to the outcome "clinically relevant non-major bleeds" by the characteristic "severity" (measured using the $CHADS_2$ score). Table 25 shows the relevant results.

Table 25: ASA population: subgroups – outcome "clinically relevant non-major bleeds" $CHADS_2$ score, RCT, direct comparison, apixaban versus ASA

Study Characteristic Subgroup	Apixaban		ASA		Apixaban vs. ASA	
	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	HR [95% CI]	P-value[b]
AVERROES						
$CHADS_2$-Score						0.118
≤ 1	973	26 (2.7)	987	30 (3.0)	0.88 [0.52; 1.48]	
> 1[c]	1632	60 (3.7)	1609	35 (2.2)	1.68 [1.10; 2.56]	
= 2	*961*	*39 (4.1)*	*867*	*18 (2.1)*	*1.97 [1.13; 3.44]*	
≥ 3	*671*	*21 (3.1)*	*742*	*17 (2.3)*	*1.36 [0.72; 2.59]*	

Numbers in italics: subgroups (from primary subgroup analyses), that were combined; see also text below
a: All percentages: Institute's calculation
b: Interaction test (relative to original subgroups)
c: Combination of the groups = 2 und ≥ 3, because paired comparison showed no heterogeneity, see also text below; all values Institute's calculation
ASA: acetylsalicylic acid; $CHADS_2$:sum score for categorizing stroke risk in atrial fibrillation on the basis of the following factors: chronic congestive heart failure (1 point); hypertension (1 point) ; age ≥75 years (1 point); diabetes mellitus (1 point); prior stroke or TIA (2 points); CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; TIA: transient ischaemic attack

The investigation across all 3 severity groups showed an indication (p = 0.118) of an effect modification. The paired comparison of adjacent subgroups revealed that the subgroup $CHADS_2$ score ≤ 1 was statistically significantly different (at level 0.2) from subgroup $CHADS_2$ score = 2 war (p = 0.039) and the latter subgroup was comparable with subgroup $CHADS_2$ score ≥ 3 (p = 0.397). The effects of the groups $CHADS_2$ score = 2 and ≥ 3 were therefore combined to a common effect.

Among patients with $CHADS_2$ score ≤ 1, the proportions of patients with bleeding events did not differ substantially between apixaban and ASA, but the direction of effect differed from that of the total population (HR 0.88 [0.42; 1.48]). In patients with $CHADS_2$ score > 1, bleeding events under ASA (2.2%) occurred statistically significantly less often than under treatment with apixaban (3.7%; HR 1.68 [1.10; 2.56]).

Summary of the subgroup results on the complex "bleeding events"

For 3 of the 4 outcomes concerning the complex "bleeding events" there was an indication or a proof of an effect modification by the characteristic "severity" (measured using the $CHADS_2$ score). It was consistently shown that in patients with a maximum of one risk factor

($CHADS_2$ score ≤ 1), there was no increased bleeding risk under apixaban. On the other hand, in patients with a $CHADS_2$ score > 1 (for extracranial bleeds > 2), there was a consistently increased risk of bleeding under apixaban. The exception was the outcome "major bleeds" overall, but this also covered haemorrhagic stroke.

Further information about the choice of outcomes, risk of bias at outcome level and outcome results can be found in Modules 4B and 4C, Sections 4.2.5.2, 4.3.1.2.1, 4.3.1.3 respectively and 4.4.1 of the dossiers and in Sections 2.7.2.2 and 2.7.2.4.2 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of the extent and probability of added benefit for the VKA and ASA populations respectively are shown below. The results at outcome level are presented first. The various outcome categories and effect sizes are considered for the derivation of the extent of added benefit at outcome level. The methods used for this purpose are explained in Appendix A of Benefit Assessment A11-02 [2].

The overall conclusions on the extent and probability of added benefit are then drawn. The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal from IQWiG. The decision regarding added benefit is made by the G-BA.

2.5.1 VKA population

2.5.1.1 Evaluation of added benefit at outcome level

The data presented in Section 2.4.1 showed indications or proof of an effect modification by the characteristics "age", "weight" and "geographical region". The results of the total population of the ARISTOTLE study shown in Table 26 below are supplemented by the results of the assessment-relevant subgroups.

