IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Apixaban –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment ("Apixaban – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 12.03.2012). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

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[3]Table numbers start with “2” in this extract as numbering follows the German full version.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
DVT	deep vein thrombosis
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
VTE	venous thromboembolic events

2. Benefit assessment

2.1 Executive summary of the benefit assessment

Background

On 14.12.2011, in accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) wrote to IQWiG to commission the benefit assessment of the drug apixaban. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company").

Research question

The benefit assessment of apixaban was undertaken in accordance with the approval status in the following therapeutic indication: "*Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery*" [1]. The assessment was conducted in comparison with enoxaparin (customized to the individual patient) as appropriate comparator therapy (ACT) with respect to patient-relevant outcomes. Only randomized controlled trials (RCTs) with a direct comparator were included in the assessment.

Results[4]

A total of two relevant studies were available. In the ADVANCE-2 study, patients undergoing elective knee replacement surgery were enrolled, whilst the ADVANCE-3 study enrolled patients undergoing elective hip replacement surgery. Both studies were carried out double-blind and each contained a treatment period (knees 12 ± 2 days; hips 35 ± 3 days) and a follow-up period of 60 ± 5 days. Where possible, the result of the entire period, i.e. the combination of treatment and follow-up periods, was used for the assessment. The risk of bias of both studies was rated as low, both at study level and for the individual outcomes. Both studies were combined for meta-analysis. If heterogeneity was present, the assessment was carried out at the level of the individual study, i.e. separately for patients undergoing elective knee or hip replacement surgery. On the basis of the available evidence (2 studies), in principle proof, e.g. of an added benefit, could be derived from the data, unless outcome-specific aspects weakened the informative value.

Mortality

The result of the meta-analysis for the outcome "mortality" was not statistically significant. An added benefit or greater harm from apixaban for this outcome is not proven. It should be borne in mind that, due to the duration of the studies and number of enrolled patients, neither

[4]. On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit of an intervention. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit 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 data not interpretable), see [2]. The extent of added benefit is graded into 6 categories: (1) major, (2) considerable, (3) minor, (4) non-quantifiable, (5) no added benefit, or (6) less benefit, see [3].

study was designed to enable differences between treatments to be detected with regard to this outcome.

Morbidity

Pulmonary embolism

Due to the heterogeneity present ($p < 0.2$), the results for pulmonary embolisms were not combined for meta-analysis. On the basis of the individual study results, the ADVANCE-2 study (Knee-OP) showed a statistically significant result to the disadvantage of apixaban. In the ADVANCE-3 study (Hip-OP), although the rate of pulmonary embolisms under enoxaparin was higher, the result was not statistically significant. The results are assessed as an indication of lesser benefit of apixaban for this outcome in patients undergoing elective knee replacement surgery. For patients undergoing elective hip replacement surgery, an added benefit of apixaban for the outcome "pulmonary embolisms" is not proven.

Symptomatic deep vein thrombosis (DVT)

In the assessment of this outcome, distal and proximal symptomatic DVTs were considered together, with more patients suffering a proximal – and hence more serious – symptomatic DVT (approx. 59%) than distal. The result of the meta-analysis of the outcome "symptomatic DVT" was statistically significant in favour of apixaban. An added benefit of apixaban for this outcome is thus proven.

Health-related quality of life

No study data were available for the outcome "health-related quality of life". An added benefit of apixaban for this outcome is therefore not proven.

Adverse events – bleeding events

The results of the bleeding outcomes included in the assessment are shown below. Since no analysis of bleeding outcomes was available for the entire period, the assessment is based on the treatment period. Overall, this appears non-critical, because the events rates in the follow-up period for all bleeding events were relatively low in comparison with the treatment period. The assessment of the added benefit is made as a summary for the complex "bleeding events".

Major bleeds and clinically relevant non-major bleeds

The result of the meta-analysis for the outcome "major bleeds or clinically relevant non-major bleeds" in the treatment period was not statistically significant.

Major bleeds

The result of the meta-analysis for the outcome "major bleeds" in the treatment period was not statistically significant.

Clinically relevant non-major bleeds

The result of the meta-analysis for the outcome "clinically relevant non-major bleeds" in the treatment period was not statistically significant. However, the meta-regression calculated by the Institute for this outcome produced an indication ($p < 0.2$) of an effect modification by the characteristic "age". For patients aged ≥ 75 years, the results showed a statistically significant difference in favour of apixaban. The subgroup differences could be largely attributed to patients undergoing elective hip replacement surgery (ADVANCE-3). In this study, the difference between apixaban and enoxaparin was most marked in the age group ≥ 75 years. In the other two age groups (< 65 years; ≥ 65 to < 75 years), there was no statistically significant result for either study, or in the meta-analysis of both of them.

Adverse events (AEs) – bleeds

Due to the heterogeneity present ($p < 0.2$), the results for the outcome "adverse events – bleeds" in the treatment period were not combined for meta-analysis. A further investigation of heterogeneity was not necessary in this case, because the result of the two individual studies was not statistically significant.

Serious adverse events (SAEs) – bleeds

Due to the heterogeneity present ($p < 0.2$), the results for the outcome "serious adverse events – bleeds" were not combined for meta-analysis. On the basis of the individual study results, the ADVANCE-3 study showed a statistically significant result to the disadvantage of apixaban. In the ADVANCE-2 study, although the rate of SAE-bleeds under enoxaparin was increased, the result was not statistically significant.

Summary of the results for bleeding events

In summary, greater or lesser harm from apixaban in comparison with enoxaparin for the complex "bleeding events" is not proven. The reasons for this are as follows:

For patients undergoing elective knee replacement surgery, none of the bleeding outcomes investigated showed a statistically significant result. This applies to the overall analysis as well as the subgroup analyses.

For patients undergoing elective hip replacement surgery, there was a statistically significant result to the disadvantage of apixaban for the outcome "serious adverse events – bleeds". This result was, however, not supported by other results of further bleeding outcomes. For patients of 75 years and over undergoing elective hip replacement surgery, there was, in contrast, an advantage for clinically relevant non-major bleeds under apixaban. But this – apparently contradictory - result compared to the SAE bleeds was not supported by further results of other bleeding outcomes. Overall, the results for the complex "bleeding events" were not of sufficient informative value to enable greater or lesser harm from apixaban to be derived for this group of patients.

Adverse events – other analyses of adverse events

When interpreting the results of the outcomes "overall rate of AEs", "overall rate of SAEs" and "treatment discontinuations due to AEs", the problem arose that in each case, patients with DVT were also recorded. However, in contrast to clinical practice, in the two studies ADVANCE-2 and ADVANCE-3 all patients were to undergo venography even when no DVT symptoms were present. This led to a large number of asymptomatic DVT being diagnosed, whereby the event rate for the 3 outcomes "AEs", "SAEs" and "treatment discontinuations due to AEs" was also potentially influenced. However, neither in the company's dossier, nor in the study reports were results for "AEs", "SAEs" and "treatment discontinuations due to AE" presented in which patients with DVT were *not* considered. Nevertheless, for all 3 outcomes, the study reports contained information regarding the number of patients in whom at least one event classified as DVT occurred. From this it could at least be estimated whether the respective result was substantially influenced by the recording of DVT. The outcome "pulmonary embolisms" was also recorded under the outcomes "AEs" and "SAEs". Since the already mentioned venography did not, however, lead to the diagnosis of asymptomatic pulmonary embolisms and, moreover, the event rate in both studies for pulmonary embolisms recorded as AEs or SAEs was well below 0.5%, it is not assumed that this led to a substantial effect on the result concerning AEs/SAEs.

Overall rate of AEs

In the meta-analysis of the two studies concerning the overall rate of AEs, there was a statistically significant result in favour of apixaban (treatment period). The meta-analysis of AEs classified as DVT also showed a statistically significant result in favour of apixaban. The absolute difference in event rates in the two analyses was of a similar order of magnitude (approx. 2 to 3%). The result on overall rate of AEs was accordingly potentially substantially influenced by the recording of DVT. Taken as a whole, there is therefore no proof of a lesser harm from apixaban compared with enoxaparin in terms of the overall rate of AEs.

Overall rate of serious adverse events (SAEs)

The meta-analysis of the two studies on the overall rate of SAEs in the treatment period showed heterogeneous results ($p < 0.2$). Because of the heterogeneous data, the effect of DVT recorded as SAEs was assessed at the individual study level. No statistically significant result was shown in the two individual studies, neither for the overall rate of SAEs nor for the DVT recorded as SAEs. The absolute difference in event rates in the ADVANCE-2 study, with a value of approx. 1% in favour of apixaban, was of a similar order of magnitude to the SAEs recorded as DVT. In the ADVANCE-3 study, the overall rate of SAEs showed a numerical difference to the disadvantage of apixaban, but the DVT recorded as SAEs showed a numerical difference in favour of apixaban. Overall, the data provide no proof of a lesser or greater harm from apixaban compared to enoxaparin in terms of the overall rate of SAEs.

Overall rate of adverse events that led to treatment discontinuation

The proportions of patients with adverse events that led to discontinuation of treatment did not differ substantially between apixaban and enoxaparin in either of the studies. The result of the meta-analysis was not statistically significant and there was no noteworthy heterogeneity between the results of the individual studies. The event rate of treatment discontinuations due to a DVT showed practically no difference between the treatment groups in either study, so it is not be assumed that the recording of treatment discontinuations due to DVT had substantially affected the result of this outcome. Taken as a whole, greater or lesser harm from apixaban for the outcome "treatment discontinuations due to AEs" is not proven.

Extent and probability of the added benefit, patient groups with therapeutically important added benefits

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

For adult **patients undergoing elective knee replacement surgery** the data provide proof of an added benefit of apixaban regarding the outcome "symptomatic DVT" and an indication of a lesser benefit of apixaban in terms of the outcome "pulmonary embolisms". The extent of the respective added benefit or lesser benefit at outcome level was estimated based on these results, taking outcome categories and effect sizes into account. This led to positive and negative results of differing extent and differing probability. On the side of added benefit, there is proof, with the extent "minor" of an added benefit (symptomatic DVT). This is accompanied by an indication of a lesser benefit, with the extent "considerable" (pulmonary embolisms). However, at individual study level (ADVANCE-2) a non-statistically significant result for the outcome "symptomatic DVT" is accompanied by a statistically significant result for the outcome "pulmonary embolisms". Therefore, in the Institute's view, from the available data it is overall not possible to conclude that the added benefit on the one hand outweighs the lesser benefit on the other. **In summary, for patients undergoing elective knee replacement surgery, there is no proof of added benefit of apixaban over the ACT enoxaparin.**

For adult **patients undergoing elective hip replacement surgery,** the data provide proof of an added benefit of apixaban regarding symptomatic DVT. The extent of the respective added benefit at outcome level was estimated based on these results, taking outcome categories and effect sizes into account. This led to a positive result in favour of apixaban with the extent "minor" and the probability "proof" (symptomatic DVT). A decision balancing benefits and harms is not required. **In summary, for patients undergoing elective hip replacement surgery, there is proof of an added benefit (extent "minor") of apixaban over the ACT enoxaparin.**

The procedure for deriving the overall conclusion on the added benefit is a proposal from IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The benefit assessment of apixaban was undertaken in accordance with the approval status for patients in the following therapeutic indication: "*Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery*" [1]. The company designated enoxaparin as ACT. Enoxaparin is a low molecular weight heparin and thus corresponds to the ACT specified by the G-BA: "*Those low molecular weight heparins that are approved for the peri- and postoperative primary prophylaxis of deep vein thrombosis in situations with a high risk of thromboembolic events (e.g. orthopaedic surgery). The drugs should be given at the dosages approved for the severity and tailored for each individual patient."* Particularly in patients undergoing elective hip replacement surgery, attention is to be paid to ensure that the duration of treatment is adjusted for each individual patient, e.g. depending on the degree of mobilization.

