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Research Article

Direct Oral Anticoagulants: Drug Selection by Means of the SOJA Method

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Introduction

Direct acting anticoagulant drugs [DOACs], consisting of apixaban, dabigatran, edoxaban and rivaroxaban have been available for various indications for 3year [edoxaban] up to over a decade [dabigatran and rivaroxaban]. These medicines have shown good clinical efficacy and are usually well tolerated compared to vitamin K antagonists or low molecular weight heparins. Because none of the DOACs is available as a generic formulation, their relatively high price is a disadvantage compared to vitamin K antagonists.

The regional formulary committee in the South of Limburg, the Netherlands has requested to define selection criteria in order to make a rational selection of DOACs. The present article is the result of this request.

In this article the properties of the available DOACs are compared on several selection criteria for formulary purposes.

Methods

The SOJA method is a model for rational drug selection. The relevant selection criteria for a certain group of drugs are defined and judged by a panel of experts [i.e. the authors of the present article]. The more important a selection criterion is considered, the higher the relative weight that is given to that criterion. The ideal properties for each selection criterion are determined and each drug is scored as a percentage of the relative weight for all selection criteria. The criteria, which were used in the present SOJA method and the weighting of the authors are presented in table 3. A Medline search was performed, as well as a search for studies in the Cochrane library. As well as these searches, the references of review articles on this subject were obtained and incorporated in the analysis when appropriate. The manuscript was sent to the pharmaceutical companies for a check on scientific completeness and correctness, as well as for addition of any relevant new information to be included in the manuscript. The relative weights of the selection criteria and the ultimate judgement of the drugs were not discussed with the companies; this was the responsibility of the authors. The drugs with the highest total score are most suitable for formulary inclusion [1].

The following drugs were included in the analysis:

- Apixaban [Eliquis]
- Dabigatran [Pradaxa]
- Edoxaban [Lixiana]
- Rivaroxaban [Xarelto]

Selection Criteria	Relative Weight Factor
Approved indications	40
Available formulations	20
Variability of the AUC	40
Drug Interactions	60
Clinical efficacy	400
Side effects	220
Dosage frequency	120
Documentation	100
Total	1000

Table 1: Selection criteria and authors' weighting. Scoring of selection criteria.

Approved indications

The number of licensed indications is a good measure of the applicability and documentation of the drugs. The fact that a drug is approved for [almost] all indications listed below is, from a formulary point of view, advantageous to another drug, which is approved for only one or two applications.

The percentage of the maximum score for approved indications was obtained as follows:

Indication	Maximum Score (%)
Prevention of DVT and pulmonary embolism after orthopaedic surgery	20
Treatment and prevention of venous thromboembolism	25
Prevention of stroke during atrial fibrillation	25
Treatment of acute coronary syndromes	15
Coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD)	15

Number of available formulations

A large number of available ready to use doses offer the possibility to give each patient an optimal dosage with minimal manipulation of the product.

This was scored as follows [percentage of the relative weight]

Solid oral formulation	80%
Liquid or dispersible oral formulation	20%

Variability of the area under the curve

A therapy may fail because of great differences in bioavailability and incomplete absorption. The score is based on the variability of bioavailability of the drugs after oral administration. This was scored as follows: The score for each product was inversely proportional to the coefficient of variation of the AUC. If the CV was 46%, the drug scored [100-46] 54% for this criterion.

Drug interactions

Interactions play a role only in patients who use other drugs which may interact with DOACs. However, it is a relevant criterion from a formulary point of view.

The score for each drug was dependent on the frequency and severity of observed drug interactions.

Clinical efficacy

The results of clinical studies were taken into account to judge the clinical efficacy of DOACs. The better the clinical efficacy, the higher the score for this medicine. All approved indications were scored separately.

Clinical efficacy was only scored for indications applicable to all DOACs.

Side effects

The extent and the severity of adverse effects is another important selection criterion for drugs. A distinction was made between "minor" side effects, such as gastrointestinal disturbances or skin reactions, occurring in clinical trials and severe or even life-threatening adverse reactions observed with large scale use of the drugs. The evaluation of the "minor" adverse effects was based on results of double blind comparative clinical studies.

Dosage frequency

The dosage frequency plays an important role in patient compliance. Compliance is not usually a problem in patients taking the drugs once or twice daily, but decreases considerably in the event dosage frequency is higher than twice daily. The method of evaluation of this criterion corresponded with that of all of the other SOJA scores.

Dosage Frequency	Weighting
1 x daily	100%
2 x daily	80%
3 x daily	40%
4 x daily	10%

NOACs are used for different indications and dosage frequency may vary according to the indication and it is possible dosage errors may occur if the wrong frequency is prescribed. In addition, dose adjustment or avoidance may be necessary for specific patient groups and if not recognised could lead to over administration which may be harmful.

Only the two indications which are applicable to all medicines were included in the judgement of dosage frequency. Therefore the dosage frequency for prevention of DVT and pulmonary embolism after orthopaedic surgery [edoxaban not approved] and treatment of acute coronary syndromes [only rivaroxaban] were not scored.

This criterion is scored as follows.

Indication	Weighting	Scoring methodology
Treatment and prevention of deep venous thrombosis	50%	According to frequency detailed above
Prevention of stroke during atrial fibrillation	50%	According to frequency detailed above

Documentation

The score for this criterion was divided over 4 subcriteria.

The first two subcriteria are indicative of the overall clinical documentation of the drugs in randomized controlled clinical studies. A large number of clinical studies and a large number of patients included in these studies leave no doubt about the clinical efficacy and safety of this drug in the studied population. The latter two criteria are indicative of the overall clinical experience with the drug. These subcriteria may introduce a bias to the advantage of older drugs, but this is done intentionally. The safety of a newly introduced drug cannot be guaranteed from the results of clinical studies, in which only a relatively small number of patients were included and most patients at risk for the development of adverse reactions [eg patients with diminished renal function] were excluded. Both the number of patients that has been treated on a worldwide basis and the period that a certain drug has been available are of importance, as it may take time until adverse reactions occur.

Number of randomised comparative studies

The number of randomised comparative clinical studies is an important determinant of the clinical documentation.

5% of the relative weight for this sub criterion was awarded for each randomised comparative study.

Number of patients in these studies

Besides the number of clinical studies, the number of patients that were treated with the drug in question must also be taken into consideration.

1% of the relative weight for this sub criterion was awarded for every 10 patients enrolled in randomised comparative studies.

Number of years marketed

The number of years that a product has been marketed in any country in the world provides information on the clinical experience with the drug. If a product is on the market for more than 10 years it is very unlikely that serious adverse reactions will be observed that have not been seen in the first 10 years after its introduction.

10% of the relative weight for this sub criterion was awarded for every year that the product is available on the market.

Number of patients treated worldwide

Besides the number of years that a product is on the market, also the number of patient days experience with the drug plays a role.

1% of the relative weight for this sub criterion was awarded for every million patient days treated with the drug in question worldwide.

The clinical documentation of the drugs is summarised below.

The documentation was scored per major indication. Only randomised comparative studies were taken into consideration.

Results

Approved indications

The exact SPC texts regarding the approved indications are summarized below [2-5].

Apixaban

Prevention of venous thromboembolic events [VTE] in adult patients who have undergone elective hip or knee replacement surgery.

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].

Treatment of deep vein thrombosis [DVT] and pulmonary embolism [PE], and prevention of recurrent DVT and PE in adults.

Dabigatran

75 mg

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

110 mg

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

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 ischemic attack [TIA]; age ≥ 75 years; heart failure [NYHA Class ≥ II]; diabetes mellitus; hypertension.

Treatment of deep vein thrombosis [DVT] and pulmonary embolism [PE], and prevention of recurrent DVT and PE in adults.

150 mg

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 ischemic attack [TIA]; age ≥ 75 years; heart failure [NYHA Class ≥ II]; diabetes mellitus; hypertension.

Treatment of deep vein thrombosis [DVT] and pulmonary embolism [PE], and prevention of recurrent DVT and PE in adults

Edoxaban

15 mg/30 mg/60 mg

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation [NVAF] with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack [TIA].

Treatment of deep vein thrombosis [DVT] and pulmonary embolism [PE], and prevention of recurrent DVT and PE in adults.

Rivaroxaban

2.5 mg

Co-administered with acetylsalicylic acid [ASA] alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome [ACS] with elevated cardiac biomarkers.

Co-administered with acetylsalicylic acid [ASA], is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease [CAD] or symptomatic peripheral artery disease [PAD] at high risk of ischaemic events.

10 mg

Prevention of venous thromboembolism [VTE] in adult patients undergoing elective hip or knee replacement surgery.

15 mg/20 mg

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

Treatment of deep vein thrombosis [DVT] and pulmonary embolism [PE], and prevention of recurrent DVT and PE in adults.

In summary: the following indications are approved in the Netherlands.