Table 26: VKA population: apixaban versus warfarin – extent of added benefit at outcome level

Outcome category **Outcome** **Subgroup**	**Effect estimate [95% CI] / proportion of events apixaban vs. warfarin / p-value / probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	HR 0.89 [0.80; 1.00] 6.6 % vs. 7.4 % p = 0.047	
Age < 65 years	*HR 1.07 [0.84; 1.35]* *5.2 % vs. 4.9 %*	*Lesser benefit/added benefit not proven.*
Age ≥ 65 years	*HR 0.85 [0.72; 0.99]* *7.2 % vs. 8.4 %* *Probability: "indication"*	*Outcome category: survival time* $0.95 \leq CI_o < 1$ *Added benefit, extent: "minor"*
Weight ≤ 60 kg	*HR 1.11 [0.86; 1.44]* *12.0 % vs. 11.1 %*	*Lesser benefit/added benefit not proven.*
Weight > 60 kg	*HR 0.85 [0.75; 0.96]* *5.9 % vs. 6.9 %* *Probability: "indication"*	*Outcome category: survival time* $0.95 \leq CI_o < 1$ *Added benefit, extent: "minor"*
Morbidity		
Stroke (ischaemic, haemorrhagic or uncertain type)	HR 0.79 [0.65; 0.95] 2.2 % vs. 2.8 % p = 0.012	
Age < 65 years	*HR 1.22 [0.80; 1.85]* *1.8 % vs. 1.5 %*	*Lesser benefit/added benefit not proven.*
Age ≥ 65 years	*HR 0.70 [0.57; 0.87]* *2.4 % vs. 3.3 %* *Probability: "indication"*	*Outcome category: serious/severe symptoms/late complications* $0.75 \leq CI_o < 0.9$ *Added benefit, extent: "considerable"*
Stroke (disabling)	HR 0.84 [0.58; 1.20] 0.6% vs. 0.7% p = 0.338	Lesser benefit/added benefit not proven.
SE	HR 0.87 [0.44; 1.75] 0.2 % vs. 0.2 % p = 0.702	Lesser benefit/added benefit not proven.
Myocardial infarction	HR 0.88 [0.66; 1.17] 1.0 % vs. 1.1 % p = 0.372	Lesser benefit/added benefit not proven.
TIA	RR 1.29 [0.91; 1.84] 0.8 % vs. 0.6 % p = 0.176	Lesser benefit/added benefit not proven.

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Table 26: VKA population: apixaban versus warfarin – extent of added benefit at outcome level (continued)

Outcome category **Outcome** **Subgroup**	**Effect estimate [95% CI] / proportion of events apixaban vs. warfarin / p-value / probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
	No evaluable data available	lesser benefit /added benefit not proven
Adverse events – Bleeding events		
Combined outcome: major bleeds, clinically relevant non-major bleeds	HR 0.68 [0.61; 0.753] 6.8% vs. 9.7% p < 0.001 Probability: "indication"	Outcome category: serious/severe adverse events[c] $0.75 \leq CI_o < 0.9$ Lesser harm; extent: "considerable"
Region: Europe	*HR 0.74 [0.62; 0.88]* *5.9% vs. 7.8%* *Probability: "indication"*	*Outcome category: serious/severe adverse events*[c] *$0.75 \leq CI_o < 0.9$* *Lesser harm; extent: "considerable"*
Major bleeds	HR 0.69 [0.60; 0.80] 3.6% vs. 5.1% p < 0.001 Probability: "indication"	Outcome category: serious/severe adverse events $0.75 \leq CI_o < 0.9$ Lesser harm; extent: "considerable"
Major bleeds extracranial	HR 0.79 [0.68; 0.93] 3.0% vs. 3.8% p < 0.001 Probability: "indication"	Outcome category: serious/severe adverse events $0.9 \leq CI_o < 1.0$ Lesser harm; extent: "minor"
Clinically relevant non-major bleeds	HR 0.70 [0.60; 0.804] 3.5% vs. 4.9% p < 0.001 Probability: "indication"	Outcome category: non-serious/non-severe adverse events $0.8 \leq CI_o < 0.9$ Lesser harm; extent: "minor"
Adverse events – other analyses of adverse events		
Overall AE, SAE, treatment discontinuations due to AE	Results were potentially influenced by the recording of events on benefit outcomes and are thus not evaluable.	Lesser/greater harm not proven