The aim of this report is therefore to assess the added benefit of apixaban versus enoxaparin in adult patients after elective hip or knee replacement surgery.

The assessment was undertaken with respect to patient-relevant outcomes. Only RCTs with a direct comparator were included in the assessment.

This benefit assessment deviates substantially from the company's assessment with regard to two points in particular:

1. This benefit assessment combines the study results for the overall therapeutic indication of elective hip or knee replacement surgery, primarily in the form of meta-analyses. The company considered the patient collectives undergoing elective hip or knee replacement surgery separately and did not carry out meta-analyses.

2. Where the corresponding data were available, the study results used for this benefit assessment covered the entire duration of the study (entire period). Each of the two studies included in the assessment consisted of a treatment period and a follow-up period. Outcome data were recorded in both periods. The company only considered the treatment period.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, 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 from the following data:

- Studies on apixaban completed by the company up to 01.10.2011 (study list of the company)
- Results of a search in trial registries for studies on apixaban (last search 21.10.2011. searches by the company)

- The Institute's own searches in trial registries for studies on apixaban to check the company's search results (search date: 03.01.2012). In addition, a check was carried out on the information retrieval by the company using the inclusion criteria specified by the Institute, which deviated substantially from that of the company in terms of population and minimum duration of prophylaxis. The check produced no deviations from the study pool presented in the company's dossier.

The resulting study pool corresponded to that used by the company.

Further information about the inclusion criteria for studies in the present benefit assessment and the methods of information retrieval can be found in Module 4, 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 in the assessment

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

Table 2: Study pool

Study	Study category		
	Pivotal study for approval of the drug to be assessed (yes/no)	**Sponsored study[a] (yes/no)**	**Third-party study (yes/no)**
Patients undergoing elective knee replacement surgery ADVANCE-2 (CV185047)	yes	yes	no
Patients undergoing elective hip replacement surgery ADVANCE-3 (CV185035)	yes	yes	no
a: Study for which the company was sponsor, or in which the company was otherwise financially involved.			

Two RCTs (ADVANCE-2 und ADVANCE-3) were submitted for the assessment of apixaban in direct comparison with enoxaparin in adult patients following elective hip or knee replacement surgery.

Section 2.6 contains a list of data sources named by the company for the studies included in its assessment.

Further information about the results of information retrieval and the study pool derived from it can be found in Module 4, Section 4.3.1.1 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 3 and Table 4 describe the studies for the benefit assessment. Table 3 shows the characteristics of the studies; Table 4 shows the characteristics of the interventions used in the studies.

Table 3: Characteristics of the studies included in the assessment

Study	Study design	Population	Interventions (number of randomized patients)	Duration of study	Location and period of study	Primary outcome; secondary outcomes[a]
ADVANCE-2 (Knee-OP)	RCT, double-blind, parallel, multicentre	Adults undergoing elective knee replacement surgery	Apixaban (n = 1528) Enoxaparin (n = 1529)	Treatment period: 12 ± 2 days Follow-up period: 60 ± 5 days	Africa, Asia, Europe (including Germany), Latin America. Period 06/2007–01/2009	Primary: combination of all VTE + all-cause mortality Secondary: all-cause mortality, pulmonary embolism, symptomatic DVT (symptomatic distal and proximal DVT), combination of major and clinically relevant non-major bleeds, major bleeds, clinically relevant non-major bleeds, other adverse events.
ADVANCE-3 (Hip-OP)	RCT, double-blind, parallel, multicentre	Adults undergoing elective hip replacement surgery	Apixaban (n = 2708) Enoxaparin (n = 2699)	Treatment period: 35 ± 3 days Follow-up period: 60 ± 5 days	Asia, Europe (including Germany), Latin America, North America. Period 03/2007–09/2009	Primary: combination of all VTE + all-cause mortality Secondary: all-cause mortality, pulmonary embolism, symptomatic DVT (symptomatic distal and proximal DVT), combination of major and clinically relevant non-major bleeds, major bleeds, clinically relevant non-major bleeds, other adverse events.

a: Extracted primary outcome criteria contain information without consideration of relevance for this benefit assessment. Extracted secondary outcome criteria contain exclusively information on the relevant available outcomes for this benefit assessment.

DVT: deep vein thrombosis; RCT: randomized controlled trial; VTE: venous thromboembolism.

Table 4: Characteristics of the interventions

Study	Apixaban	Enoxaparin
ADVANCE-2 (Knee-OP)	12 ± 3h preoperatively: placebo injection postoperatively after wound closure: apixaban 2 x daily 2.5 mg oral placebo 1 x daily subcutaneously	12 ± 3h preoperatively: enoxaparin injection postoperatively after wound closure: placebo 2 x daily oral + enoxaparin 40 mg 1 x daily subcutaneously
ADVANCE-3 (Hip-OP)	12 ± 3h preoperatively: placebo injection postoperatively after wound closure: apixaban 2 x daily 2.5 mg oral + placebo 1 x daily subcutaneously	12 ± 3h preoperatively: enoxaparin injection postoperatively after wound closure: placebo 2 x daily oral + enoxaparin 40 mg 1 x daily subcutaneously

The two studies included in the assessment were approval studies of the company in patients undergoing elective knee replacement surgery (ADVANCE-2) or elective hip replacement surgery (ADVANCE-3). Both studies were randomized, active-controlled and double-blind. A total of 3057 patients were randomized in the ADVANCE-2 study and 5407 in the ADVANCE-3 study. The total duration of the ADVANCE-2 study was 72 ± 7 days and comprised a treatment period of 12 ± 2 days and a follow-up period of 60 ± 5 days. In the ADVANCE-3 study, treatment was carried out for 35 ± 3 days and the follow-up period was likewise 60 ± 5 days, giving a total study duration of 95 ± 8 days. Treatment was always started 12 ± 3 hours before surgery with an injection of placebo or 40 mg enoxaparin. After wound closure - generally on the morning after surgery - the patients received the study medication as follows: apixaban 2.5 mg orally twice daily or enoxaparin 40 mg subcutaneously once daily, with in each case placebo given as the other medication. In both studies, venography was carried out at the end of the treatment period. If symptomatic DVT or pulmonary embolism occurred during the study, treatment with the study medication was discontinued after diagnostic confirmation. At the discretion of the physician and according to standard practice, the treatment could then be continued with other antithrombotic agents. This also applied if an asymptomatic DVT was diagnosed by venography at the end of the treatment period, where, as a general rule, the treating physician could switch to another treatment at the end of the treatment period. Patients remained in the study and were followed-up regardless of premature discontinuation of treatment with the study medication.

With regard to the duration of treatment with enoxaparin, it should be noted that in the ADVANCE-3 study, this may not necessarily have been customized to each patient (for some patients it was too long). According to the enoxaparin Summary of Product Characteristics, this individualized treatment is a requirement and hence also a constituent of the ACT. However, the Institute agrees with the basic assessment of the company, according to which the ADVANCE-3 study can be used for the assessment. Nevertheless the matter must, if necessary, be considered – especially in the case of heterogeneity between the studies ADVANCE-2 and -3 – when interpreting the results.

Table 5 shows the characteristics of patients in the assessed studies. There were no substantial differences between the treatment groups in terms of age, sex or BMI in either study. Patients undergoing knee replacement surgery were on average 5 years older than those undergoing hip replacement surgery. Whereas between 71 and 74% female patients were enrolled for knee replacement surgery, the corresponding figure for hip replacement was 53 to 54%. The average BMI was 28 to 30 kg/m^2.

Table 5: Characteristics of the study population

Study Group	N	Age in years mean (SD)	Sex f /m (%)	BMI mean (SD)	Type of surgery
ADVANCE-2 (Knee-OP)					Patients undergoing elective knee replacement surgery including revisions, uni- or bilateral
Apixaban	1528	66 (10)	71 / 29	29 (5)	
Enoxaparin	1529	66 (10)	74 / 26	30 (5)	
ADVANCE-3 (Hip-OP)					Patients undergoing elective hip replacement surgery including revisions, no emergency operations such as hip fractures
Apixaban	2708	61 (12)	53 / 47	28 (5)	
Enoxaparin	2699	61 (12)	54 / 46	28 (5)	
BMI: Body Mass Index; f: female, m: male; N: number of randomized patients; SD: standard deviation					

Table 6 shows the risk of bias at study level. The risk of bias at study level was classed as low for both studies. This concurs with the company's assessment.

Table 6: Risk of bias at study level

Study	Random sequence generation	Allocation concealment	Blinding		Selective reporting	Other sources of bias	Risk of bias at study level
			Participants	Personnel			
ADVANCE-2 (Knee-OP)	yes	yes	yes	yes	no	no	low
ADVANCE-3 (Hip-OP)	yes	yes	*yes*	yes	no	no	low

Further information about the study design, study populations and risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1 and 4.3.1.2.2 of the dossier and in Section 2.7.2.4.1 of the full dossier assessment.

2.4 Results concerning added benefit

Relevant outcomes

This assessment covers the following patient-relevant outcomes (for reasoning, see Sections 2.7.2.2 and 2.7.2.4.2 of the full dossier assessment):

- Mortality
- Pulmonary embolism
- Symptomatic DVT (symptomatic distal and proximal DVT)
- Health-related quality of life
- Bleeding outcomes:
  - combination: major bleeds and clinically relevant non-major bleeds
  - major bleeds
  - clinically relevant non-major bleeds
  - bleeds recorded as an adverse event (AE)
  - bleeds recorded as a serious adverse event (SAE)
- Other adverse events:
  - overall rate of AEs
  - overall rate of SAEs
  - overall rate of AEs that led to treatment discontinuation

The Institute deviated in its choice of patient-relevant outcomes from that of the company, which used additional outcomes in its dossier (Module 4). The Institute also included the additional following outcomes: symptomatic DVT, health-related quality of life, combination: major bleeds and clinically relevant non-major bleeds and the single components clinically relevant non-major bleeds, AE bleeds, SAE bleeds. The overall rates of AE, SAE and treatment discontinuations due to AE were interpreted under consideration of the DVT contained in each category.

Data availability and risk of bias

Table 7 shows for which outcomes data were available in the studies included. Table 8 describes the risk of bias for these outcomes.