Indications	Weight	Api	Dab	Edo	Riv
Prevention of DVT and pulmonary embolism after orthopaedic surgery	20%	20%	20%	-	20%
Treatment and prevention of deep venous thrombosis	25%	25%	25%	25%	25%
Prevention of stroke during atrial fibrillation	25%	25%	25%	25%	25%
Treatment of acute coronary syndromes	15%	-	-	-	15%
Coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD)	15%	-	-	-	15%
Total	100%	70%	70%	50%	100%

Number of available formulations

The following solid oral presentations are available:

- Apixaban: 2.5 mg and 5 mg
- Dabigatran: 75 mg, 110 mg and 150 mg
- Edoxaban: 15 mg, 30 mg and 60 mg
- Rivaroxaban: 2.5 mg, 10 mg, 15 mg and 20 mg.

No liquid or dispersible formulations are available for any compound.

This results in identical scores for all DOACs.

	Api	Dab	Edo	Riv
Solid oral formulation	80%	80%	80%	80%
Liquid or dispersible oral formulation	-	-	-	-
Score	80%	80%	80%	80%

Variability of the area under the curve

The results are shown in the table below.

	CV Range	CV Mean	Ref	Score
Apixaban	24-27%	25%	6-9	75%
Dabigatran	42-69%	52%	10-13	48%
Edoxaban	20-28%	25%	14-17	75%
Rivaroxaban	19-33%	25%	6, 18-21	72%

In general a low variability of the pharmacokinetics is found for most drugs. The variability of dabigatran pharmacokinetics is higher than that of the other medicines.

Drug interactions

Pharmacokinetic interactions

Summary to the effect on AUC of individual DOACs.

From references: 2-5, 7, 22-24.

Interactions as described in the SPCs

Apixaban

Inhibitors of CYP3A4 and P-gp

The use of apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics [e.g., ketoconazole, itraconazole, voriconazole and posaconazole] and HIV protease inhibitors [e.g., ritonavir] [2].

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Ketoconazole	100% increase (K 400 mg)	153% increase (K 400 mg)	87% increase (K 400 mg)	160% increase (K 400 mg)
Ritonavir				150% increase (R 600 mg bid)
Diltiazem	40% increase (D 360 mg)			
Naproxen	50% increase (N 500 mg)			
Amiodarone		60% increase (A 600 mg SD)	40% increase (A 600 mg qd)	
Quinidine		56% increase (Q 600-1000 mg)	77% increase (Q 300 mg tid)	
Verapamil		70% increase (V: SR formulation)	63% increase (V: SR 240 mg)	
Clarithromycin		19% increase (C: 500 mg bid)	19% increase (C: 500 mg bid)	50% increase (C: 500 mg bid)
Erythromycin			85% increase (E: 500 mg qid)	30% increase (E: 500 mg tid)
Ciclosporin			74% increase (C: 500 mg qd)	
Ticagrelor		46% increase (T: 90 mg bid)		
Rifampicin	54% decrease	67% decrease (RL 600 mg qd)	34% decrease (RL 600 mg qd)	50% decrease (RL 600 mg qd)

Inducers of CYP3A4 and P-gp

The concomitant use of apixaban with strong CYP3A4 and P-gp inducers [e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort] may lead to reduced apixaban plasma concentrations. No dose adjustment for apixaban is required during concomitant therapy with such agents, however in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp apixaban should be used with caution for the prevention of VTE in elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE. Apixaban is not recommended for the treatment of DVT and PE in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp since efficacy may be compromised [2].

Anticoagulants, platelet aggregation inhibitors and NSAIDs

Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated. Apixaban should be used with caution when coadministered with NSAIDs because these medicinal products typically increase the bleeding risk. A significant increase in bleeding risk was reported with the triple combination of apixaban, ASA and clopidogrel in a clinical study in patients with acute coronary syndrome [2].

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban was coadministered with atenolol or famotidine [2].

Effect of apixaban on other medicinal products

Apixaban did not inhibit or induce CYP1A2, CYP2B6, CYP3A4/5. Therefore, apixaban is not expected to alter the metabolic clearance of coadministered drugs that are metabolised by these enzymes. Apixaban is not a significant inhibitor of P-gp [2].

Dabigatran

Anticoagulants and antiplatelet aggregation medicinal products

There is no or only limited experience with the following treatments which may increase the risk of bleeding when used concomitantly with dabigatran: anticoagulants such as unfractionated heparin [UFH], low molecular weight heparins [LMWH], and heparin derivatives [fondaparinux, desirudin], thrombolytic medicinal products, and vitamin K antagonists, rivaroxaban or other oral anticoagulants, and platelet aggregation medicinal products such as, GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, ticagrelor, dextran, and sulfinpyrazone. UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter [3].

Clopidogrel

In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times compared to clopidogrel monotherapy. In addition, dabigatran $AUC_{\tau,ss}$ and Cmax, ss and the coagulation measures for dabigatran effect or the inhibition of platelet aggregation as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective mono-treatments [3].

ASA

The effect of concomitant administration of dabigatran etexilate and ASA on the risk of bleeds was studied in patients with atrial fibrillation in a phase II study in which a randomized ASA co-administration was applied. Based on logistic regression analysis, co-administration of ASA and 150 mg dabigatran etexilate twice daily may increase the risk for any bleeding from 12% to 18% and 24% with 81 mg and 325 mg ASA, respectively [3].

NSAIDs

NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use NSAIDs increased the risk of bleeding by approximately 50 % on both dabigatran etexilate and Warfarin [3].

LMWH

This is considered to be due to the carry-over effect of enoxaparin treatment and regarded as not clinically relevant. Other dabigatran related anti-coagulation tests were not changed significantly by the pre-treatment of enoxaparin [3].

Interactions linked to dabigatran etexilate and dabigatran metabolic profile

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and have no in vitro effects on human cytochrome P450 enzymes. Therefore, related medicinal product interactions are not expected with dabigatran [3].

Transporter interactions

P-gp inhibitors

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of P-gp inhibitors [such as amiodarone, verapamil, quinidine, ketoconazole, dronedarone, clarithromycin and ticagrelor] is expected to result in increased dabigatran plasma concentrations [3].

The following strong P-gp inhibitors are contraindicated: systemic ketoconazole, cyclosporine, itraconazole and dronedarone, Concomitant treatment with tacrolimus is not recommended. Caution should be exercised with mild to moderate P-gp inhibitors [e.g. amiodarone, posaconazole, quinidine, verapamil and ticagrelor] [3].

The following potent P-gp inhibitors have not been clinically studied but from in vitro results a similar effect as with ketoconazole may be expected: Itraconazole and cyclosporine, which are contra-indicated.

Tacrolimus has been found in vitro to have a similar level of inhibitory effect on P-gp as that seen with itraconazole and cyclosporine. Based on these data concomitant treatment with tacrolimus is not recommended.

Posaconazole also inhibits P-gp to some extent but has not been clinically studied. Caution should be exercised when Pradaxa is co-administered with posaconazole [3].

P-gp inducers

Concomitant administration of a P-gp inducer [such as rifampicin, St. John´s wort [Hypericum perforatum], carbamazepine, or phenytoin] is expected to result in decreased dabigatran concentrations and should be avoided [3].

Other medicinal products affecting P-gp

Protease inhibitors including ritonavir and its combinations with other protease inhibitors affect P-gp [as inhibitor or as inducer]. They have not been studied and are therefore not recommended for concomitant treatment with dabigatran [3].

Edoxaban

P-gp inhibitors

Edoxaban is a substrate for the efflux transporter P-gp. In pharmacokinetic [PK] studies, concomitant administration of edoxaban with the P-gp inhibitors: ciclosporin, dronedarone, erythromycin, ketoconazole, quinidine, or verapamil resulted in increased plasma concentrations of edoxaban. Concomitant use of edoxaban with ciclosporin, dronedarone, erythromycin, or ketoconazole requires dose reduction to 30 mg once daily. Concomitant use of edoxaban with quinidine, verapamil, or amiodarone does not require dose reduction based on clinical data [4].

P-gp inducers

Co-administration of edoxaban with the P-gp inducer rifampicin led to a decrease in mean edoxaban AUC and a shortened half-life, with possible decreases in its pharmacodynamic effects. The concomitant use of edoxaban with other P-gp inducers [e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort] may lead to reduced edoxaban plasma concentrations. Edoxaban should be used with caution when co-administered with P-gp inducers [4].

Anticoagulants, antiplatelets, and NSAIDs

Anticoagulants

Co-administration of edoxaban with other anticoagulants is contraindicated due to increased risk of bleeding [4].