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Table 26: VKA population: apixaban versus warfarin – extent of added benefit at outcome level (continued)

Outcome category **Outcome** **Subgroup**	**Effect estimate [95% CI] / proportion of events apixaban vs. warfarin / p-value / probability[a]**	**Derivation of extent[b]**
Combined outcome: mortality, morbidity and adverse events		
Stroke, SE, major bleeds or mortality	HR 0.85 [0.78; 0.92] 11.1% vs. 12.9% p < 0.001	
Age < 65 years	*HR 1.05 [0.87; 1.26]* *8.3% vs. 8.0%*	*Added benefit /lesser harm not proven*
Age ≥ 65 years	*HR 0.80 [0.73; 0.88]* *12.2% vs. 15.0%* *Probability: "indication"*	*Outcome category: serious/severe symptoms/late complications[d]* *$0.75 \leq CI_o < 0.9$* *Added benefit; extent: considerable*

Numbers in italics: information of effects for subgroups, in which there were indications or proof of effect modification.

a: Probability provided if statistically significant differences were present

b: Estimations of effect size made depending on outcome category with different limits based on the upper limit of the confidence interval (CI_o)

c: This category was chosen because more major than non-major bleeds occurred.

d: This category was chosen because most events of the combined outcome were not fatal and the effect was substantially due to non-fatal events.

AE: adverse event; CI: confidence interval; CI_o: upper limit confidence interval; HR: hazard ratio; RR: relative risk, SAE: serious adverse event; SE: systemic embolism; TIA: transient ischaemic attack

The results showed that for the outcomes "mortality" and "stroke" relevant effect modifications by the characteristic "age" were present. In both cases, the treatment effect of apixaban in comparison with warfarin was not demonstrable in patients under 65 years. This was confirmed by an effect in the same direction in the combined outcome "stroke, SE, major bleeds and mortality". For all 3 named outcomes, the direction of effect was actually reversed in patients under 65 years in comparison with the total population. Therefore separate conclusions on added benefit are necessary for the two age groups.

In contrast, no such consistent effect modification was shown by the characteristic "weight". An effect modification was only present for "all-cause mortality" that was not confirmed in the combined outcome. Therefore, no separate conclusions on the extent of added benefit are drawn for weight groups.

2.5.1.2 Overall conclusion on added benefit: VKA population

Age < 65 years

The results that determined the overall conclusion on added benefit for patients < 65 years are summarized in Table 27.

Table 27: Positive and negative effects from the assessment: apixaban versus warfarin, age < 65 years

Positive effects	**Negative effects**
Indication of lesser harm – extent: "minor" to "considerable" (complex "bleeding events")	Unclear, because results on AE, SAE and treatment discontinuations due to AE are not evaluable
Combined outcome "stroke, SE, major bleeds and mortality": no effect to the advantage or disadvantage of apixaban	
AE: adverse events; SAE: serious adverse events; SE: systemic embolism	

Overall, for patients of the VKA population aged < 65 years there is a positive result with the certainty of results "indication" in favour of apixaban in the complex "bleeding events". This advantage is shown for major as well as clinically relevant non-major bleeds. The extent with consideration of the combined bleeding outcome is "considerable", but is "minor" when the extracranial major bleeds are considered. The advantage in the complex "bleeding events" is not mirrored in the combined outcome of "stroke, SE, major bleeds and mortality". Numerically, actually more events occurred under apixaban with respect to this outcome and also with respect to the outcome "all-cause mortality" in patients under 65 years. In addition, due to a lack of data, it is unclear whether AEs other than bleeds occur more or less frequently under apixaban.

In summary, for patients of the VKA population aged < 65 years there is no proof of added benefit versus warfarin.

This deviates from the conclusion of the company, which derived proof of a major added benefit for the entire VKA population.