Table 7: Matrix of outcomes, data availability

Study	All-cause mortality	Pulmonary embolism	Symptomatic DVT (proximal and distal)	Health-related quality of life	Major bleeds and clinically rel. non-major bleeds	Major bleeds	Clinically rel. non-major bleeds	AE bleeds	SAE bleeds	AE[a]	SAE[a]	Discontinuations due to AE[a]
Treatment period												
ADVANCE-2 (Knee-OP)	yes	yes	yes	-[b]	yes	yes	yes	yes	no	(yes)	(yes)	(yes)
ADVANCE-3 (Hip-OP)	yes	yes	yes	-[b]	yes	yes	yes	yes	no	(yes)	(yes)	(yes)
Follow-up period												
ADVANCE-2 (Knee-OP)	yes	yes	yes	-[b]	yes	yes	yes	yes	no	(yes)	(yes)	n. a.
ADVANCE-3 (Hip-OP)	yes	yes	yes	-[b]	yes	yes	yes	yes	no	(yes)	(yes)	n. a.
Total period (treatment and follow-up periods)												
ADVANCE-2 (Knee-OP)	yes	yes	yes	-[b]	no	no	no	no	yes[c]	no	no	n. a.
ADVANCE-3 (Hip-OP)	yes	yes	yes	-[b]	no	no	no	no	yes[c]	no	no	n. a.

a: Data on AEs, SAEs and treatment discontinuations due to AEs only usable to a limited extent because DVTs were also recorded in each case (see Section 2.4.4.2).

b: Parameter was not recorded.

c: Institute's calculation, the SAE – bleeds for the entire study duration were taken from the "Listing of Bleeding-Related Adverse Events – Enrolled Subjects" of the respective study reports.

AE: adverse event, DVT: deep vein thrombosis, n. a: not applicable, SAE: serious adverse event

Table 8: Risk of bias at study and outcome level

Outcome / Study	Study level	All-cause mortality	Pulmonary embolism	Symptomatic DVT (proximal and distal)	Health-related quality of life	Major bleeds + clinically rel. non-major bleeds	Major bleeds	Clinically rel. non-major bleeds	AE bleeds	SAE bleeds	AE[a]	SAE[a]	Discontinuation due to AE[a]
ADVANCE-2 (Knee-OP)	low	low	low	low	-[b]	low	low	low	low	low	(low)	(low)	(low)
ADVANCE-3 (Hip-OP)	low	low	low	low	-[b]	low	low	low	low	low	(low)	(low)	(low)

a: Data on AEs, SAEs and treatment discontinuations due to AEs only usable to a limited extent, because DVTs were also recorded in each case (see Section 2.4.4.2).

b: Parameter was not recorded.

AE: adverse event, DVT: deep vein thrombosis, SAE: serious adverse event

Apart from the non-recorded data on the health-related quality of life, an overall good availability of outcomes can be assumed (see Table 7: Matrix of outcomes, data availability). However, in the Institute's opinion, it would have been desirable to have also submitted an analysis of the event frequency for the harm outcomes during the entire duration of the study (entire period). For SAE bleeds, the information for the entire period was extracted from the individual listings of the adverse events for bleeds.

The risk of bias for all outcomes was rated as low. The results on overall rates of AEs, SAEs and treatment discontinuations were, however, usable to only a limited extent, because DVTs were also recorded in each case (see Section 2.4.4.2).

The assessment of risk of bias concurs with that of the company, provided the outcomes were also used by the company. The assessment applies to all study periods, whereby account was taken of the fact that the discontinuation rate after the treatment period was relatively low and blinding was also maintained through the follow-up period. The company had only assessed the risk of bias for the treatment period.

Further information about the choice of outcome and risk of bias at outcome level can be found in Module 4, Sections 4.2.5.2 and 4.3.1.3 of the dossier and in Sections 2.7.2.2 and 2.7.2.4 of the full dossier assessment.

Results

Table 9 summarizes the results of the comparison of apixaban and enoxaparin in patients undergoing elective knee- or hip replacement surgery. Data from Module 4 of the dossier were supplemented by additional outcomes, data from the follow-up and entire periods and a meta-analysis of the two studies included in the assessment. For the outcome "symptomatic DVT" the event numbers were additionally shown separately according to location (proximal or distal). In addition, in the interpretation of the overall rates of AEs, SAEs and treatment discontinuations due to AEs, the events classified as DVT for these 3 outcomes were shown in each case.

Effects (effect estimator, confidence interval, p-value) were always calculated and shown if they were necessary for the interpretation of the results.

In the case of very low event rates (event numbers of ≤ 1% in at least one cell) per outcome (e.g. mortality) the Peto OR was calculated as effect measure instead of the relative risk and used for the assessment.

Table 9: Results on the comparison of apixaban vs. enoxaparin, patients undergoing elective knee (ADVANCE-2) or hip replacement surgery (ADVANCE-3)

Outcome	Apixaban		Enoxaparin		Apixaban vs. enoxaparin	
Period Study	N	Events n (%)	N	Events n (%)	RR/Peto OR[a] [95% CI]	p-value[a]
Mortality						
Treatment period						
ADVANCE-2	1528[b]	2 (0.13)[c]	1529[b]	0 (0)	-	-
ADVANCE-3	2708[b]	3 (0.11)[c]	2699[b]	1 (0.04)[c]	-	-
Follow-up period						
ADVANCE-2	1458	1 (0.07)	1469	1 (0.07)	-	-
ADVANCE-3	2598	2 (0.08)	2577	1 (0.04)	-	-
Total period						
ADVANCE-2	1528[b]	3 (0.20)	1529[b]	1 (0.07)	2.72 [0.38; 19.35][c]	0.375[d]
ADVANCE-3	2708[b]	5 (0.18)	2699[b]	2 (0.07)	2.35 [0.53; 10.35][c]	0.453[d]
Meta-analysis[e]					2.48 [0.76; 8.09]	0.132
Morbidity						
Pulmonary embolism						
Treatment period						
ADVANCE-2	1528[b]	4 (0.26)	1529[b]	0 (0)	-	-
ADVANCE-3	2708[b]	3 (0.11)	2699[b]	5 (0.19)	-	-
Follow-up period						
ADVANCE-2	1458	3 (0.21)	1469	1 (0.07)	-	-
ADVANCE-3	2598	0 (0)	2577	4 (0.16)	-	-
Total period						
ADVANCE-2	1528[b]	7 (0.46)	1529[b]	1 (0.07)	4,50 [1.12; 18,02][c]	0.039[d]
ADVANCE-3	2708[b]	3 (0.11)	2699[b]	9 (0.33)	0.37 [0.12; 1.14][c]	0.091[d]
Meta-analysis[e]	Heterogeneity: Q = 7.54, df = 1. p = 0.006, I^2 = 86.7%					
Symptomatic DVT						
Treatment period						
ADVANCE-2	1528[b]	3 (0.20)	1529[b]	7 (0.46)	-	-
ADVANCE-3	2708[b]	1 (0.04)	2699[b]	5 (0.19)	-	-
Follow-up period						
ADVANCE-2	1458	2 (0.14)	1469	1 (0.07)	-	-
ADVANCE-3	2598	0 (0)	2577	3 (0.12)	-	-
Total period						
ADVANCE-2	1528[b]	5 (0.33)	1529[b]	8 (0.52)	0.63 [0.21; 1.87][c]	0.580[d]
ADVANCE-3	2708[b]	1 (0.04)	2699[b]	8 (0.30)	0.21 [0.06; 0.78][c]	0.021[d]
Meta-analysis[e]					0.40 [0.17; 0.93]	0.033

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Table 9: Results on the comparison of apixaban vs. enoxaparin, patients undergoing elective knee (ADVANCE-2) or hip replacement surgery (ADVANCE-3) (continued)

Outcome	Apixaban		Enoxaparin		Apixaban vs. enoxaparin	
Period Study	**N**	**Events n (%)**	**N**	**Events n (%)**	**RR/Peto-OR[a] [95% CI]**	**p-value[a]**
Of which symptomatic proximal DVT						
Treatment period						
ADVANCE-2	1528[b]	1 (0.07)	1529[b]	1 (0.07)	-	-
ADVANCE-3	2708[b]	1 (0.04)	2699[b]	4 (0.15)	-	-
Follow-up period						
ADVANCE-2	1458	2 (0.14)	1469	1 (0.07)	-	-
ADVANCE-3	2598	0 (0)	2577	3 (0.12)	-	-
Total period						
ADVANCE-2	1528[b]	3 (0.20)	1529[b]	2 (0.13)	-	-
ADVANCE-3	2708[b]	1 (0.04)	2699[b]	7 (0.26)	-	-
Of which symptomatic distal DVT						
Treatment period						
ADVANCE-2	1528[b]	3 (0.20)	1529[b]	7 (0.46)	-	-
ADVANCE-3	2708[b]	1 (0.04)	2699[b]	1 (0.04)	-	-
Follow-up period						
ADVANCE-2	1458	0 (0)	1469	0 (0)	-	-
ADVANCE-3	2598	0 (0)	2577	0 (0)	-	-
Total period						
ADVANCE-2	1528[b]	3 (0.20)	1529[b]	7 (0.46)	-	-
ADVANCE-3	2708[b]	1 (0.04)	2699[b]	1 (0.04)	-	-
Health-related quality of life						
ADVANCE-2			outcome was not recorded			
ADVANCE-3			outcome was not recorded			
Adverse events						
Major bleeds[f] and clinically relevant non-major bleeds[g]						
Treatment period						
ADVANCE-2	1501	53 (3.53)	1508	72 (4.77)	0.74 [0.52¸1.05][c]	0.100[d]
ADVANCE-3	2673	129 (4.83)	2659	134 (5.04)	0.96 [0.76; 1.21][c]	0.752[d]
Meta-analysis[h]					0.87 [0.68; 1.11]	0.264
Follow-up period						
ADVANCE-2	1457	4 (0.27)	1469	8 (0.54)	-	-
ADVANCE-3	2599	2 (0.08)	2576	9 (0.35)	-	-

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Table 9: Results on the comparison of apixaban vs. enoxaparin, patients undergoing elective knee (ADVANCE-2) or hip replacement surgery (ADVANCE-3) (continued)

Outcome	Apixaban		Enoxaparin		Apixaban vs. enoxaparin	
Period Study	N	Events n (%)	N	Events n (%)	RR/Peto-OR[a] [95% CI]	p-value[a]
Major bleeds[f]						
Treatment period						
ADVANCE-2	1501	9 (0.60)	1508	14 (0.93)	0.65 [0.29; 1.47][c]	0.403[d]
ADVANCE-3	2673	22 (0.82)	2659	18 (0.68)	1.22 [0.65; 2.27][c]	0.635[d]
Meta-analysis[e]					0.97 [0.59; 1.59]	0.894
Follow-up period						
ADVANCE-2	1457	0 (0)	1469	4 (0.27)	-	-
ADVANCE-3	2599	0 (0)	2576	2 (0.08)	-	-
Clinically relevant non-major bleeds[g]						
Treatment period						
ADVANCE-2	1501	44 (2.93)	1508	58 (3.85)	0.76 [0.52; 1.12][c]	0.190[d]
ADVANCE-3	2673	109 (4,08)	2659	120 (4.51)	0.90 [0.70; 1.16][c]	0.458[d]
Meta-analysis[h]					0.86 [0.69; 1.06]	0.157
Follow-up period						
ADVANCE-2	1457	4 (0.27)	1469	4 (0.27)	-	-
ADVANCE-3	2599	2 (0.08)	2576	7 (0.27)	-	-
AE bleeds						
Treatment period						
ADVANCE-2	1501	90 (6.00)[c]	1508	112 (7.43)[c]	0.81 [0.62; 1.06][c]	0.126[d]
ADVANCE-3	2673	268 (10.03)[c]	2659	268 (10.08)[c]	0.99 [0.85; 1.17][c]	0.964[d]
Meta-analysis[h]	Heterogeneity: Q = 1.72. df = 1. p = 0.190. I^2 = 41.7%					
Follow-up period						
ADVANCE-2	1457	9 (0.62)[c]	1469	11 (0.75)[c]	-	-
ADVANCE-3	2599	15 (0.58)[c]	2576	21 (0.82)[c]	-	-
SAE bleeds						
Total period						
ADVANCE-2	1501[i]	8[i] (0.53)[c]	1508[i]	14[i] (0.93)[c]	0.58 [0.25; 1.34][c]	0.285[d]
ADVANCE-3	2673[i]	25[i] (0.94)[c]	2659[i]	9[i] (0.34)[c]	2.56 [1.31; 5.03][c]	0.009[d]
Meta-analysis[e]	Heterogeneity: Q = 7.33, df = 1. p = 0.007, I^2 = 86.4					