Acetylsalicylic acid [ASA]

Co-administration of ASA [100 mg or 325 mg] and edoxaban increased bleeding time relative to either medicine alone. Co-administration of high dose ASA [325 mg] increased the steady state Cmax and AUC of edoxaban by 35% and 32%, respectively. The concomitant chronic use of high dose ASA [325 mg] with edoxaban is not recommended. Concomitant administration of higher doses than 100 mg ASA should only be performed under medical supervision. In clinical studies concomitant use of ASA [low dose. 100 mg/day], other antiplatelet agents, and thienopyridines was permitted and resulted in approximately a 2-fold increase in major bleeding in comparison with no concomitant use, although to a similar extent in the edoxaban and warfarin groups. Co-administration of low dose ASA [. 100 mg] did not affect the peak or total exposure of edoxaban either after single dose or at steady-state. Edoxaban can be co-administered with low dose ASA [max 100 mg/day] [4].

Platelet inhibitors

In ENGAGE AF-TIMI 48 concomitant use of thienopyridines [e.g. clopidogrel] monotherapy was permitted and resulted in increased clinically relevant bleeding although with a lower risk of bleeding on edoxaban compared to warfarin.

NSAIDs

Co-administration of naproxen and edoxaban increased bleeding time relative to either medicine alone. Naproxen had no effect on the Cmax and AUC of edoxaban. In clinical studies, co-administration of NSAIDs resulted in increased clinically relevant bleeding. Chronic use of NSAIDs with edoxaban is not recommended.

Rivaroxaban

CYP3A4 and P-gp inhibitors

The use of rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp [5].

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways [such as macrolides], either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent [5].

Anticoagulants

After combined administration of enoxaparin [40 mg single dose] with rivaroxaban [10 mg single dose] an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests [PT, aPTT]. Enoxaparin did not affect the pharmacokinetics of rivaroxaban. Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants [5].

NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban [15 mg] and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel [300 mg loading dose followed by 75 mg maintenance dose] did not show a pharmacokinetic interaction with rivaroxaban [15 mg] but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs [including acetylsalicylic acid] and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk [5].

Warfarin

Converting patients from the vitamin K antagonist warfarin [INR 2.0 to 3.0] to rivaroxaban [20 mg] or from rivaroxaban [20 mg] to warfarin [INR 2.0 to 3.0] increased prothrombin time/INR [Neoplastin] more than additively [individual INR values up to 12 may be observed], whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, antifactor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests [including PT, aPTT, inhibition of factor Xa activity and ETP] reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the Ctrough of rivaroxaban [24 hours after the previous intake of rivaroxaban] as this test is minimally affected by rivaroxaban at this time point [5].

CYP3A4 inducers

The concomitant use of rivaroxaban with strong CYP3A4 inducers [e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort [Hypericum perforatum]] may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis [5].

A more recent study showed that the bleeding risk of DOACs is increased when these medicines are used concurrently with amiodarone, fluconazole, rifampin and phenytoin. No differences became apparent between DOACs in this respect [25].

There are no major differences in the incidence and severity of drug interactions between individual DOACs. The extent of drug interactions appears to be a bit smaller for edoxaban.

This drug is awarded 50%, the other medicines are awarded 45%.

Clinical efficacy

The judgement of the relative clinical efficacy should ideally be based on a large number of double-blind direct comparative studies between the DOACs using clinically relevant endpoints. Unfortunately, there are no direct comparative studies between two or more DOACs.

The main results of comparative studies are summarised in table 1-21. Statistically significance was indicated when applicable.

Orthopaedic surgery

Apixaban

Four randomized comparative studies were performed between apixaban and enoxaparin. The first study was a dose-finding study using enoxaparin and open-label warfarin as comparators. No relevant differences between the 3 drugs became apparent. The table only contains the results for the usual 2.5 mg bid dosage of apixaban. Higher dosages did not increase efficacy [26].

Three large scale studies compared apixaban to enoxaparin [two studies in hip replacement surgery and one in hip replacement]. Enoxaparin was used in either the US or European dosages of 30 mg bid and 40 mg qd, respectively.

The Advance 1 study did not show a difference in the composite endpoint [asymptomatic and symptomatic deep-vein thrombosis, non-fatal pulmonary embolism and death from any cause] between both medicines: 9.0% for apixaban and 8.8% for enoxaparin [27].

The Advance-2 study showed a significant difference in clinical efficacy, using the same composite endpoint: 15% for apixaban and 24% for enoxaparin, almost entirely caused by a different effect on asymptomatic deep venous thrombosis [28].

The Advance-3 study showed a significant difference in clinical efficacy in hip fracture surgery, again using the same composite endpoint: 1.4% for apixaban and 3.9% for enoxaparin, again almost entirely caused by a different effect on asymptomatic deep venous thrombosis [29].

Dabigatran

One open-label dose escalating studies comparing different dosages of dabigatran was not considered relevant for this analysis and was not taken into consideration [67]. A Japanese placebo-controlled study in knee surgery is also not discussed in detail. The drug was more effective than placebo regarding the composite endpoint of VTE + all-cause mortality [68].

Dabigatran was compared to enoxaparin in five double-blind, double-dummy studies in hip and knee surgery. None of the studies using the "European dosage" of enoxaparin [40 mg qd] showed a statistically significant difference in clinical efficacy on any of the studied endpoints between dabigatran and enoxaparin, but the Re-Mobilize study, using the 30 mg bid dosage of enoxaparin showed a statistically significant difference in favour of enoxaparin on the composite endpoint of VTE + all-cause mortality: 25.3% for enoxaparin vs 31.1% for dabigatran 220 mg [$p = 0.02$] and 33.7% for dabigatran 150 mg [$p < 0.001$] [C OR D6].. Most studies were designed to demonstrate non-inferiority of dabigatran compared to enoxaparin and demonstrated non-inferiority of 150 mg and 220 mg dabigatran compared to enoxaparin [31,32].

Two pooled analyses and a meta-analysis of the comparative studies confirmed similar efficacy of dabigatran 220 mg and enoxaparin [68-71].

Edoxaban

Edoxaban was compared to dalteparin or enoxaparin in four, relatively small scale double-blind studies, most of which were performed in Japan and/or Korea [35-38]. None of these studies used the European dosage schedule for enoxaparin. One study showed a significant difference in the incidence of VTE in favour of edoxaban 15 mg and 30 mg compared to enoxaparin 20 mg bid. This difference was entirely caused by asymptomatic DVT, no differences were seen in the incidence of symptomatic VTE [35]. No significant differences were seen in the other studies.

One placebo-controlled study and one small scale open label comparison with enoxaparin are not discussed [72,73].

Rivaroxaban

Four large scale randomized comparative studies were performed between rivaroxaban and enoxaparin, of which two studies in knee surgery and two in hip surgery.

The Record 1 study compared both drugs for administered for 5 weeks, the Record 2 study compared rivaroxaban for 5 weeks to enoxaparin for 2 weeks. Both studies showed significantly bet-

ter results for rivaroxaban on the composite primary endpoint, as well as other endpoints. These differences were however entirely caused by a better effect on asymptomatic deep venous thrombosis [39,40].

The Record 3 and 4 studies compared rivaroxaban to the European and US dosages of enoxaparin. Both studies showed a significant difference on the composite primary endpoint, again caused by a more favourable effect on asymptomatic deep venous thrombosis [C OR 41, 42]. The FDA described the Record 4 study as being unreliable because of systemic discarding of medical records, unauthorized unblinding, falsification, and concerns regarding improprieties in randomization [74].

A more recent study compared rivaroxaban to aspirin in patients undergoing knee of hip arthroplasty. All patients received rivaroxaban until postoperative day 5 and were then randomised to rivaroxaban 10 mg or aspirin 81 mg for an additional 9 [knee] to 30 [hip] days. The primary endpoint was symptomatic venous thromboembolism. The outcome of both treatments was quite similar: 0.70% for rivaroxaban and 0.64% for aspirin [43].

A meta-analysis showed that rivaroxaban had a significantly lower rate of symptomatic venous thromboembolism, symptomatic deep venous thrombosis, asymptomatic deep venous thrombosis, distal deep venous thrombosis, and proximal deep venous thrombosis compared to enoxaparin in patients undergoing knee surgery [75].

Atrial fibrillation

Vitamin K antagonists such as warfarin or acenocoumarol are the drugs of choice to prevent stroke in patients with atrial fibrillation. A meta-analysis showed that warfarin was substantially more effective than antiplatelet agents [76].

The key results of all studies are summarized in Tables 6-12.

Apixaban

Two large-scale comparative studies were performed with apixaban.

The Averroes study compared apixaban 5 mg bid to aspirin [81 to 324 mg] in patients with atrial fibrillation who could not be treated with vitamin K antagonists [such as difficulties in maintaining the correct INR range, adverse events, interacting medication or patient refusal to take vitamin K antagonists]. The study was performed in North and Latin America, Europe, Asia and South Africa. In case of renal function impairment the dosage of apixaban was reduced to 2.5 mg bid. This was the case in 6% of patients. Most patients [64%] used the low dose of aspirin of 81 mg]. The primary endpoint was a composite of stroke or systemic embolism [SE]. The primary endpoint was reached in significantly more patients in the aspirin group [3.7% per year] than in the apixaban group [1.6% per year]. A larger reduction was seen in high risk patients: 2.5% vs 8.3% per year [44].