Age ≥ 65 years

The results that determined the overall conclusion on added benefit for patients ≥ 65 years are shown in Table 28.

Table 28: Positive and negative effects from the assessment: apixaban versus warfarin, age ≥ 65 years

Positive effects	Negative effects
Indication of added benefit – extent: "minor" (survival: all-cause mortality)	Unclear, because results on AE, SAE and treatment discontinuations due to AE are not evaluable
Indication of added benefit – extent: "considerable" (serious/severe symptoms/late complications: stroke)	
Indication of lesser harm – extent: "minor" to "considerable" (complex "bleeding events")	
Indication of added benefit – extent: "considerable" (serious/severe symptoms/late complications: combined outcome of "stroke, SE, major bleeds and mortality)	
AE: adverse events; SAE: serious adverse events; SE: systemic embolism	

Overall, for patients of the VKA population aged ≥ 65 years there remain consistently positive results of the same certainty of result (indication) in favour of apixaban. The extent is "minor" for the outcome "all-cause mortality" and "minor" to "considerable" for the complex "bleeding events". For the combined outcome "stroke, major bleeds and mortality", the extent is "considerable". On the other hand, informative data on AE, SAE and treatment discontinuations due to AE are missing. However, on the basis of the consistently positive results on mortality and on bleeds in this group of patients, it does not appear appropriate to therefore downgrade the extent of the added benefit of apixaban.

In summary, there is an indication of an added benefit (extent: "considerable") of apixaban versus warfarin for patients of the VKA population aged ≥ 65 years.

This deviates from the conclusion of the company, which derived proof of a major added benefit for the entire VKA population.

2.5.2 ASA population

2.5.2.1 Evaluation of added benefit at outcome level

The data presented in Section 2.4.2 showed indications or proof of an effect modification by the characteristics "age", "severity" (measured using the $CHADS_2$ score) and "unsuitability for VKA therapy". The corresponding results are shown in Table 29 below, and overall it is checked whether there are different conclusions on the extent of added benefit for the individual patient groups.

Table 29: ASA population: apixaban versus ASA – extent of added benefit at outcome level

Outcome category **Outcome** **Subgroup**	**Effect estimate [95% CI] / proportion of events apixaban vs. ASA / p-value / probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	HR 0.83 [0.65; 1.08] 4.2% vs. 5.1% p = 0.161	Lesser benefit/added benefit not proven
Age < 65 years	*HR 1.75 [0.88; 3.48]* *2.8% vs. 1.6%*	*Lesser benefit/added benefit not proven*
Age ≥ 65 years	*HR 0.75 [0.57; 0.996]* *4.8% vs. 6.6%* *Probability: "hint"*[c]	*Outcome category: survival time* *$0.95 \leq CI_o < 1$* *Added benefit; extent: "minor"*
Morbidity		
Stroke (ischaemic, haemorrhagic or uncertain type)	HR 0.49 [0.35; 0.69] 1.9% vs. 3.8% p < 0.001 Probability: "indication"	Outcome category: serious/severe symptoms/late complications $CI_o < 0.75$ and risk < 5% Added benefit; extent: "considerable"
unsuitable for VKA treatment (demonstrated)	*HR 0.36 [0.20; 0.63]* *1.6% vs. 4.5%* *Probability: "indication"*	*Outcome category: serious/severe symptoms/late complications* *$CI_o < 0.75$ and risk < 5%* *Added benefit; extent: "considerable"*
Stroke (disabling)	HR 0.34 [0.20; 0.58] 0.7% vs. 2.0% p < 0.001 Probability: "indication"	Outcome category: serious/severe symptoms/late complications $CI_o < 0.75$ and risk < 5% Added benefit; extent: "considerable"
SE	HR 0.15 [0.04; 0.68] 0.1% vs. 0.5% p = 0.014 Probability: "indication"	Outcome category: serious/severe symptoms/late complications $CI_o < 0.75$ and risk < 5% Added benefit; extent: "considerable"
Myocardial infarction	HR 0.96 [0.54; 1.70] 0.9% vs. 0.9% p = 0.892	Lesser benefit/added benefit not proven
TIA	No evaluable data available	Lesser benefit/added benefit not proven
Health-related quality of life		
	No evaluable data available	Lesser benefit/added benefit not proven