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Table 9: Results on the comparison of apixaban vs. enoxaparin, patients undergoing elective knee (ADVANCE-2) or hip replacement surgery (ADVANCE-3) (continued)

Outcome	Apixaban		Enoxaparin		Apixaban vs. enoxaparin	
Period Study	N	Events n (%)	N	Events n (%)	RR/Peto-OR[a] [95% CI]	p-value[a]
Overall rate of AEs						
Treatment period						
ADVANCE-2	1501	786 (52.37)	1508	836 (55.44)	0.94 [0.88; 1.01]	0.093[d]
ADVANCE-3	2673	1752 (65.54)	2659	1811 (68.11)	0.96 [0.93; 1.00]	0.048[d]
Meta-analysis[h]					0.96 [0.93, 0.99]	0.010
Follow-up period						
ADVANCE-2	1457	167 (11.46)[c]	1469	168 (11.44)[c]	-	-
ADVANCE-3	2599	318 (12.24)[c]	2576	324 (12.58)[c]	-	-
Of which DVT						
Treatment period						
ADVANCE-2	1501	99 (6.60)[c]	1508	148 (9.81)[c]	0.67 [0.53; 0.86][c]	0.001[d]
ADVANCE-3	2673	45 (1.68)[c]	2659	69 (2.59)[c]	0.65 [0.45; 0.94][c]	0.023[d]
Meta-analysis[h]					0.66 [0.54, 0.82]	< 0.001
Follow-up period						
ADVANCE-2	1457	7 (0.48)[c]	1469	10 (0.68)[c]	-	-
ADVANCE-3	2599	2 (0.08)[c]	2576	12 (0.47)[c]	-	-
Overall rate of SAEs						
Treatment period						
ADVANCE-2	1501	72 (4.79)	1508	88 (5.84)	0.82 [0.61; 1.11]	0.223[d]
ADVANCE-3	2673	184 (6.88)	2659	172 (6.47)	1.06 [0.87; 1.30]	0.547[d]
Meta-analysis[h]	Heterogeneity: Q = 1.94, df = 1. p = 0.164, I^2 = 48.4%					
Follow-up period						
ADVANCE-2	1457	13 (0.89)[c]	1469	15 (1.02)[c]	-	-
ADVANCE-3	2599	18 (0.69)[c]	2576	18 (0.70)[c]	-	-
Of which DVT						
Treatment period						
ADVANCE-2	1501	11 (0.73)[c]	1508	22 (1.46)[c]	-	-
ADVANCE-3	2673	8 (0.30)[c]	2659	18 (0.68)[c]	-	-
Follow-up period						
ADVANCE-2	1457	0 (0)	1469	3 (0.20)[c]	-	-
ADVANCE-3	2599	0 (0)	2576	0 (0)	-	-

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Table 9: Results on the comparison of apixaban vs. enoxaparin, patients undergoing elective knee (ADVANCE-2) or hip replacement surgery (ADVANCE-3) (continued)

Outcome	Apixaban		Enoxaparin		Apixaban vs. enoxaparin	
Period Study	N	Events n (%)	N	Events n (%)	RR/Peto-OR[a] [95% CI]	p-value[a]
Treatment discontinuations due to AEs						
Treatment period						
ADVANCE-2	1501	40 (2.66)	1508	44 (2.92)	0.91 [0.60; 1.39]	0.740[d]
ADVANCE-3	2673	91 (3,40)	2659	111 (4,17)	0.82 [0.62; 1.07]	0.151[d]
Meta-analysis[h]					0.84 [0.67; 1.06]	0.143
Of which DVT						
Treatment period						
ADVANCE-2	1501	10 (0.67)[c]	1508	11 (0.73)[c]	-	-
ADVANCE-3	2673	6 (0.22)[c]	2659	7 (0.26)[c]	-	-

a: Effects (effect estimator, confidence interval, p-value) were always calculated and shown if they were necessary for the interpretation of the results. Values of the Peto OR (Institute's calculation) instead of RR in the case of event numbers of 1% and lower in at least one cell.
b: All randomized patients.
c: Institute's calculation.
d: Institute's calculation, Fisher's exact test.
e: Institute's calculation, meta-analysis, model with fixed effect for Peto OR in the case of event numbers of 1% and lower in at least one cell.
f: At least one of the following criteria: decrease in Hb level of ≥ 2 g / dl over a 24-hour period, transfusion of ≥ 2 units of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, into the operated joint necessitating re-operation or intervention, retroperitoneal, intramuscular with compartment syndrome) and fatal bleeding.
g: Acute clinically overt bleeding such as epistaxis (duration ≥ 5 min and requiring treatment), gastrointestinal bleeding (vomiting, endoscopy or in stools), haematuria (duration ≥ 24 hours), bruising/ecchymosis, wound haematoma, haemoptysis.
h: Institute's calculation, meta-analysis, model with random effects (according to DerSimonian and Laird [4]).
i: Institute's calculation, the SAE – bleeds for the entire study duration were taken from the "Listing of Bleeding-Related Adverse Events – Enrolled Subjects" of the respective study reports. However, all listed patients had been assigned to a treatment, so that here reference to the "treated subjects" can be made.
AE: adverse event; CI: confidence interval; DVT: deep vein thrombosis; N: number of analysed patients; n: number of patients with event; OR: odds ratio; RR: relative risk; SAE: serious adverse event.

The derivation of proof, e.g. of added benefit, is in principle possible through the meta-analysis summary of the 2 available studies. This assessment concurs with that of the company. Reference is made below in the presentation of the results for the individual outcomes to a possible weakening through outcome-specific aspects. If available - unlike the company's procedure – the results of the entire period were used for the assessment.

The following aspects are to be considered outcome-specific in the interpretation of the results:

- Duration of treatment with enoxaparin in the ADVANCE-3 study possibly not customized to the individual patient to be taken into account – particularly in the case of heterogeneity between ADVANCE-2 and -3.
- Proportion of patients diagnosed with asymptomatic DVT after venography and who received corresponding treatment with anticoagulants (in both studies, this was statistically significantly higher in the enoxaparin than in the apixaban group) to be taken into account – especially for the assessment of bleeding events in the follow-up period.

2.4.1 Mortality

The proportion of patients who died in the two studies did not differ substantially between apixaban and enoxaparin. The result of the meta-analysis was not statistically significant and there was no noteworthy heterogeneity between the results of the individual studies (Figure 1). Figure 1An added benefit or greater harm from apixaban for this outcome is not proven. This concurs with the company's assessment. It should be borne in mind that, due to the duration of the studies and number of enrolled patients, neither study was designed to enable differences between treatments with regard to this outcome to be detected.

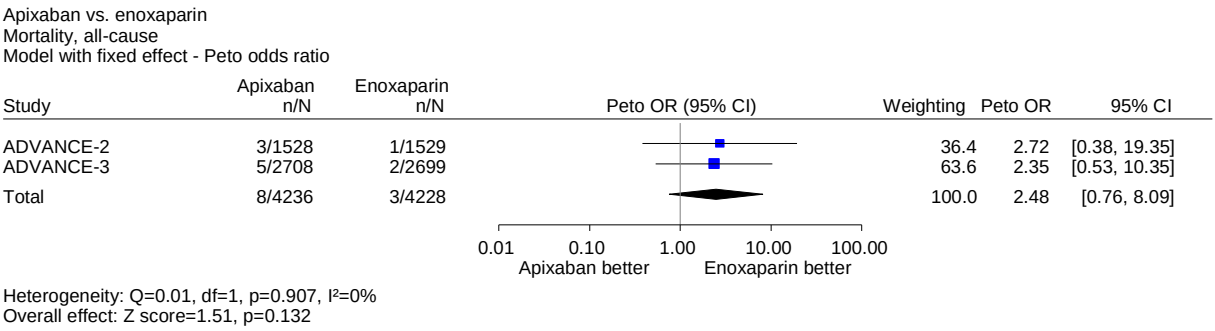

Figure 1: Meta-analysis, apixaban vs. enoxaparin, mortality, entire period

CI: confidence interval, OR: odds ratio

2.4.2 Morbidity

Pulmonary embolisms

Due to the heterogeneity present ($p < 0.2$), the results for pulmonary embolism were not combined for meta-analysis. Therefore no overall effect estimator was illustrated (Figure 2). On the basis of the individual study results, the ADVANCE-2 study showed a statistically significant result to the disadvantage of apixaban. The rate of pulmonary embolisms under enoxaparin was admittedly higher in the ADVANCE-3 study, but the result was not statistically significant. The sometimes excessively long treatment duration with enoxaparin in the ADVANCE-3-study – the aspect to be considered particularly in the case of heterogeneity – does not alter the assessment of this data. The results are assessed as an

indication of lesser benefit of apixaban for this outcome in patients undergoing elective knee replacement surgery. For patients undergoing elective hip replacement surgery, an added benefit of apixaban for the outcome "pulmonary embolisms" is not proven. The company derived no proof of added benefit of apixaban for either population.

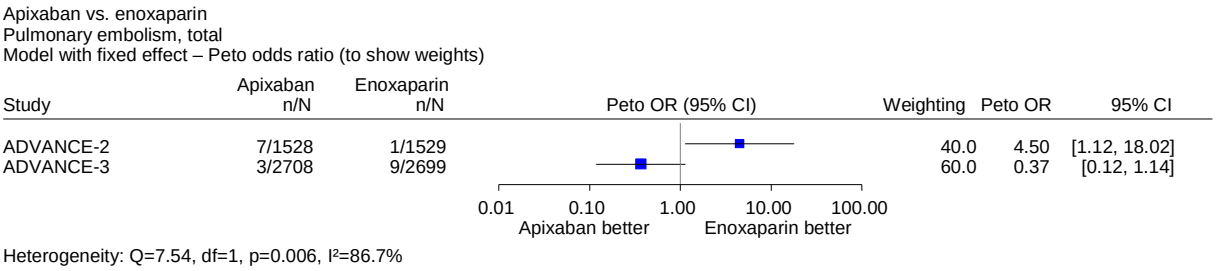

Figure 2: Meta-analysis, apixaban vs. enoxaparin, pulmonary embolisms, entire period

CI: confidence interval, OR: odds ratio

Symptomatic deep vein thrombosis (DVT)

For the assessment of this outcome, distal and proximal symptomatic DVT were considered together in the meta-analysis the proportion of patients with a proximal – and hence more serious – symptomatic DVT being approx. 59% (13 of a total of 22 symptomatic DVT; see Table 9). Symptomatic DVT occurred more often in the patients treated with enoxaparin than in those who received apixaban. The overall effect of the meta-analysis was statistically significant and there was no noteworthy heterogeneity between the results of the individual studies (Figure 3). An added benefit of apixaban for the outcome "symptomatic DVT" is therefore proven. The company did not show this outcome separately, since, in its view, symptomatic DVT represents only a part of the outcome "all DVT".