No significant difference was observed in the composite of clinical ischemic stroke and covert embolic-pattern infarction [77].

The Aristotle study compared apixaban 5 mg bid to warfarin, dosed to a target INR of 2.0 to 3.0. The study was performed in North and Latin America, Europe and Asia. The primary endpoint was a composite of stroke or systemic embolism [SE]. The trial was designed to test for noninferiority, with key secondary objectives with respect to the primary efficacy outcome and the rates of major bleeding and death from any cause. The rate of the primary endpoint was 1.27% per year in the apixaban group as compared to 1.60% per year in warfarin group, $p < 0.001$ for noninferiority and $p = 0.01$ for superiority. Hemorrhagic stroke was significantly less frequent in the apixaban group: 0.24% vs 0.47% per year [45].

In an analysis of the Aristotle study, it was found that the effects of apixaban and warfarin were consistent whether or not the patient had previously suffered from previous stroke or TIA [78]. This was also true in patients who had atrial fibrillation and valvular heart disease [79].

The FDA criticized the Aristotle study because of altered patient records in a large Chinese site. When the data from this site were excluded, the significance disappeared [74].

This also has an impact on the results of meta-analyses regarding the effects of apixaban in atrial fibrillation [80].

Dabigatran

The RE-LY study compared dabigatran 110 mg of 150 mg bid to warfarin, again dosed to a target INR of 2.0 to 3.0. The primary

endpoint was a composite of stroke or systemic embolism [SE]. The trial was designed to test for noninferiority. Non Inferiority was demonstrated on the primary endpoint for both dosages. The 150 mg dosage was significantly better than warfarin on the primary endpoint: 1.11% vs 1.69% per year. The difference between the 110 mg [1.54% per year] and warfarin was not statistically significant. The difference in the incidence of the primary endpoint was significantly lower for the high dose of dabigatran compared to the low dose [p = 0.005], the incidence of stroke was also significantly lower in the high dose group: RR 0.70, p = 0.003 [46]. The presence of any degree of valvular heart disease did not affect the difference in treatment outcome between dabigatran and warfarin [81].

A post hoc analyses of those patients in which the current EU label dosages were applied [Dabigatran 150 mg in AF patients who are aged < 80 years without an increased risk for bleeding, e.g. HAS-BLED score <3, and not on concomitant verapamil. In other patients, D110 is recommended] showed significant reduction of stroke and systemic embolism.

Haemorrhagic stroke, and vascular death compared to warfarin [82].

A long term observational study [RELY-ABLE] as follow-up of the RE-LY study showed a similar incidence of stroke or SE for the 110 mg and 150 mg bid dosages: 1.60% and 1.46%, respectively [83]. The absolute reduction of stroke or SE was higher in patients with diabetes mellitus than in those without diabetes [84].

A large-scale [over 19,000 patients] database study showed similar efficacy outcomes [incidence of stroke] for dabigatran and warfarin [85]. On the other hand, a Danish nationwide cohort study showed a higher incidence of stroke or TIA in patients with atrial fibrillation and a history of stroke or TIA: 110 mg hazard ratio 1.99 [95% CI 1.42-2.78] and 150 mg hazard ratio 2.34 [95% CI 1.60-3.41] [86].

One retrospective study suggested a favourable risk-benefit ratio for dabigatran over warfarin in patients with mild to moderate renal function impairment, whereas warfarin performed better in patients with normal renal function [87].

Edoxaban

Edoxaban 30 mg and 60 mg once daily was compared to warfarin, dosed to a target INR of 2.0 to 3.0 in the Engage-TIMI 48 study. The primary endpoint was a composite of stroke or systemic embolism in a modified intent to treat analysis [SE]. The trial was designed to test for noninferiority. Noninferiority was demonstrated on the primary endpoint for both dosages. The 30 mg dose performed worse than warfarin, whereas better results were obtained with the 60 mg dose in the prespecified superiority analysis at the end of the study period, but neither difference was statistically significant. Ischaemic stroke was observed more frequently with the low dose than with warfarin or 60 mg edoxaban [49]. Mortality was slightly, but significantly lower in the low dose edoxaban dose [3.80% per year] compared to warfarin [4.25% per year, p-=0.006], whereas no significant difference was seen between high dose edoxaban [3.99% per year, p-0.08] and warfarin [88].

Both dosages of edoxaban resulted in lower rates of various subtypes of intracranial bleeding compared to warfarin [89]. The incidence of systemic embolism was too low to demonstrate a difference in the rates of edoxaban and warfarin [90]. Fewer cardiovascular and total deaths were observed for edoxaban, predominantly caused by the lower rate of major bleeding [91]. A greater absolute difference in mortality and risk of severe bleeding was found in patients with a high risk of falling at baseline [92]. The high dose of edoxaban performed better than warfarin regarding annualized intracranial bleeding in patients with a history of cerebrovascular events: 0.62% vs 1.09%, p = 0.02 [93].

A small scale open label phase 2 study, comparing 30 mg and 60 mg qd and 30 mg and 60 mg bid and warfarin will not be discussed in detail, also because of the short term follow-up period of 12 weeks [94].

The ENSURE-AF study compared edoxaban 60 mg per day [n = 1095] with enoxaparin/warfarin [n = 1104] in patients undergoing cardioversion of atrial fibrillation in an open label manner. The primary endpoint was a composite of stroke, systemic embolic event, myocardial infarction and cardiovascular mortality at day 28. The primary endpoint was observed in 0.5% of patients treated with edoxaban and in 1% of patients treated with the combination, the difference was not statistically significant [95].

Rivaroxaban

The Rocket AF study compared 20 mg rivaroxaban to warfarin, again dosed to a target INR of 2.0 to 3.0. The primary endpoint was similar to the studies described above. The trial was designed to test for noninferiority. Noninferiority was demonstrated on the

primary endpoint in a per protocol as treated analysis. Rivaroxaban was more effective than warfarin in reducing the primary endpoint during the study period: 1.7 vs 2.2% per year, p = 0.02, but no superiority was demonstrated on the primary endpoint in the intent-to-treat population: 2.1 vs 2.4% per year, p = 0.12 [50].

Various substudies and analyses of the Rocket AF study have been performed. The incidence of the primary endpoint was higher for both medicines in patients with previous stroke or TIA [2.79% per year and 2.96% per year for rivaroxaban and warfarin respectively] than in patients with no history of stroke or TIA [1.44% per year and 1.88% per year for rivaroxaban and warfarin respectively] [96]. The relative efficacy of both medicines was unaltered in younger and older individuals, with a higher absolute rate of the primary endpoint in elderly subjects [97]. The time that the INR was in the therapeutic range for patients receiving warfarin did not affect the outcomes [98]. The relative efficacy of both medicines was also similar in the presence or absence of diabetes [99]. Rivaroxaban performed better than warfarin regarding vascular death in a subgroup of patients who developed worsening renal function during treatment: 1.41 vs 2.21 events per 100 patient years [p = 0.026] [100].

The X-VeRT study compared 20 mg rivaroxaban to warfarin in patients with atrial fibrillation undergoing cardioversion. The patients were stratified into early [1-5 days after randomization] and late [3-8 weeks after randomization] cardioversion. The mean time to cardioversion was significantly shorter for rivaroxaban than for warfarin. No significant differences in efficacy were observed between rivaroxaban and warfarin on the primary endpoint [composite of stroke, TIA, PE, MI and CV death] or any other endpoint [51].

One systematic review and network meta-analysis of clinical studies with patients with atrial fibrillation studied the incidence of stroke and systemic embolism [SSE] of DOACs compared to warfarin. As a group the incidence of SSE was lowered significantly by DOACs [RR 0.78-0.82]. In randomised controlled trials, dabigatran, apixaban and edoxaban were associated with a significant reduction of SSE compared to warfarin [RR 0.70-0.80], whereas rivaroxaban did not show a positive effect on SSE [RR 1.04] [101]. On the other hand a nonsignificant reduction of thromboembolic stroke was found for rivaroxaban compared to dabigatran [RR 0.81; 95% CI: 0.65-1.01] in another analysis [102].

Another network meta-analysis involved 23 clinical trials in AF. Apixaban 5 mg twice daily [odds ratio 0.79, 95% confidence interval 0.66 to 0.94], dabigatran 150 mg twice daily [0.65, 0.52 to 0.81], edoxaban 60 mg once daily [0.86, 0.74 to 1.01], and rivaroxaban 20 mg once daily [0.88, 0.74 to 1.03] reduced the risk of stroke or systemic embolism compared with warfarin. The risk of stroke or systemic embolism was higher with edoxaban 60 mg once daily [1.33, 1.02 to 1.75] and rivaroxaban 20 mg once daily [1.35, 1.03 to 1.78] than with dabigatran 150 mg twice daily. The risk of all-cause mortality was lower with all DOACs than with warfarin [76].