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Table 29: ASA population: apixaban versus ASA – extent of added benefit at outcome level (continued)

Outcome category **Outcome** **Subgroup**	**Effect estimate [95% CI] / proportion of events apixaban vs. ASA / p-value / probability**[a]	**Derivation of extent**[b]
Adverse events – Bleeding events		
Combined outcome major bleeds, clinically relevant non-major bleeds	HR 1.38 [1.05; 1.81] HR[d] 0.72 [0.55; 0.95] 4.8% vs. 3.5% p = 0.019 Probability: "indication"	Outcome category: non-serious/non-severe adverse events[e] $CI_o > 0.9$ Greater harm not proven
$CHADS_2$ score ≤ 1	*HR 0.95 [0.59; 1.55]* *3.3% vs. 3.4%*	*Lesser/greater harm not proven*
$CHADS_2$ score > 1	*HR 1.65 [1.18; 2.29]* *HR[d] 0.61 [0.44; 0.85]* *5.7% vs. 3.5%* *Probability: "indication"*	*Outcome category: non-serious/non-severe adverse events[e]* *$0.80 \leq CI_o < 0.9$* *Greater harm; extent: "minor"*
Major bleeds	HR 1.54 [0.95; 2.50] 1.6% vs. 1.0% p = 0.080	Lesser/greater harm not proven
Major bleeds. extracranial	HR 1.92 [1.05; 3.51] HR[d] 0.52 [0.28; 0.95] 1.2% vs. 0.6% p = 0.034 Probability: "indication"	Outcome category: serious/severe adverse events $0.9 \leq CI_o < 1$ Greater harm; extent: "minor"
$CHADS_2$ score ≤ 2	*HR 1.00 [0.47; 2.12]* *0.7% vs. 0.7%*	*Lesser/greater harm not proven*
$CHADS_2$ score ≥ 3	*HR 6.19 [1.82; 21.13]* HR[d] 0.16 [0.05; 0.55] *2.5% vs. 0.4%* *Probability: "indication"*	*Outcome category: serious/severe adverse events* *$CI_o < 0.75$ and risk< 5%* *Greater harm; extent: "considerable"*
Clinically relevant non-major bleeds	HR 1.32 [0.95; 1.82] 3.3% vs. 2.5% p = 0.095	Lesser/greater harm not proven
CHADS2 score ≤ 1	*HR 0.88 [0.52; 1.48]* *2.7% vs. 3.0%*	*Lesser/greater harm not proven*
CHADS2 score > 1	*HR 1.68 [1.10; 2.56]* *HRd 0.60 [0.39; 0.91]* *3.7% vs. 2.2%* *Probability: "indication"*	*Outcome category: non-serious/non-severe adverse events* *CIo > 0.9* *Lesser/greater harm not proven*

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Table 29: ASA population: apixaban versus ASA – extent of added benefit at outcome level (continued)

Outcome category **Outcome** **Subgroup**	**Effect estimate [95% CI] / proportion of events apixaban vs. ASA / p-value / probability[a]**	**Derivation of extent[b]**
Adverse events – other analyses of adverse events		
Overall rate AE, SAE, treatment discontinuations due to AE	Results were potentially influenced by the recording of events on benefit outcomes and are therefore not evaluable. However, in each case there is no evidence that the rate under apixaban would be higher than under ASA:	Lesser/greater harm not proven
Combined outcome: mortality, morbidity and adverse events		
Stroke (ischaemic, haemorrhagic or uncertain type), SE, major bleeds or mortality	HR 0.73 [0.60; 0.89] 6.4% vs. 8.7% p = 0.002 Probability: "indication"	Outcome category: serious/severe symptoms/late complications[f] $0.80 \leq CI_o < 0.9$ Added benefit/lesser harm; extent: "considerable"

Numbers in italics: information of effects for subgroups, in which there were indications or proof of effect modification.