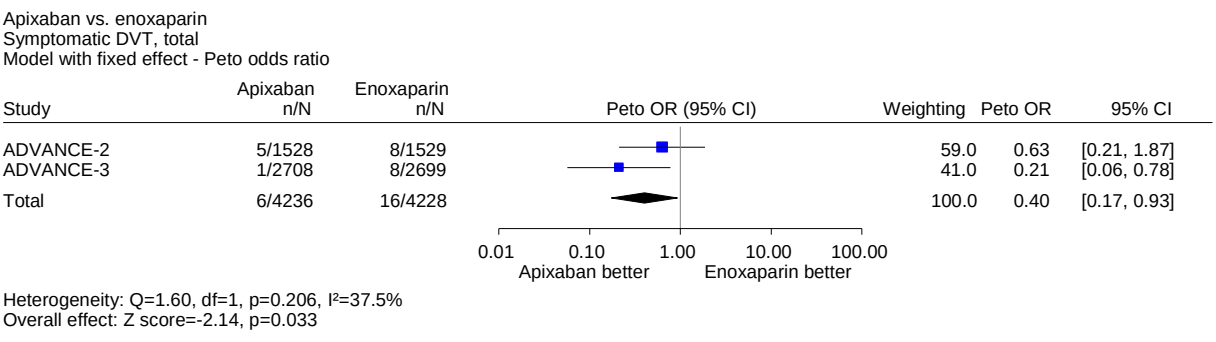

Figure 3: Meta-analysis, apixaban vs. enoxaparin, deep vein thrombosis, entire period

CI: confidence interval, OR: odds ratio

2.4.3 Health-related quality of life

No study data are available for the outcome “health-related quality of life”. An added benefit of apixaban for this outcome is therefore not proven.

2.4.4 Adverse events

2.4.4.1 Bleeding events

The results of the bleeding outcomes included in the assessment are shown below. Since no analysis of bleeding outcomes was available for the entire period, the assessment is based on the treatment period. Overall, this appears non-critical, because the events rates in the follow-up period for all bleeding events were relatively low in comparison with the treatment period.

The assessment of the added benefit is made as a summary of the complex “bleeding events” at the end of this section.

Major bleeds and clinically relevant non-major bleeds

In the two studies the proportions of patients with major bleeds and clinically relevant non-major bleeds did not differ substantially between apixaban and enoxaparin. The result of the meta-analysis for the treatment period (Figure 4) was not statistically significant and there was no noteworthy heterogeneity between the individual study results.

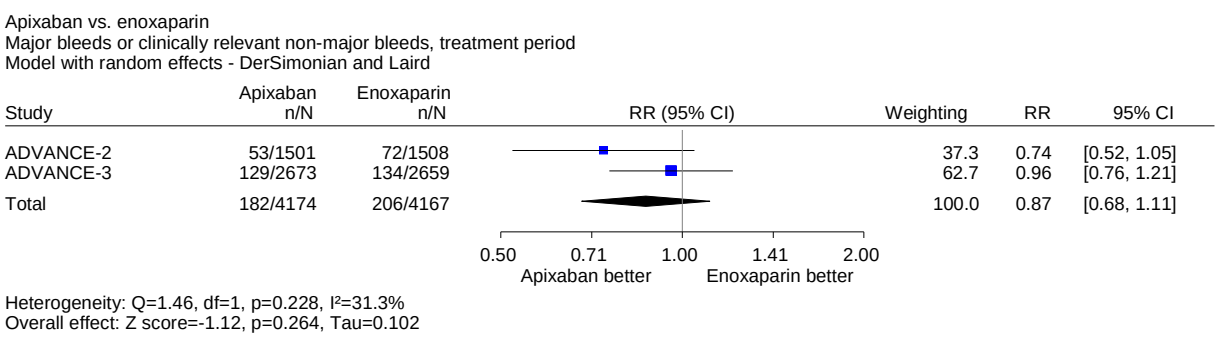

Figure 4: Meta-analysis, apixaban vs. enoxaparin, major bleeds or clinically relevant non-major bleeds, treatment period

CI: confidence interval, RR: relative risk

Major bleeds

In the two studies the proportions of patients with major bleeds did not differ substantially between apixaban and enoxaparin. The result of the meta-analysis for the treatment period (Figure 5) was not statistically significant and there was no noteworthy heterogeneity between the individual study results.

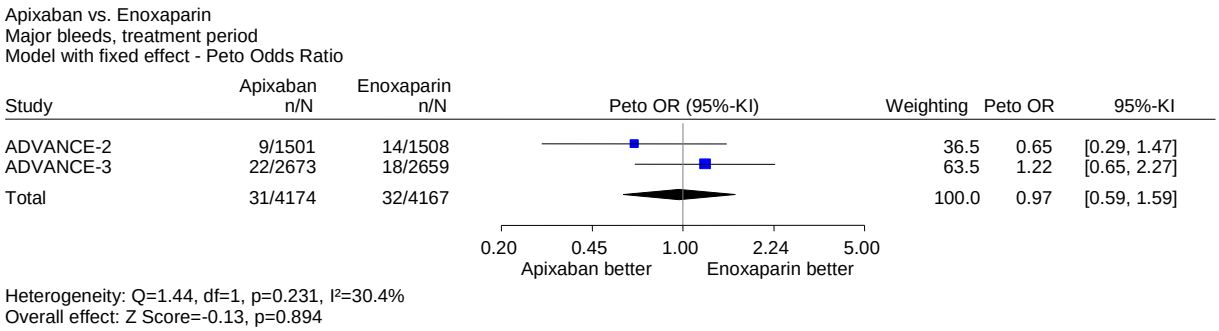

Figure 5: Meta-analysis, apixaban vs. enoxaparin, major bleeds, treatment period

CI: confidence interval, OR: odds ratio

Clinically relevant non-major bleeds

In the two studies the proportions of patients clinically relevant non-major bleeds did not differ substantially between apixaban and enoxaparin. The result of the meta-analysis for the treatment period (Figure 6) was not statistically significant and there was no noteworthy heterogeneity between the individual study results.

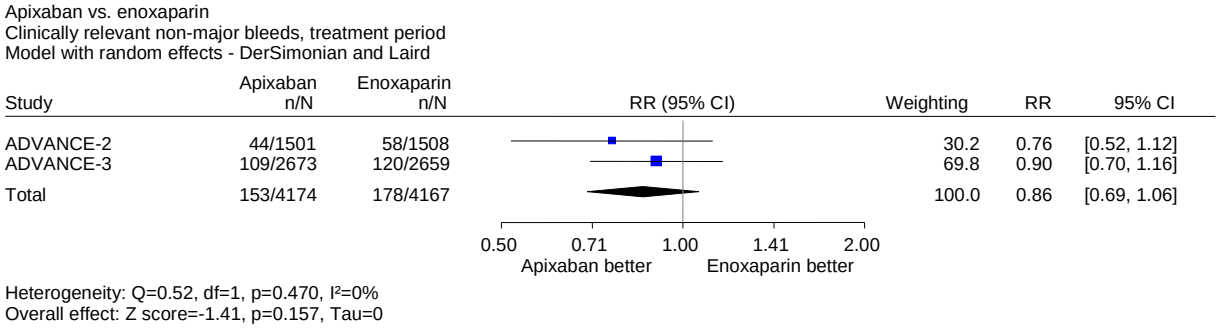

Figure 6: Meta-analysis, apixaban vs. enoxaparin, clinically relevant non-major bleeds, treatment period

CI: confidence interval, RR: relative risk

Adverse events – bleeds

In the two studies the proportions of patients with adverse events – bleeds did not differ substantially between apixaban and enoxaparin. Due to the heterogeneity present ($p < 0.2$), the results for the treatment period were not combined for meta-analysis. Therefore no overall effect estimator was illustrated (Figure 7). Further investigation of the heterogeneity was not necessary in this case, because the result of the two individual studies was not statistically significant.

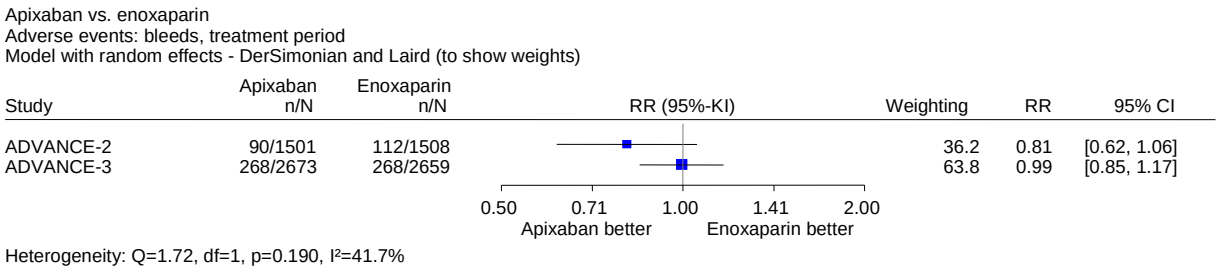

Figure 7: Meta-analysis, apixaban vs. enoxaparin, adverse events – bleeds, treatment period

CI: confidence interval, RR: relative risk

Serious adverse events – bleeds

Due to the heterogeneity present ($p < 0.2$), the results for serious adverse events – bleeds were not combined for meta-analysis. Therefore no overall effect estimator was illustrated (Figure 8). On the basis of the individual study results, the ADVANCE-3 study showed a statistically significant result to the disadvantage of apixaban. In the ADVANCE-2 study, although the rate of serious adverse events - bleeds under enoxaparin was increased, the result was not statistically significant. The sometimes excessively long treatment duration of enoxaparin in the ADVANCE-3 study – the aspect to be considered particularly in the case of heterogeneity – can be neglected with this data, because this would, rather, have led to an overestimation of the bleeding effect of enoxaparin in ADVANCE-3, whereas here, however, even a disadvantage of apixaban is present.

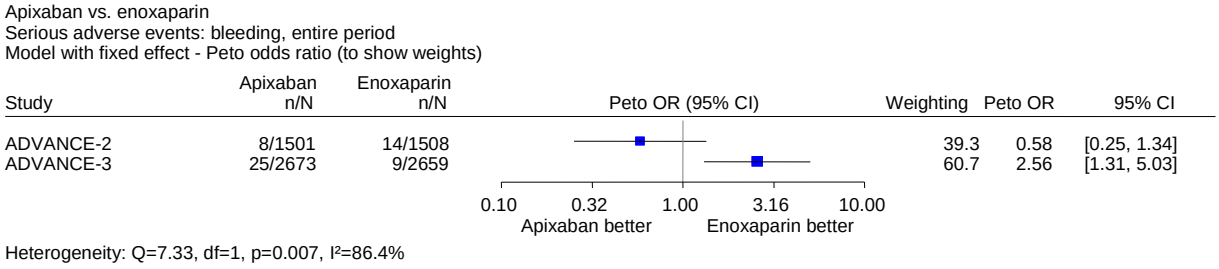

Figure 8: Meta-analyses, apixaban vs. enoxaparin, serious adverse events – bleeds, entire period

CI: confidence interval, OR: odds ratio

Summary of the results for bleeding events

In summary, the results of all bleeding outcomes considered were not statistically significant, with the exception of serious adverse events – bleeds. For this outcome there was a

statistically significant result to the disadvantage of apixaban for patients undergoing elective hip replacement surgery (ADVANCE-3).