No direct comparative studies between DOACs have been performed. Seven indirect comparisons were summarised in a document of Healthcare improvement Scotland [103]. The following conclusions were drawn from this analysis:

- Similar effects on SSE were found for apixaban 5 mg, edoxaban 60 mg and dabigatran 150 mg. Dabigatran 150 mg was more effective than rivaroxaban 20 mg [OR 0.75, 95% CI 0.57-0.99].
- Low doser edoxaban [30 mg] was less effective than standard dose apixaban [5 mg], dabigatran [150 mg] or edoxaban [60 mg].
- In analysis of absolute risks, rather than relative risks, the absolute risk of SSE for patients with atrial fibrillation treated with a standard dose DOAC was lowest for dabigatran 150 mg [103].

Non randomized studies

So-called Real World Data [RWD] have been published which have investigated efficacy and safety of DOACs in daily practice. Data were collected from insurance databases and from national healthcare databases. In order to make more or less reliable comparisons between DOACs patient populations need to be corrected by propensity scoring matching. Nevertheless significant bias cannot be excluded and all results should be interpreted with caution.

One Taiwanese retrospective cohort study was conducted in patients with nonvalvular atrial fibrillation taking dabigatran [n = 5,921], rivaroxaban [n = 3,916] or warfarin [n = 5,251]. The vast majority of patients used low dose dabigatran [10 mg bid] or rivaroxaban [10 - 15 mg qd]. The risk of ischemic stroke or systemic embolism during short term follow-up was significantly reduced

by dabigatran [HR 0.64, p = 0.0005] and rivaroxaban [HR 0.51, p = 0.0007] compared to warfarin. No significant difference was seen between dabigatran and rivaroxaban. Other endpoints, such as intracranial hemorrhage and all cause mortality [HR for dabigatran 0.40, p < 0.0001 and rivaroxaban 0.47, p < .00001, respectively] were also more favourable compared to warfarin [104].

A propensity-matched analysis reporting results regarding death, stroke or TIA, bleeding and major bleeding compared DOACs [rivaroxaban 55%, apixaban 22% and dabigatran 22%] to warfarin in the long term treatment of over 5,000 patients with atrial fibrillation. No significant difference was observed between DOACs and warfarin regarding death, but the incidence of stroke/TIA, major bleeding and bleeding was significantly reduced with DOACs [105].

Another propensity weighted nationwide cohort study from Denmark showed no significant differences between DOACs and warfarin in over 60,000 patients with atrial fibrillation [106].

The same study group performed a propensity weighted nationwide study of reduced dose non-vitamin K antagonist oral anticoagulant regimen, involving over 55,000 patients. Apixaban 2.5 mg twice a day was associated with a trend towards higher rates of ischaemic stroke/systemic embolism compared with warfarin, while rivaroxaban 15 mg once a day and dabigatran 110 mg twice a day showed a trend towards lower thromboembolic rates. The results were not significantly different. Rates of bleeding [the principal safety outcome] were significantly lower for dabigatran, but not significantly different for apixaban and rivaroxaban compared with warfarin [107].

The Revisit-US study used retrospective MarketScan claims in patients with nonvalvular atrial fibrillation in the US. After matching 11,411 rivaroxaban users to 11,411 warfarin users, the combined endpoint of ischaemic stroke and intracranial hemorrhage was reached more frequently for warfarin [HR=0.61, 95% CI 0.45 - 0.82]. There was no significant difference in the incidence of stroke between rivaroxaban and warfarin [108].

No differences in clinical efficacy determined as composite of ischaemic stroke, systemic embolism and death between apixaban [n = 2358], dabigatran [n = 1415] and rivaroxaban [n = 5139] were observed in an American study in Medicare patients. All DOACs were more effective than warfarin [n = 12,353] [109].

This ARISTOPHANES study used multiple data sources to compare stroke/systemic embolism [SE] and major bleeding [MB] among a large number of nonvalvular atrial fibrillation patients on non–vitamin K antagonist oral anticoagulants [NOACs] or warfarin. A total of 285,292 patients were included in the 6 matched cohorts. Apixaban [hazard ratio [HR], 0.61; 95% CI, 0.54–0.69], dabigatran [HR, 0.80; 95% CI, 0.68–0.94], and rivaroxaban [HR, 0.75; 95% CI, 0.69–0.82] were associated with lower rates of stroke/SE compared with warfarin [110].

An independent retrospective new-user cohort study of US Medicare patients with nonvalvular atrial fibrillation enrolled patients who initiated warfarin [n = 183,318], or a standard dose of dabigatran [150 mg twice daily; n = 86,198], rivaroxaban [20 mg once daily; n = 106,389], or apixaban [5 mg twice daily; n = 73,039. Compared with warfarin, each NOAC was associated with reduced risks of thromboembolic stroke [20%-29% reduction; P = .002 [dabigatran], P < 0.001 [rivaroxaban, apixaban]], intracranial hemorrhage [35%-62% reduction; P < 0.001 [each DOAC]], and mortality [19%-34% reduction; P < .001, each DOAC [111].

Treatment and prophylaxis of Deep vein thrombosis and pulmonary embolism

The double-blind studies in deep vein thrombosis are summarised in table 13-17.

Apixaban

Three randomized studies were performed with apixaban.

The Amplify study compared 10 mg apixaban twice daily during 7 days, followed by 5 mg bid for 6 months and subcutaneous enoxaparin 40 mg qd for at least 5 days, followed by warfarin titrated to an INR of 2.0 to 3.0 in patients with acute venous thromboembolism. The primary efficacy endpoint was recurrent symptomatic venous thromboembolism or death related to venous thromboembolism. The study was designed to show non-inferiority of apixaban. The incidence of the primary endpoint was similar in both groups, confirming non inferiority of apixaban compared to warfarin. Various other composite endpoints were reached at similar rates for both treatments [52].

An analysis of the Amplify study showed that apixaban reduced the incidence of hospitalization compared to enoxaparin/warfarin: 5.7% vs 7.1%, p = 0.045 [112]. A relatively large difference in

the primary endpoints was seen in cancer patients participating in the Amplify study: 1.1% vs 6.3% [113].

The Amplify-EXT study compared 2.5 mg apixaban twice daily with placebo in patients with venous thromboembolism during a treatment period of 12 months, after patients had completed initial anticoagulation treatment for 6-12 months. The primary efficacy endpoint was recurrent symptomatic venous thromboembolism or death related to venous thromboembolism. The study was designed to show non-inferiority of apixaban. The incidence of the primary endpoint was significantly lower for apixaban: 1.7% vs 8.8%. All composite endpoints for efficacy were significantly more favourable for apixaban [53].

The ADOPT trial compared 2.5 mg twice daily apixaban for prolonged prophylaxis for 30 days to subcutaneous enoxaparin 40 mg qd for 6-14 days in medically ill patients with congestive heart failure or respiratory failure or other medical conditions and at least one additional risk factor for venous thromboembolism. The primary efficacy endpoint was the 30-day composite of death related to venous thromboembolism, pulmonary embolism, symptomatic deep-vein thrombosis, or asymptomatic proximal-leg deep-vein thrombosis on day 30. Despite the longer duration of prophylaxis, the incidence of the primary endpoint was comparable in both groups: 2.71% for apixaban vs 3.07% for enoxaparin [54].

The relatively small scale open label Botticelli DVT dose ranging study is not discussed in detail in this analysis [114].

Dabigatran

Four large scale randomized studies were performed with dabigatran.

The Re-cover study compared dabigatran 150 mg bid to warfarin [titrated to an INR of 2.0 - 3.0] in patients with acute venous thromboembolism during 6 months after initial parenteral anticoagulation therapy for a median of 9 days. The primary efficacy endpoint was recurrent symptomatic venous thromboembolism or death related to venous thromboembolism. The study was designed to show non inferiority of dabigatran. The incidence of the primary endpoint was similar in both groups: 2.4% for dabigatran vs 2.1% for warfarin, confirming non inferiority of dabigatran compared to warfarin [55].

The Re-cover II study compared dabigatran 150 mg bid to warfarin [titrated to an INR of 2.0 - 3.0] during 6 months after treatment with heparin or low molecular weight heparin for 5 - 11 days in patients with acute venous thromboembolism. The primary efficacy endpoint was recurrent symptomatic venous thromboembolism or death related to venous thromboembolism. The study was also designed to show non inferiority of dabigatran. The incidence of the primary endpoint was similar in both groups: 2.3% for dabigatran vs 2.2% for warfarin, confirming non inferiority of dabigatran compared to warfarin [56].