a: Probability is provided if statistically significant differences were present

b: Estimations of effect size made depending on outcome category with different limits based on the upper limit of the confidence interval (CI_o)

c: Probability "hint", since there is an indication and not proof of an effect modification and there was no statistically significant difference in the total population

d. Proportion of events apixaban versus ASA (reversed direction of effect, to enable immediate use of the limits for deriving the extent of added benefit

e: This category was chosen because most events of the combined outcome were non-major bleeds.

f: This category was chosen because the effect was substantially due to non-fatal events

AE: adverse event; ASA: acetylsalicylic acid; $CHADS_2$:sum score for categorizing stroke risk in atrial fibrillation on the basis of the following factors: chronic congestive heart failure (1 point); hypertension (1 point) ; age ≥75 years (1 point); diabetes mellitus (1 point); prior stroke or TIA (2 points); CI: confidence interval; CI_o: upper limit confidence interval; HR: hazard ratio; SAE: serious adverse event; SE: systemic embolism; TIA: transient ischaemic attack

2.5.2.2 Overall conclusion on added benefit: ASA population

The summary of results that determine the overall conclusion on added benefit is shown in Table 30. Initially, possible subgroup effects are not considered. Thereafter, it is checked for each of the subgroup characteristics "age" and "severity" whether there are conclusions deviating from the total population. The results presented previously show that the effect modification by the characteristic "suitability for VKA therapy" with respect to the outcome "stroke" has no influence on the overall conclusion, since in both the total population as well as in the population demonstrated as unsuitable, the extent is the same ("considerable") for this outcome. The effect modification by the characteristic "suitability for VKA therapy" is therefore not considered further.

Table 30: Positive and negative effects from the assessment: apixaban versus ASA – consideration of the results of the total population

Positive effects	**Negative effects**
Indication of added benefit – extent: "considerable" (serious/severe symptoms/late complications: stroke); this is also reflected in the outcome "disabling strokes"	Indication of greater harm – extent: "minor" (complex "bleeding events")
Indication of added benefit – extent: "considerable" (serious/severe symptoms/late complications: SE)	
Indication of added benefit/lesser harm – extent: "considerable" (serious/severe symptoms/late complications: stroke, SE, major bleeds and mortality)	
SE: systemic embolism	

Overall, when considering the total populations, there remain indications of added benefit, with the extent "considerable" in each case, for the outcomes "stroke" and "SE". This is accompanied by an indication of greater harm with the extent "minor" (predominantly non-major bleeds). Since there is also an indication of considerable added benefit in the combined outcome of "stroke, SE, major bleeds and mortality", it does not appear justified to downgrade the extent from "considerable" to "minor". Overall, there is thus an indication, when considering the total population, of considerable added benefit of apixaban versus ASA.

Effect modifier "age"

There is no change for patients under 65 years when the effect modifier "age" is considered, because the extent of added benefit for the outcome "mortality" in this subgroup corresponds to the total population.

For patients ≥ 65 years there is also a hint of a minor added benefit for the outcome "mortality". This has no effect on the overall result (indication of considerable added benefit).

Accordingly, there are no changes when the effect modifier "age" is considered.

Effect modifier "severity"

The indication of greater harm (extent "minor") with respect to the combined bleeding outcome no longer applies for patients with severity $CHADS_2$ score ≤ 1. Since no downgrading of the extent because of this outcome was undertaken for the total population, this does not affect the extent of added benefit for such patients.

There is no change for patients with the severity $CHADS_2$ score = 2, because the extent of added benefit for the complex "bleeding events" in this subgroup corresponds to that of the total population.

For patients with the severity $CHADS_2$ score ≥ 3, the indication of greater harm in the combination bleeding outcome is rated as "considerable" instead of "minor". However, this also has no effect on the combined outcome of "stroke, SE, major bleeds and mortality" for this group of patients. For this outcome, the effects for patients with the severity $CHADS_2$ score ≥ 3 are the same as in the total population. It also does not appear appropriate in this constellation, to downgrade the extent to "minor".

Accordingly, when the effect modifier "severity" is considered, no changes arise.

Summary

Since none of the identified effect modifiers lead to a different conclusion regarding added benefit, for the ASA population as a whole there is an indication of a considerable added benefit of apixaban in comparison with ASA.

This deviates from the conclusion of the company, which derived proof of a major added benefit for the entire ASA population.