However during the course of further assessment of subgroup characteristics, there was an indication of an effect modification by the characteristic "age" for the outcome "clinically relevant non-major bleeds". This meant that any conclusions on added benefit in terms of the overall complex "bleeding events" are drawn on the basis of the subgroups. The subgroup analyses and the related interpretation of the results and evidence can be found in Section 2.4.5.1. Taking these subgroup results into account, there is no proof of greater or lesser harm from apixaban compared to enoxaparin. This applies both to patients undergoing knee surgery as well as those undergoing hip surgery. This assessment concurs with that of the company.

2.4.4.2 Other analyses of adverse events

The results concerning the overall rate of AEs, overall rate of SAEs and treatment discontinuations due to AEs are shown below.

When interpreting the results of these 3 outcomes, the problem arose that in each case patients with DVT were also recorded. However, as described earlier, in contrast to clinical practice, in the two studies ADVANCE-2 and ADVANCE-3 all patients were to undergo venography even when no DVT symptoms were present. This led to a large number of asymptomatic DVT being diagnosed, whereby the event rate for the 3 outcomes "AEs", "SAEs", "treatment discontinuations due to AEs" was also potentially influenced. However, neither in the company's dossier nor in the study reports were results on these 3 outcomes presented in which patients with DVT were *not* considered. Nevertheless, for all 3 outcomes, the study reports contained information regarding the number of patients in whom at least one event classified as DVT occurred. From this it could at least be estimated whether the respective result was substantially influenced by the recording of DVT.

The outcome "pulmonary embolisms" was also recorded for the outcomes "AEs" and "SAEs". Since the already mentioned venography did not, however, lead to the diagnosis of asymptomatic pulmonary embolisms and, moreover, the event rate for pulmonary embolisms recorded as AEs or SAEs was well below 0.5% in both studies, it is not assumed that this led to a substantial effect on the result concerning AEs/SAEs.

Overall rate of AEs

Results for the overall rate of AEs were available for the treatment period and the follow-up period. There was no summarizing analysis for the entire period. Since the majority of events occurred in the treatment period and, moreover, there was no noteworthy difference between the treatment groups in the follow-up period, the assessment was carried out solely on the basis of the results of the treatment period.

In the meta-analysis of the two studies concerning the overall rate of AEs, there was a statistically significant result in favour of apixaban (Figure 9). The meta-analysis of the AEs

classified as DVT also showed a statistically significant result in favour of apixaban (Figure 10).

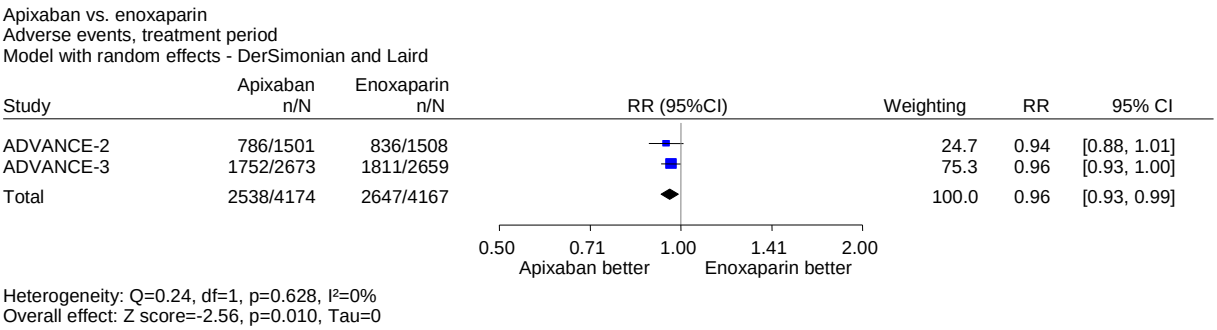

Figure 9: Meta-analysis, apixaban vs. enoxaparin, overall rate of AEs, treatment period

CI: confidence interval, RR: relative risk

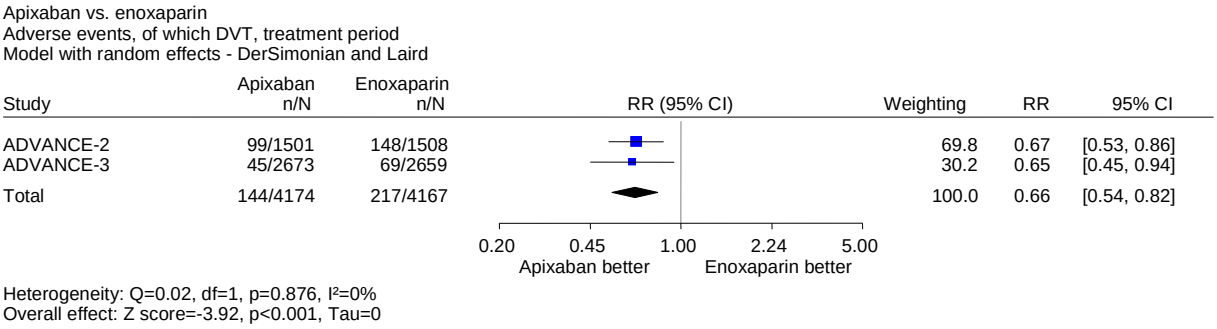

Figure 10: Meta-analysis, apixaban vs. enoxaparin, AE-DVT, treatment period

CI: confidence interval, RR: relative risk

The absolute difference of the event rates in the two analyses was of a similar order of magnitude (approx. 2 to 3%). The result on overall rate of AEs was accordingly potentially influenced by the recording of DVT. Taken as a whole, there is therefore no proof of a lesser harm from apixaban compared with enoxaparin in terms of the overall rate of AEs. In contrast, the company undertook the assessment solely on the basis of the overall rate of AEs with DVT and thereby derived an indication of an added benefit of apixaban for both patient populations.

Overall rate of SAEs

For the overall rate of SAEs, results were available for the treatment and follow-up periods. There was no summary analysis for the entire period. Since the great majority of events with SAEs also occurred in the treatment period and there was likewise no noteworthy difference in the follow-up period between the treatment groups, the assessment of SAEs was also carried out exclusively on the basis of the results of the treatment period.

The meta-analysis of the two studies on the overall rate of SAEs showed heterogeneous results ($p < 0.2$), so no overall effect estimator was illustrated (Figure 11). Due to the heterogeneous data, the influence of DVT recorded as SAEs was assessed at individual study level.

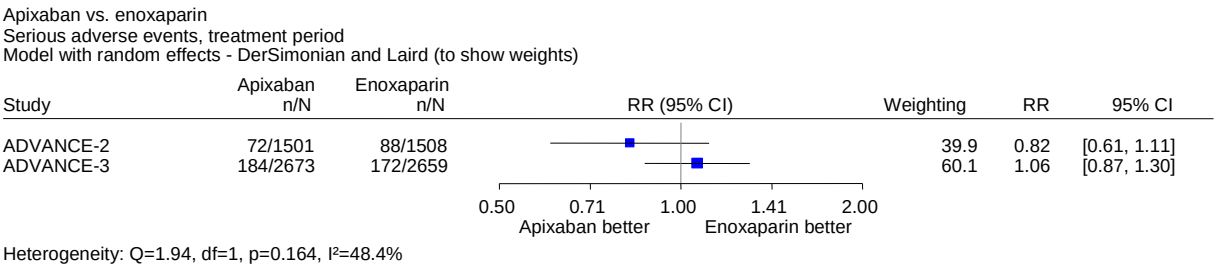

Figure 11: Meta-analysis, apixaban vs. enoxaparin, overall rate of SAEs, treatment period

CI: confidence interval, RR: relative risk

No statistically significant result was shown in the two individual studies, neither for the overall rate of SAEs nor for the DVT recorded as SAEs. The absolute difference in event rates in the ADVANCE-2 study, with a value of approx. 1% in favour of apixaban, was of a similar order of magnitude to the SAEs recorded as DVT. In the ADVANCE-3 study, the overall rate of SAEs showed a numerical difference to the disadvantage of apixaban, but the DVT recorded as SAEs showed a numerical difference in favour of apixaban. Overall, the data provided no proof of a lesser or greater harm from apixaban compared to enoxaparin in terms of the overall rate of SAEs. This concurs with the assessment of the company, whose assessment is based solely on the overall rate of SAEs with DVT.

Treatment discontinuations due to AE

The proportions of patients with adverse events that led to discontinuation of treatment did not differ substantially between apixaban and enoxaparin in either of the studies. The result of the meta-analysis was not statistically significant and there was no noteworthy heterogeneity between the results of the individual studies (Figure 12). The event rate of treatment discontinuations due to a DVT showed practically no difference between the treatment groups in either study, so it is not be assumed that the recording of treatment discontinuations due to DVT had substantially affected the result of this outcome. Taken as a whole, greater or lesser harm from apixaban for the outcome “treatment discontinuations due to AEs” is not proven. This concurs with the assessment of the company, whose assessment is based solely on the number of treatment discontinuations due to AEs (including DVT).

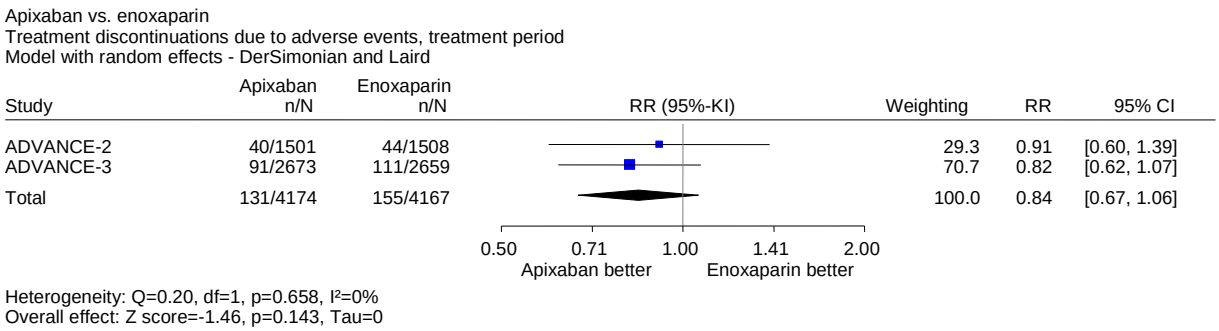

Figure 12: Meta-analysis, apixaban vs. enoxaparin, overall rate of adverse events that led to treatment discontinuation, treatment period

CI: confidence interval, RR: relative risk

2.4.5 Subgroup analyses

In order to analyse possible effect modifiers, the respective interactions were investigated on the basis of both studies at aggregated level using meta-regressions. In the case of very low event rates (≤ 1% in at least one cell), as in the previous meta-analyses, the Peto odds ratio was used as the effect measure.

This was undertaken as far as possible for the subgroup characteristics "age" (< 65 years; ≥ 65 to < 75 years and ≥ 75 years), sex and BMI (≤ 28 kg/m^2; > 28 to 33 kg/m^2 and > 33 kg/m^2), which the Institute considered relevant. The named limits for age and BMI were defined in the studies beforehand. Corresponding analyses could only be undertaken for the treatment period because no data were available for the entire and/or follow-up periods. Subgroup analyses for the BMI were available only for part of the bleeding events (major bleeds or clinically relevant non-major bleeds or their combination). No subgroup analyses were available for the outcomes "symptomatic DVT" and "(serious) adverse events – bleeds". In addition, only analyses including DVT were available for the overall rate of AEs or SAEs and treatment discontinuations due to an AE. The corresponding subgroup analyses for age and sex were not considered further, because no information was available for these analyses as to how many of the AEs or SAEs were attributable to DVT. For this reason, an assessment as in Section 2.4.4.2 was not possible.