The results of the Remedy and Resonate studies were reported in one publication [57]. The first study compared 150 mg twice daily dabigatran to warfarin in the extended treatment of venous thromboembolism for 6 months after initial treatment for at least 3 months. The patients were partly pretreated during the Re-cover and Re-cover II studies. The primary efficacy endpoint was recurrent venous thromboembolism. The study was designed to show non inferiority of dabigatran. The primary endpoint was reached in 1.8% or patients treated with dabigatran versus 1.3% for warfarin, confirming non inferiority. Acute coronary syndromes were seen more frequently for dabigatran: 0.9% vs 0.2%, p = 0.02 [57].

The Resonate study compared dabigatran to placebo, using similar methodology and endpoints as the study described above. The primary endpoint was seen significantly less frequent for dabigatran compared to placebo: 0.4% vs 5.6%. The incidence of myocardial coronary syndromes was similar for both drugs: 0.1% [57].

Edoxaban

Two studies were performed with edoxaban.

The Hokusai VTE study compared edoxaban 60 mg [or 30 mg in case of a creatinine clearance of 30-50 ml/min] to warfarin for 3-12 months in patients with symptomatic deep venous thrombosis after initial treatment with heparin.

The primary efficacy endpoint was recurrent symptomatic venous thromboembolism. The study was designed to show non inferiority of edoxaban. The incidence of the primary endpoint was similar in both groups: 3.3% for edoxaban vs 3.5% for warfarin, showing noninferiority of edoxaban compared to warfarin [58].

The Hokusai VTE Cancer study compared edoxaban 60 mg to dalteparin 150 IU for 6-12 months in patients with symptomatic deep venous thrombosis due to cancer after initial 5 days treatment with heparin.

The primary efficacy endpoint was recurrent symptomatic venous thromboembolism. The study was designed to show non inferiority of edoxaban. The incidence of the primary endpoint was similar in both groups: 12.8% for edoxaban vs 13.5% for dalteparin, showing noninferiority of edoxaban compared to warfarin [59].

Rivaroxaban

Four large scale studies were performed with rivaroxaban.

The Einstein study compared rivaroxaban [15 mg bid for 3 weeks, followed by 20 mg qd] to subcutaneous enoxaparin 1 mg/kg and warfarin or acenocoumarol. Enoxaparin was discontinued when the INR was 2.0 or more for two consecutive days. The duration of treatment was 6-12 months, using an open-label design. The primary efficacy endpoint was recurrent venous thromboembolism. The study was designed to show non inferiority of edoxaban. The incidence of the primary endpoint was similar in both groups: 2.1% for rivaroxaban vs 3.0% for warfarin, demonstrating non inferiority of rivaroxaban compared to warfarin [60].

The results of a placebo-controlled study were reported in the same publication. All patients had completed 6 - 12 months of treatment of venous thromboembolism at baseline. The primary efficacy endpoint was recurrent venous thromboembolism. The study was designed to show non inferiority of edoxaban. The incidence of the primary endpoint was significantly lower for rivaroxaban: 1.3% vs 7.1% for placebo [60].

The Einstein PE study used a similar design, including patients with acute venous thromboembolism. The primary efficacy endpoint was symptomatic recurrent venous thromboembolism. The duration of treatment with rivaroxaban or warfarin was 3 - 12 months. The incidence of the primary endpoint was similar in both groups: 2.1% for rivaroxaban vs 1.8% for warfarin [61].

The Magellan study compared rivaroxaban 10 mg once daily for 35 days to enoxaparin 40 mg once daily for 10 days in acute ill medical patients. The primary endpoint was the composite of asymptomatic proximal or symptomatic venous thromboembolism up to day 10 [non inferiority test] and up to 35 days [superiority test]. An identical incidence of the primary endpoint was seen at day 10 [2.7% in both groups, confirming non inferiority]. Rivaroxaban was superior to the other treatment arm at day 35: 4.4% vs 5.7%, p = 0.02 [62].

The Einstein Choice study compared rivaroxaban [10 mg or 20 mg] with 100 mg aspirin in patients with venous thromboembolism who had completed 6 to 12 months of anticoagulation and who were in equipoise regarding the need for continued anticoagulation. Study drugs were continued for up to 12 months. The risk of a recurrent event [symptomatic fatal or nonfatal venous thromboembolism] was significantly lower for both the 10 mg and 20 mg dose of rivaroxaban compared to aspirin: 1.2% and 1,5% vs 4.4% [63].

Two smaller scale studies with rivaroxaban [ODIXa-DVT and Einstein DVT-dose ranging study] are not discussed in this analysis [115,116].

A Cochrane review demonstrated no differences between DOACs and warfarin in the treatment of pulmonary embolism [117] or deep venous thrombosis [118].

Acute coronary syndromes [ACS]

Only few studies were performed in patients with ACS.

Apixaban

The Appraise study was a phase 2 dose-finding study comparing apixaban dosages of 2.5 mg twice daily [n = 317], 10 mg once daily [n = 318], 10 mg twice daily [n = 248] and 20 mg once daily [n = 221] to placebo for 6 months in patients with recent STEMI or N-STEMI acute coronary syndromes. Almost all patients also received aspirin and 76% received clopidogrel. The primary outcome was the ISTH major or clinically relevant nonmajor bleeding. A secondary efficacy endpoint was the composite of cardiovascular death, myocardial infarction, severe recurrent ischaemia or ischaemic stroke. The study was mainly designed to investigate safety and was not powered to detect differences in efficacy. The higher dosage arms were prematurely discontinued because of a high incidence of bleeding. No difference was noted between apixaban 2.5 mg bid and 10 mg qd and placebo in the primary efficacy endpoint: 7.6%, 6.0% and 8.7% or in any of the other endpoints [119].

The Appraise II study compared an apixaban dosage 5 mg twice daily to placebo. The details of the study are presented in table 18-21. The results of the study were unfavourable. The primary endpoint [composite of cardiovascular death, myocardial infarction or ischaemic stroke] was seen in 7.5% of patients and in 7.9% of patients treated with placebo, this difference was not statistically significant. On the other hand, a significant increase in bleeding was observed in the apixaban group, see section on bleeding [64].

Dabigatran

One double-blind, phase II, placebo [n = 371] controlled dose escalation trial was performed with dabigatran, using dosages of 50 mg [n = 369], 75 mg [n = 368], 110 mg [n = 406] and 150 mg [n = 347] twice daily for 6 months. The primary outcome was major or clinically relevant nonmajor bleeding. The incidence of bleeding were significantly higher for the 110 mg and 150 mg compared to placebo [HR 3.92 and 4.27, respectively] and numerically higher than placebo for the lower dosages. The study was not powered to detect differences in efficacy. No differences in efficacy endpoints, such as a composite of cardiovascular death, myocardial infarction or non-hemorrhagic stroke were seen between the groups [120].

Edoxaban

No studies have been published with edoxaban.

Rivaroxaban

The Atlas ACS TIMI-46 study was a double-blind, phase II dose escalation study comparing rivaroxaban dosages of 5 mg, 10 mg, 15 mg and 20 mg to placebo in patients with acute coronary syndromes. Patients were stratified on use of aspirin only [n = 761] or use of a combination of aspirin and a thienopyridine [n = 2730]. The primary safety endpoint was clinically significant bleeding [TIMI major, TIMI minor or requiring medical attention]. The primary efficacy endpoint was a composite of death, myocardial infarction, stroke or severe recurrent ischaemia requiring revascularization during 6 months. Rivaroxaban resulted in a decrease of the secondary efficacy endpoint of death, myocardial infarction or stroke compared to placebo: 3.9% vs 5.5%, p = 0.027. No significant differences were seen on the primary efficacy endpoint or other efficacy endpoints [121].

The Atlas ACS2 TIMI-51 study compared rivaroxaban 2.5 mg and 5 mg bid to placebo. The details of the study are presented in Tables 18-21. Rivaroxaban was associated with a significant decrease of the primary endpoint [composite of death from cardiovascular causes, myocardial infarction or stroke] compared to placebo: pooled data: 8.9% vs 10.7%, p = 0.008. Each dosage of rivaroxaban individually also decreased the primary endpoint significantly compared to placebo. The lower dose reduced the rate of death from cardiovascular causes or death from any cause compared to placebo, whereas this was not the case for the higher dosage [65].

The Gemini ACS-1 study compared rivaroxaban [2.5 mg bid] to aspirin 100 mg qd in patients with ACS. All patients received background therapy with P2Y12 inhibitors [clopidogrel or ticagrelor]. Treatment was continued for one year. The primary endpoint was TIMI clinically significant bleeding. Efficacy was also investigated. No differences in clinical efficacy were noted regarding the composite endpoint of cardiovascular death, myocardial infarction, stroke or definite stent thrombosis or any of its components [66].

Coronary artery disease or peripheral artery disease

Rivaroxaban

Only rivaroxaban was investigated for this indication.