2.5.3 Extent and probability of added benefit – summary

The conclusions on the probability and extent of added benefit of apixaban are summarized in Table 31 below.

Table 31: Apixaban: Extent and probability of added benefit

Population	Appropriate comparator therapy	Extent and probability of added benefit
VKA population	VKA (phenprocoumon or warfarin)	
Age < 65 years		Added benefit not proven
Age ≥ 65 years		Indication of considerable added benefit
ASA population	ASA	Indication of considerable added benefit
ASA: acetylsalicylic acid; VKA: vitamin K antagonist		

This global assessment deviates substantially from that of the company, which claimed proof of a major added benefit for the entire VKA and the entire ASA population.

Further information on the extent and probability of added benefit can be found in Modules 4B and 4C, in each case in Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

For the two relevant studies ARISTOTLE and AVERROES the company cited the entry in the registry ClinicalTrials.gov both from the original registry and via the meta-registry International Clinical Trials Registry Platform (ICTRP). In the following text only the entries from the original registry are listed.

ARISTOTLE

Bristol-Myers Squibb. Apixaban for the prevention of stroke in subjects with atrial fibrillation (ARISTOTLE): full text view [online]. In: Clinicaltrials.gov. 29.11.2011 [accessed 15.03.2013]. URL: http://clinicaltrials.gov/show/NCT00412984.

Bristol-Myers Squibb, Pfizer. A phase 3, active (warfarin) controlled, randomized, double-blind, parallel arm study to evaluate the efficacy and safety of apixaban in preventing stroke and systemic embolism in subjects with non-valvular atrial fibrillation: study CV185030; clinical study report [unpublished]. 2011.

Bristol-Myers Squibb, Pfizer. Additional analyses of endpoints and subgroups for study CV185030: a phase 3, active (warfarin) controlled, randomized, double-blind, parallel arm study to evaluate the efficacy and safety of apixaban in preventing stroke and systemic embolism in subjects with non-valvular atrial fibrillation [unpublished]. 2012.

Easton JD, Lopes RD, Bahit MC, Wojdyla DM, Granger CB, Wallentin L et al. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. Lancet Neurol 2012; 11(6): 503-511.

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365(11): 981-992.

Lopes RD, Alexander JH, Al-Khatib SM, Ansell J, Diaz R, Easton JD et al. Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. Am Heart J 2010; 159(3): 331-339.

Lopes RD, Al-Khatib SM, Wallentin L, Yang H, Ansell J, Bahit MC et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. Lancet 2012; 380(9855): 1749-1758.

AVERROES

Bristol-Myers Squibb. A phase III study of apixaban in patients with atrial fibrillation (AVERROES): full text view [online]. In: Clinicaltrials.gov. 23.02.2012 [accessed 21.11.2012]. URL: http://clinicaltrials.gov/show/NCT00496769.

Bristol-Myers Squibb, Pfizer. Apixaban versus acetylsalicylic acid (ASA) to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment: a randomized double-blind trial; study CV185048; clinical study report [unpublished]. 2011.

Bristol-Myers Squibb, Pfizer. Analyses of endpoints and subgroups for patients excluding missing dose or 324 mg ASA/ASA placebo for study CV185048: apixaban versus acetylsalicylic acid (ASA) to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment; a randomized double-blind trial [unpublished]. 2012.

Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011; 364(9): 806-817.

Diener HC, Eikelboom J, Connolly SJ, Joyner CD, Hart RG, Lip GY et al. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. Lancet Neurol 2012; 11(3): 225-231.

Eikelboom JW, O'Donnell M, Yusuf S, Diaz R, Flaker G, Hart R et al. Rationale and design of AVERROES: apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment. Am Heart J 2010; 159(3): 348-353.

References for English extract

Please see full dossier assessment for full reference list.

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3. European Medicines Agency. Eliquis: European public assessment report; product information [online]. 23.05.2013 [accessed: 23.05.2013]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf.

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The full report (German version) is published under https://www.iqwig.de/de/projekte_ergebnisse/projekte/arzneimittelbewertung/a12_20_apixaban_nutzenbewertung_gemass_35a_sgb_v_dossierbewertung.3262.html.