Only results for subgroups are presented and discussed below for which the different effects for the relevant outcomes were present. The condition for proof of different subgroup effects was a statistically significant homogeneity test (interaction test), ($p < 0.05$). A p-value between 0.05 and 0.2 provided an indication of different effects. This was only the case for the characteristic "age" for clinically relevant non-major bleeds. In all cases, the subgroup analyses for BMI (major bleeds or clinically relevant non-major bleeds or their combination) produced no indication of different effects. For the outcomes "mortality", "pulmonary

embolisms", "combination of major bleeds and clinically relevant non-major bleeds", and "major bleeds", neither the characteristic "age" nor "sex" showed different treatment effects.

The results for the characteristics and outcomes with an indication of effect modification are shown below.

2.4.5.1 Bleeding events

Clinically relevant non-major bleeds

The meta-regression calculated by the Institute for the outcome "clinically relevant non-major bleeds" produced an indication ($p < 0.2$) of an effect modification through the characteristic "age" (Figure 13). For patients aged ≥ 75 years, the results showed a statistically significant difference in favour of apixaban. The subgroup differences can be mainly attributed to patients undergoing elective hip replacement surgery (ADVANCE-3) (Figure 14). In this study the difference between apixaban and enoxaparin was most marked in the age group ≥ 75 years. In the other two age groups (< 65 years; ≥ 65 to < 75 years) there was no statistically significant result in either study or in the meta-analysis summary of both of them.

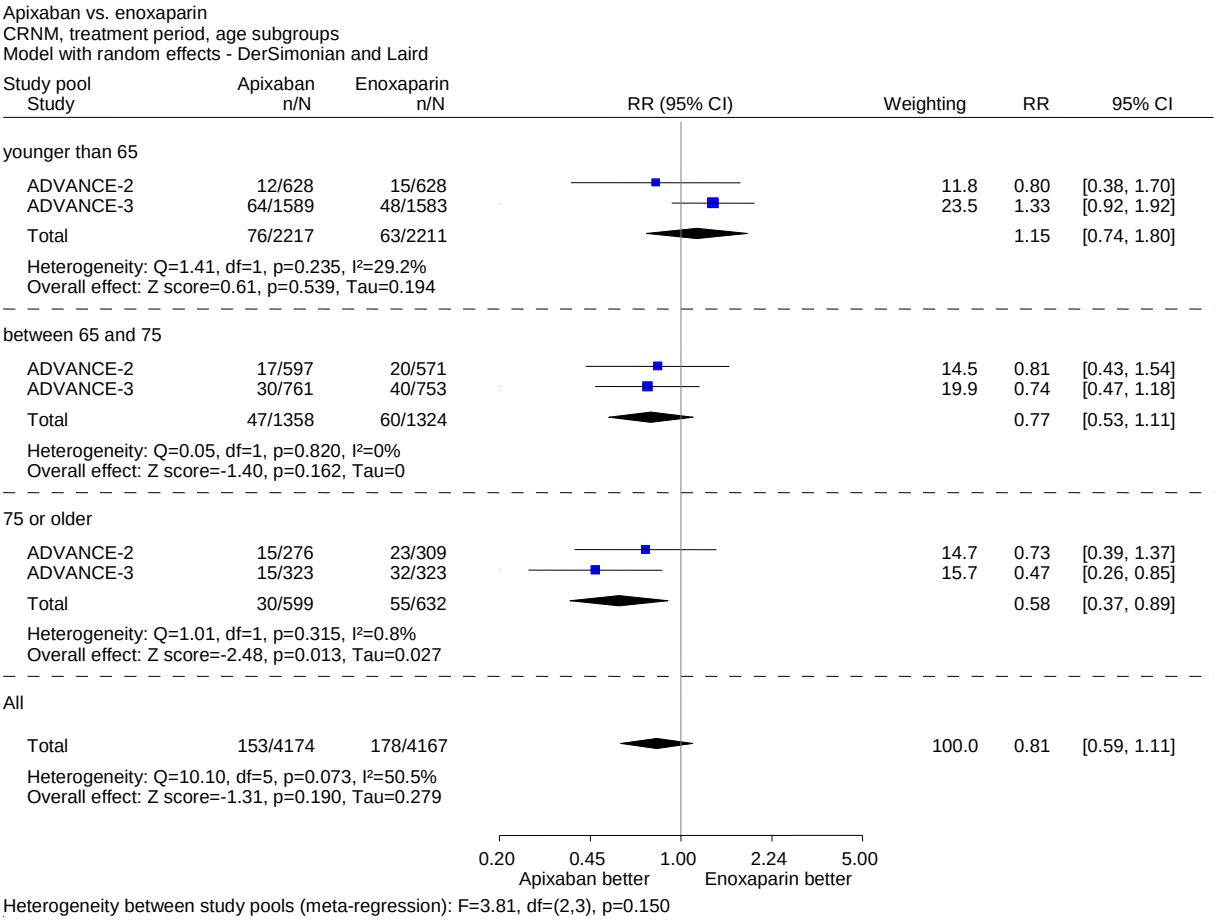

Figure 13: Subgroup analysis – age, clinically relevant non-major bleeds, apixaban vs. enoxaparin, interaction test p: 0.150

CI: confidence interval, CRNM: clinically relevant non-major bleeds, RR: relative risk

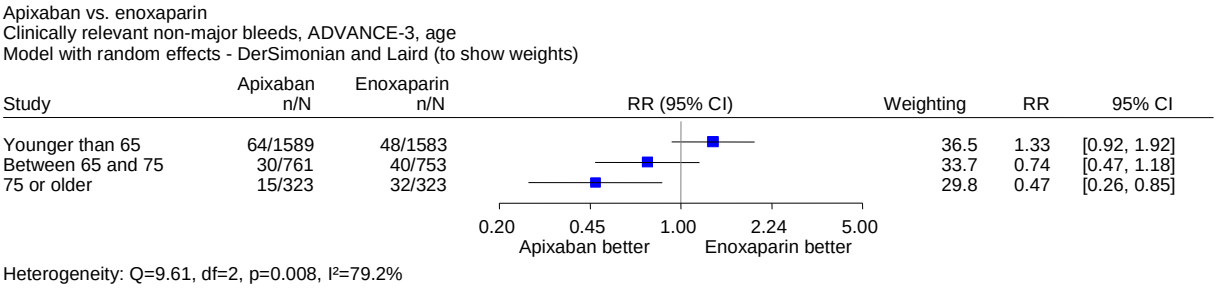

Figure 14: Subgroup analysis – age (ADVANCE-3), clinically relevant non-major bleeds, apixaban vs. enoxaparin, interaction test p: 0.008

CI: confidence interval, RR: relative risk

Table 10: Subgroup results on the comparison of apixaban vs. enoxaparin, patients undergoing elective knee (ADVANCE-2) or hip replacement surgery (ADVANCE-3)

Outcome **Subgroup** **Study**	**Apixaban**		**Enoxaparin**		**Apixaban vs. enoxaparin**	
	N	**Events n (%)**	**N**	**Events n (%)**	**RR [95% CI]; p-value**	**Inter-action test (p-value)**
Clinically relevant non-major bleeds[a]						
Age						
ADVANCE-2						
< 65	628	12 (1.91)	628	15 (2.39)	0.80[b] [0.38; 1.70][b]; 0.698[c]	n.d.
65–< 75	597	17 (2.85)	571	20 (3.50)	0.81[b] [0.43; 1.54][b]; 0.617[c]	
≥ 75	276	15 (5.43)	309	23 (7.44)	0.73[b] [0.39; 1.37][b]; 0.338[d]	
ADVANCE-3						
< 65	1589	64 (4.03)	1583	48 (3.03)	1.33[b] [0.92; 1.92][b]; 0.149[c]	0.008[b]
65–< 75	761	30 (3.94)	753	40 (5.31)	0.74[b] [0.47; 1.18][b]; 0.222[c]	
≥75	323	15 (4.64)	323	32 (9.91)	0.47[b] [0.26; 0.85][b]; 0.010[d]	
Meta-analysis[e]						0.150
< 65					1.15 [0.74; 1.80]; 0.539	
65–< 75					0.77 [0.53; 1.11]; 0.162	
≥ 75					0.58 [0.37; 0.89]; 0.013	

a: Acute clinically overt bleeding such as epistaxis (duration ≥ 5 min and requiring treatment), gastrointestinal bleeding (vomiting, endoscopy or in stools), haematuria (duration ≥ 24 hours), bruising/ecchymosis, wound haematoma, haemoptysis.
b: Institute's calculation.
c: Institute's calculation, Fisher's exact test.
d: Institute's calculation, unconditional exact test (CSZ method according to [5]).
e: Institute's calculation, meta-regression, model with random effects (according to DerSimonian and Laird [4]).
CI: confidence interval; CSZ: convex, symmetry, z score; N: number of analysed patients; n: number of patients with event; n.d.: no data; RR: relative risk; vs.: versus.

Summary assessment for bleeding events as a whole

In summary, greater or lesser harm from apixaban compared to enoxaparin for the complex "bleeding events" is not proven. The reasons for this are as follows:

For patients undergoing elective knee replacement surgery, none of the bleeding outcomes investigated showed a statistically significant result. This applies to the overall analyses as well as the subgroup analyses.

For patients undergoing elective hip replacement surgery, there was a statistically significant result to the disadvantage of apixaban for the outcome "serious adverse events – bleeds". This result was, however, not supported by further results of other bleeding outcomes. For patients of 75 years and over undergoing elective hip replacement surgery there was, in contrast, an advantage for clinically relevant non-major bleeds under apixaban. But this – apparently contradictory - result compared to the SAE bleeds was not supported by further results of other bleeding outcomes. Overall, the results for the complex "bleeding events" were not of sufficient informative value to enable greater or lesser harm from apixaban to be derived for this group of patients.

In the overall review of these data, it also appears possible to neglect the fact that a significantly higher proportion of patients in the enoxaparin group than in the apixaban group received treatment with anticoagulants because of DVT diagnosed using post-treatment venography (see dossier, Module 4, Table 4-40). This could have potentially led to more bleeding events under enoxaparin in the follow-up period. However, in the Institute's view, the relatively low event rates in the follow-up period suggest that this does not represent a substantial influence on the above overall interpretation of bleeds.

Further information about the choice of outcome, risk of bias at outcome level, and outcome results can be found in Module 4, Sections 4.2.5.2 and 4.3.1.3 of the dossier and in Sections 2.7.2.2 and 2.7.2.4 of the full dossier assessment.

2.5 Extent and probability of the added benefit

The derivation of the extent and probability of the added benefit for patients undergoing elective knee or hip replacement surgery is shown separately at outcome level below. The various outcome categories and the effect sizes are taken into account. The methods used are explained in Appendix A of Benefit Assessment A11-02 [3].

In the case of low numbers of events, the odds ratio offers a good approximation of the relative risk. Therefore in the case of event rates of $\leq 1\%$, the relative risks in the above-mentioned method of benefit assessment are replaced by the estimated Peto odds ratio (together with their confidence intervals).