The large scale [n = 27,395] COMPASS study compared rivaroxaban [2.5 mg bid] combined with aspirin [100 mg once daily] to rivaroxaban and aspirin monotherapy in patients with stable cardiovascular disease. The primary endpoint was a composite of cardiovascular death, stroke or myocardial infarction. The study was stopped for superiority in the combination group vs aspirin alone after a mean follow-up of 23 months. The primary endpoint occurred in 4.1% of patients in the combination group vs 5.4% in the aspirin monotherapy group, HR 0.76 95% CI: 0.66 - 0.86] p < 0.001. The combination also showed superiority compared to aspirin regarding death from any cause [3.4% vs 4.1%, HR 0.82, 95% CI: 0.71 - 0.96], cardiovascular death [1.7% vs 2.2%, HR 0.78 95% CI: 0.64 - 0.96] and stroke [0.9% vs 1.6%, HR 0.58 95% CI: 0.44 - 0.76].

No significant difference in the primary endpoint was found between rivaroxaban [4.9%] and aspirin monotherapy [5.4%]. No significant difference was found in the incidence of stroke, but ischaemic stroke occurred significantly more often for aspirin, whereas hemorrhagic stroke was observed more frequently for rivaroxaban [122].

Two publications reported the effects of the above treatments in patients with stable coronary artery disease [123] and in patients with stable peripheral or carotid artery disease [124].

The results in these subgroups were in line with the whole group. A significant reduction of the primary endpoint was seen patients with stable coronary disease [4% vs 6%, HR 0.74, 95% CI 0.65 - 0.87] [123] and in patients with stable peripheral or carotid artery disease [5% vs 7%, HR 0.72, 95% CI 0.57 - 0.90] [124].

There are no clear indications for clinically relevant differences between the DOACs. Judgement of relative efficacy is complicated by the fact that there are no direct comparative studies between two or more DOACs for any indication.

Orthopaedic surgery

Apixaban was more effective than enoxaparin regarding the primary endpoint in 2 of 4 studies, dabigatran in 1 of 5 studies, edoxaban in 1 of 4 studies and rivaroxaban in all 4 studies.

Atrial fibrillation

Apixaban was more effective than warfarin regarding the primary endpoint in all 2 studies, dabigatran in one study, although this was only valid for the high dose, edoxaban in 0 of 1 study and rivaroxaban in 1 of 2 studies. A recent meta-analysis showed the best result for apixaban 5 mg twice daily [125].

Dabigatran has shown a reduction of the clinical endpoint ischaemic stroke and a reduced mortality compared to warfarin in the Re-Ly study [126].

Apixaban and dabigatran are awarded a higher score than rivaroxaban and edoxaban, because of a documented positive effect on the incidence of ischaemic stroke.

Deep venous thrombosis

All comparative studies were designed to demonstrate non inferiority compared to enoxaparin. This was confirmed in all studies. There are no indications for major differences in clinical efficacy between the DOACs, but direct comparative data are lacking. Edoxaban was assigned a lower score because of limited clinical data

It should be stated that no direct comparative studies have been performed, which limits the value of [network] meta-analyses to a certain extent.

The overall score for efficacy was calculated as follows.

Score

	Atrial fibrillation	Venous thromboembolism	Score (%)
Weight	70%	30%	
Apixaban	70%	70%	70%
Dabigatran	70%	70%	70%
Edoxaban	60%	70%	63%
Rivaroxaban	65%	70%	67%

Side effects

Bleeding

The main results of comparative studies regarding safety are summarised in table 1-21 [26-66].

Apixaban

Orthopaedic surgery

Four randomized comparative studies were performed between apixaban and enoxaparin. No differences between both medicines became apparent regarding safety, both regarding bleeding and nonbleeding adverse events [26-29].

Atrial fibrillation

There were no significant differences between apixaban and aspirin in the incidence of bleeding in the Averroes study [44]. Apixaban was associated with a lower incidence of bleeding compared to warfarin in the Aristotle study, the incidence of major bleeding, intracranial bleeding and any bleeding was significantly lower [45]. The rate of major bleeding was 2.1% per year in the apixaban group versus 3.1% in the warfarin group. Major extracranial hemorrhage was associated with reduced hospitalisation, medical or surgical intervention or transfusion for apixaban compared to warfarin [126].

A history of bleeding at baseline was associated with higher risk of major bleeding [127].

Treatment or prophylaxis of deep venous thrombosis

Apixaban showed a lower incidence of bleeding compared to enoxaparin followed by warfarin in the Amplify study. Both the incidence of major bleeding [0.6% vs 1.8%] and the incidence of Major or Clinically relevant nonmajor bleeding [4.3 vs 9.7%] were significantly lower for apixaban [52].

The Amplify-EXT study showed a similar incidence of bleeding of apixaban and placebo [53].

On the other hand, apixaban showed a higher incidence of major bleeding compared to enoxaparin in the Adopt trial [54].

Acute coronary syndromes

The Appraise study was a phase 2 dose-finding study comparing apixaban dosages of 2.5 mg twice daily [n = 317], 10 mg once daily [n = 318], 10 mg twice daily [n = 248] and 20 mg once daily [n = 221] to placebo for 6 months in patients with recent STEMI or N-STEMI acute coronary syndromes. The primary outcome was the ISTH major or clinically relevant nonmajor bleeding. The higher dosage arms were prematurely discontinued because of a high incidence of bleeding. The primary safety endpoint was reached in 3.0% for placebo and in 5.7% and 7.9% for the 2.5 mg bid and 10 mg qd dosages of apixaban, respectively. The difference between the high dose of apixaban and placebo was statistically significant, p = 0.005 [119].

The details of the Appraise 2 study are summarized in tables 18-21. The incidence of all forms of bleeding were significantly higher for apixaban compared to placebo, without a favourable effect on the efficacy endpoint. Apixaban resulted in a higher incidence of the primary safety endpoint of major bleeding according to the TIMI criteria: 1.3% vs 0.5%, p = 0.001 [64].

Meta-analyses and registry studies

A Bayesian meta-analysis, including over 12,000 patients showed a similar risk of major bleeding [OR 1.03] and total bleeding [OR 0.92] for apixaban and enoxaparin [128].

Another meta-analysis, including over 24,000 patients compared the risk of bleeding for apixaban and vitamin K antagonists. Apixaban was associated with a lower risk of any bleeding [RR 0.73, 95% CI 0.59-0.90] and a composite of major and clinically relevant non-major bleeding [RR 0.60, 95% CI 0.40-0.88] [129].

An indirect comparison of all studies performed for the treatment of acute venous thromboembolism suggested a lower incidence of major bleeding for apixaban compared to the other DOACs [130]. A systematic review and meta-analysis of DOACs in the initial and long-term treatment and prevention of venous thromboembolism also reported a reduced risk of major or clinically relevant non-major bleeding compared to dabigatran [RR 0.69, 95% CI 0.51-0.94], edoxaban [RR 0.54 [95% CI 0.41-0.69] and rivaroxaban [0.47 [95% CI 0.36-0.61] [131]. These results should be interpreted with caution, because of different inclusion criteria and study populations.

Dabigatran

Orthopaedic surgery

Five randomized comparative studies were also performed between dabigatran and enoxaparin. Again, no differences between both medicines became apparent regarding safety, both regarding bleeding and non bleeding adverse events [30-34].

Atrial fibrillation

Dabigatran resulted in a significantly lower incidence of bleeding compared to warfarin in the Re-Ly study [46]. On the other hand a higher incidence of gastrointestinal bleeding was found for dabigatran 150 mg [but not 110 mg] compared to warfarin [132].

In a long term observational study [RELY-ABLE] as follow-up of 2.3 years duration of the RE-LY study, the incidence of major bleeding was significantly lower for the 110 mg bid dosage than for the 150 mg bid dosage: 2.99% vs 3.74% per year [82].

The Re-Circuit study showed a lower risk of bleeding during and up to 8 weeks after ablation in patients with AF [47].

A lower risk of bleeding was observed for dabigatran 110 mg or 150 mg compared to warfarin plus aspirin [all patients in combination with clopidogrel or ticagrelor] [48].

Treatment or prophylaxis of deep venous thrombosis

Dabigatran showed a lower incidence of major or clinically relevant non-major bleeding than warfarin in three direct comparative studies [51-53]. One placebo-controlled study showed a higher incidence of major or clinically relevant nonmajor bleeding for dabigatran: 5.3% vs 1.8%. The overall incidence of bleeding was also higher for dabigatran: 10.5% vs 5.9% [53].

A pooled analysis of the Re-cover studies showed a significant decrease of any bleeding event [HR 0.70] and major bleeding or clinically relevant non-major bleeding [HR 0.62] [133].