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

2.5.1 Patients undergoing elective knee replacement surgery

2.5.1.1 Evaluation of added benefit at outcome level

The data presented in Section 2.4 produced proof of an added benefit in terms of severe DVT and an indication of a lesser benefit in terms of pulmonary embolisms for patients undergoing elective knee replacement surgery. The extent of the respective added benefit at outcome level was estimated on the basis of these results (see Table 11).

Table 11: Patients undergoing elective knee replacement surgery: apixaban vs. enoxaparin – extent of added benefit at outcome level

Outcome	**Effect estimator [95% CI]/ Proportion of events Apixaban vs. enoxaparin/ p-value/ Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	Entire period: Peto OR[c] 2.48 [0.76; 8.09][d] 0.19% vs. 0.07% p = 0.132	Added benefit / greater harm not proven.
Morbidity		
Pulmonary embolism	Entire period: Peto OR[c] 0.22 [0.06; 0.89][e] 0.46% vs. 0.07% p = 0.039 Probability: “indication”	Outcome category: serious/severe symptoms/late complications $0.75 < CI_o < 0.90$ Lesser benefit, extent: “considerable”
Symptomatic deep vein thrombosis	Entire period: Peto OR[c] 0.40 [0.17; 0.93][d] 0.14% vs. 0.38% p = 0.033 Probability: “proof”	Outcome category: serious/severe symptoms/late complications[f] $0.90 < CI_o < 1.00$ Added benefit, extent: “minor”
Health-related quality of life		
	No evaluable data available.	Added benefit / greater harm not proven.
Adverse events – bleeding events		
Major bleeds or clinically relevant non-major bleeds (combined and as single components), AE – bleeds, SAE – bleeds	Summary analysis of all bleeding outcomes taking into account partly contradictory results and age-dependent effects: data overall not informative enough to derive greater or lesser harm from apixaban.	Greater/lesser harm not proven.

(continued on next page)

Table 11: Patients undergoing elective knee replacement surgery: apixaban vs. enoxaparin – extent of added benefit at outcome level (continued)

Outcome	Effect estimator [95% CI]/ Proportion of events Apixaban vs. enoxaparin/ p-value/ Probability[a]	Derivation of extent[b]
Adverse events - other analyses on adverse events		
AEs	Results on overall rate of AEs are potentially considerably affected by the recording of DVT and are therefore not evaluable.	Greater/lesser harm not proven.
SAEs[g]	Treatment period: RR 0.82 [0.61; 1.11] 4.79% vs. 5.84% p = 0.223	Greater/lesser harm not proven.
Discontinuation due to AE[g]	Treatment period: RR 0.84 [0.67; 1.06][d] 3.14% vs. 3.72% p = 0.143	Greater/lesser harm not proven.

a: Probability provided, if statistically significant differences are present.

b: Estimations of effect size are made depending on outcome category with different limits based on the upper limit of the confidence interval (CI_0).

c: In the case of low numbers of events, the odds ratio offers a good approximation of the relative risk. Therefore in the case of event rates of ≤ 1%, the relative risks in the above-mentioned method of benefit assessment are replaced by the estimated Peto odds ratio (together with their confidence intervals).

d: Result of the meta-analysis for patients undergoing elective knee or hip replacement surgery.

e: Institute's calculation, proportion of events enoxaparin/apixaban (effect direction reversed to enable use of thresholds for the extent of the added benefit).

f: Classification in this outcome category because the proportion of patients with a proximal – and therefore more serious – symptomatic DVT was approx. 59%.

g: Recording of events classified as DVT, but data allows interpretation of results.

AE: adverse event, CI: confidence interval, CI_0: upper limit of confidence interval, DVT: deep vein thrombosis, OR: odds ratio, RR: relative risk, SAE: serious adverse event, vs.: versus

2.5.1.2 Overall conclusion on added benefit

Table 12 summarizes the results considered in the overall conclusion about the extent of added benefit.

Table 12: Patients undergoing elective knee replacement surgery: overall conclusion regarding added benefit

Positive effects	Negative effects
Proof of an added benefit – extent: "minor" (serious/severe symptoms: symptomatic DVT)	Indication of a lesser benefit – extent: "considerable" (serious/severe symptoms: pulmonary embolisms)
DVT: deep vein thrombosis	

Taken as a whole, positive and negative results remain of differing extent and differing probability. On the side of added benefit, there is proof with the extent "minor" (symptomatic DVT), but this is accompanied by an indication of a lesser benefit with the extent "considerable" (pulmonary embolisms). At individual study level (ADVANCE-2), there is a non-statistically significant result for the outcome "symptomatic DVT", but this is accompanied by a statistically significant result for the outcome "pulmonary embolisms". Therefore, in the Institute's view, from the available data it is not possible to deduce that the added benefit outweighs the greater harm.

In summary, for patients undergoing elective knee replacement surgery, there is no proof of an added benefit of apixaban over the ACT enoxaparin.

2.5.2 Patients undergoing elective hip replacement surgery

2.5.2.1 Evaluation of added benefit at outcome level

The data presented in Section 2.4 produced proof of added benefit in terms of symptomatic DVT for patients undergoing elective hip replacement surgery. Based on these results, the extent of the respective added benefit was estimated at outcome level (see Table 13).

Table 13: Patients undergoing elective hip replacement surgery: apixaban vs. enoxaparin – extent of added benefit at outcome level

Outcome	**Effect estimator [95% CI]/ Proportion of events Apixaban vs. enoxaparin/ p-value/ Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	Entire period: Peto OR[c] 2.48 [0.76; 8.09][d] 0.19% vs. 0.07% p = 0.132	Added benefit / greater harm not proven.
Morbidity		
Pulmonary embolism	Entire period: Peto OR[c] 0.37 [0.12; 1.14] 0.11% vs. 0.33% p = 0.091	Added benefit / greater harm not proven.
Symptomatic deep vein thrombosis	Entire period: Peto OR[c] 0.40 [0.17; 0.93][d] 0.14% vs. 0.38% p = 0.033 Probability: "proof"	Outcome category: serious/severe symptoms/late complications[e] $0.90 < CI_o < 1.00$ Added benefit, extent: "minor"
Health-related quality of life		
	No evaluable data available.	Added benefit / greater harm not proven.

(continued on next page)

Table 13: Patients undergoing elective hip replacement surgery: apixaban vs. enoxaparin – extent of added benefit at outcome level (continued)

Outcome	**Effect estimator [95% CI]/ Proportion of events Apixaban vs. enoxaparin/ p-value/ Probability**[a]	**Derivation of extent**[b]
Adverse events - bleeding events		
Major bleeds or clinically relevant non-major bleeds (combined and as single components), AE – bleeds, SAE – bleeds	Summary analysis of all bleeding outcomes taking into account partly contradictory results and age-dependent effects: data overall not informative enough to derive greater or lesser harm from apixaban.	Greater/lesser harm not proven.
Adverse events - other analyses on adverse events		
AEs	Results on overall rate of AEs had been potentially considerably affected by the recording of DVT and are therefore not evaluable.	Greater/lesser harm not proven.
SAEs[f]	Treatment period: RR 1.06 [0.87; 1.30] 6.88% vs. 6.47% p = 0.547	Greater/lesser harm not proven.
Discontinuation due to AE[f]	Treatment period: RR 0.84 [0.67; 1.06][d] 3.14% vs. 3.72% p = 0.143	Greater/lesser harm not proven.

a: Probability provided, if statistically significant differences are present.

b: Estimations of effect size are made depending on outcome category with different limits based on the upper limit of the confidence interval (CI_0).

c: In the case of numbers of events, the odds ratio offers a good approximation of the relative risk. Therefore in the case of event rates of ≤ 1%, the relative risks in the above-mentioned method of benefit assessment are replaced by the estimated Peto odds ratio (together with their confidence intervals).

d: Result of the meta-analysis for patients undergoing elective knee or hip replacement surgery.

e: Classification in this outcome category because the proportion of patients with a proximal – and therefore more serious – symptomatic DVT was approx. 59%.

f: Recording of events classified as DVT, but data allows interpretation of results.

AE: adverse event, CI: confidence interval, CI_0: upper limit of confidence interval, DVT: deep vein thrombosis, OR: odds ratio, RR: relative risk, SAE: serious adverse event, vs.: versus

2.5.2.2 Overall conclusion on added benefit

Table 14 summarizes the results considered in the overall conclusion about the extent of added benefit.

Table 14: Patients undergoing elective hip replacement surgery: overall conclusion on added benefit

Positive effects	Negative effects
Proof of an added benefit – extent: "minor" (serious/severe symptoms: symptomatic DVT)	
AE: adverse event, DVT: deep vein thrombosis	

Taken as a whole, a positive result remains in favour of apixaban with the extent "minor" and the probability "proof" (symptomatic DVT). No decision based on a balancing of benefits and harms is necessary.

In summary, for patients undergoing elective hip replacement surgery, there is proof of an added benefit (extent "minor") of apixaban over the ACT enoxaparin.

2.5.3 Extent and probability of the added benefit – summary

The following summary of the extent and probability of the added benefit for the relevant patient populations arises for the benefit assessment of apixaban in comparison with the ACT:

Table 15: Apixaban: extent and probability of the added benefit

Population	Appropriate comparator therapy	Extent and probability of the added benefit
Adults patients undergoing elective knee replacement surgery	Enoxaparin	No proof of an added benefit of apixaban
Adult patients undergoing elective hip replacement surgery	Enoxaparin	Proof of an added benefit (extent "minor") of apixaban

This overall assessment deviates substantially from that of the company, which claimed proof of a considerable added benefit for both populations.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment

2.6 List of included studies

ADVANCE-2

1. Bristol-Myers Squibb. Study of an investigational drug for the prevention of thrombosis-related events following knee replacement surgery (ADVANCE-2) [online]. In: ClinicalTrials.gov. 24.01.2011 [Accessed on: 01.03.2012]. URL: http://clinicaltrials.gov/show/NCT00452530.

2. Bristol-Myers Squibb, Pfizer. A phase 3, randomized, double-blind, active-controlled (enoxaparin 40 mg QD), parallel group, multi-center study to evaluate the safety and efficacy of apixaban in subjects undergoing elective total knee replacement surgery: study CW185047; final clinical study report [unpublished]. 2009.

3. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010; 375(9717): 807-815.

ADVANCE-3

1. Bristol-Myers Squibb. Study of an investigational drug for the prevention of thrombosis-related events following hip replacement surgery [online]. In: ClinicalTrials.gov. 17.09.2009 [Accessed on: 01.03.2012]. URL: http://clinicaltrials.gov/show/NCT00423319.

2. Bristol-Myers Squibb, Pfizer. A phase 3, randomized, double-blind, active-controlled, parallel-group, multi-center study to evaluate the safety and efficacy of apixaban in subjects undergoing elective total hip replacement surgery (the Advance-3 study apixaban doses orally versus anticoagulation with injectable enoxaparin to prevent venous thromboembolism): study CV185035; final clinical study report [unpublished]. 2009.

3. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med 2010; 363(26): 2487-2498.

References for English extract

Please see full dossier assessment for full reference list.

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5. Andrés AM, Mato AM. Choosing the optimal unconditioned test for comparing two independent proportions. Comput Stat Data Anal 1994; 17: 555-574.

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