Acute coronary syndromes

One double-blind, placebo [n = 371] controlled dose escalation trial was performed with dabigatran, using dosages of 50 mg [n = 369], 75 mg [n = 368], 110 mg [n = 406] and 150 mg [n = 347] twice daily for 6 months. The primary outcome was major or clinically relevant nonmajor bleeding. The incidence of bleeding were significantly higher for the 110 mg and 150 mg compared to placebo [HR 3.92 and 4.27, respectively] and numerically higher than placebo for the lower dosages [120].

Meta-analyses and registry studies

A study from New Zealand comparing two inception cohorts of patients above 65 years of age using either dabigatran or warfarin showed a lower incidence of any bleeding or intracerebral bleeding for dabigatran [134].

A French propensity-matched cohort study in patients with atrial fibrillation including 19,713 new users of vitamin K antagonists, 8,443 new users of dabigatran and 4,651 new users of rivaroxaban showed a similar risk of bleeding for all compounds [135].

Another "real world setting" study showed an incidence of major bleeding in patients with atrial fibrillation that was comparable to that found in clinical studies: 0.5% [95% CI 0.23-0.77]. A low incidence of intracranial bleeding [0.19%] and fatal bleeding [0.08%] was observed in 2,579 patients treated with dabigatran or rivaroxaban [136].

The risk of gastrointestinal bleeding was comparable for dabigatran, rivaroxaban and warfarin in a US population based cohort study [137].

Another meta-analysis confirmed a lower higher incidence of bleeding for dabigatran in 14 randomised controlled studies: OR 0.88 [95% CI 0.79-0.99, p = 0.029] for dabigatran versus comparators enoxaparin, warfarin or placebo [138].

A large scale cohort study showed a lower annual rate of major bleeding for dabigatran [2.6] than for warfarin [5.5] in patients with atrial fibrillation at about 5 months of follow-up [139].

Edoxaban

Orthopaedic surgery

Edoxaban was compared to dalteparin or enoxaparin in four, relatively small scale studies, most of which were performed in Japan and/or Korea. No significant differences were seen regarding safety [35-38].

Atrial fibrillation

The incidence of all investigated forms of bleeding [major, intracranial, fatal, clinically relevant non-major and minor bleeding] was significantly lower for edoxaban than for warfarin in the Engage TIMI48 study [49].

A small scale study in Asian patients with non-valvular atrial fibrillation showed a similar incidence of bleeding for edoxaban and warfarin [140].

Treatment or prophylaxis of deep venous thrombosis

Edoxaban showed a lower incidence of clinically relevant nonmajor bleeding [7.2 vs 8.9%] and minor bleeding [21.7% vs 25.6%] than warfarin in a direct comparative study [49].

Meta-analyses and registry studies

A Chinese meta-analysis of randomised controlled trials with edoxaban, including over 31,000 patients showed a lower incidence of major and clinically relevant nonmajor bleeding for apixaban [RR 0.78, 95% CI 0.74 - 0.82] and any bleeding [RR 0.82, 95% CI 0.79 - 0.85]. Edoxaban also reduced all-cause mortality [RR 0.92, 95% CI 0.85 - 0.99] and cardiovascular mortality [RR 0.87, 95% 0.79 - 0.96]. A dose of 120 mg edoxaban was associated with a significantly higher risk of bleeding [141].

Rivaroxaban

Orthopaedic surgery

Four randomized comparative studies were also performed between rivaroxaban and enoxaparin, showing a very similar tolerability and safety profile for both medicines [39-42].

A more recent study compared rivaroxaban to aspirin in patients undergoing knee of hip arthroplasty. All patients received rivaroxaban until postoperative day 5 and were then randomised to rivaroxaban 10 mg or aspirin 81 mg for an additional 9 [knee] to 30 [hip] days. The primary safety endpoint were bleeding complications. The outcome of both treatments regarding major bleeding was quite similar: 0.29% for rivaroxaban and 0.45% for aspirin [43].

Atrial fibrillation

Rivaroxaban resulted in a significantly lower incidence of bleeding compared to warfarin in the Rocket AF study. The incidence of intracranial bleeding, fatal bleeding and bleeding in a critical organ was significantly lower than for warfarin [50]. No differences in the incidence of bleeding were found in another, smaller scale study in patients with atrial fibrillation undergoing cardioversion [51].

Rivaroxaban was associated with a higher risk of gastrointestinal bleeding compared to warfarin in the Rocket AF study [142].

The Revisit-US study used retrospective MarketScan claims in patients with nonvalvular atrial fibrillation in the US. After matching 11,411 rivaroxaban users to 11,411 warfarin users, the combined endpoint of ischaemic stroke and intracranial hemorrhage was reached more frequently for warfarin [HR=0.61, 95% CI 0.45 - 0.82]. The incidence of intracranial bleeding was significantly lower for rivaroxaban as well: HR 0.53 [95% CI 0.35 - 0.79] [108].

Direct comparative studies in atrial fibrillation between DOACs have not been performed. However, several observational studies showed a significantly higher rate of major bleeding for rivaroxaban compared to dabigatran [102,143-152]. Apixaban consistently showed the lowest rate of bleeding compared to rivaroxaban and dabigatran [143,145,149,150,152].

One systematic review and network meta-analysis of clinical studies with patients with atrial fibrillation showed a higher frequency of major bleeding for dabigatran [RR 1.17] and rivaroxaban [RR 1.12] compared with warfarin, although this difference was not statistically significant. A significantly lower degree of bleeding, compared to warfarin, was found for apixaban [RR 0.67]. The incidence of intracranial bleeding was lower than warfarin for dabigatran and apixaban, but not for rivaroxaban [101].

Coronary artery disease or peripheral artery disease

The large scale [n = 27,395] COMPASS study compared rivaroxaban [2.5 mg bid] combined with aspirin [100 mg once daily] to rivaroxaban and aspirin monotherapy in patients with stable cardiovascular disease. Major bleeding occurred more frequently for the combination than for aspirin monotherapy: 3.1% vs 1.9%, HR 1.70 [95% CI 1.40-2.05]. Minor bleeding was also more frequent for the combination [122].

Two publications reported the effects of the above treatments in patients with stable coronary artery disease [123] and in patients with stable peripheral or carotid artery disease [124].

The results in these subgroups were in line with the whole group. A significantly incidence of major bleeding was seen in the combination group in patients with stable coronary disease [3% vs 2%, HR 1.66, 95% CI 1.37 - 2.03] [123] and in patients with stable peripheral or carotid artery disease [3% vs 2%, HR 1.61, 95% CI 1.12 - 2.31] [124].

No direct comparative studies between DOACs have been performed. Four indirect comparisons in the treatment of atrial fibrillation were summarised in a document of Healthcare improvement Scotland [103]. The following conclusions were drawn from this analysis:

- Major bleeding occurred less frequently for apixaban 5 mg compared to dabigatran 150 mg [OR 0.74].
- Major bleeding occurred less frequently for dabigatran 150 mg compared to rivaroxaban 20 mg [OR 0.78].
- Major bleeding occurred less frequently for edoxaban 30 mg compared to apixaban 5 mg [OR 0.67], dabigatran 110 mg [OR 0.58] and 150 mg [OR 0.5], rivaroxaban 20 mg [OR 0.45] and edoxaban 60 mg [OR 0.59].
- Major bleeding occurred less frequently for apixaban 5 mg compared to rivaroxaban 20 mg [OR 0.67].
- Major bleeding occurred less frequently for edoxaban 60 mg compared to rivaroxaban 20 mg [OR 0.76].
- Intracranial hemorrhage was reported less frequently for dabigatran 110 mg [OR 0.45] and edoxaban 30 mg [OR 0.48] compared to rivaroxaban 20 mg.

These results were confirmed in a US Medicare study. A lower risk of bleeding was observed for apixaban compared to warfarin, whereas a higher risk of bleeding was observed for rivaroxaban [109].

Another American study studied propensity matched cohorts with non-valvular atrial fibrillation using apixaban, dabigatran or rivaroxaban. This study came to similar conclusions: the lowest bleeding risk was found for apixaban, followed by dabigatran and rivaroxaban [AF 153].

Treatment or prophylaxis of deep venous thrombosis

Rivaroxaban showed a lower incidence of major bleeding in compared to enoxaparin followed by warfarin in the Einstein PE study: 1.1% vs 2.2% [C DV R2]. On the other hand a higher incidence of major bleeding was observed compared to enoxaparin in the Magellan study: 1.2% vs 0.4% [62].

An analysis of the Einstein DVT and Einstein PE studies showed a lower incidence of bleeding for rivaroxaban compared to enoxaparin, followed by warfarin. The HR for bleeding in the first weeks of the study was 0.43 [95% CI 0.23 - 0.80] and 0.60 [95% CI 0.37 - 1.00] for bleeding later than 3 weeks after the start of the study [154]. Bleeding with rivaroxaban occurred less frequently and had a milder presentation than the comparator [155].

Acute coronary syndromes

The Atlas ACS TIMI-46 study was a double-blind, phase II dose escalation study comparing rivaroxaban dosages of 5 mg, 10 mg, 15 mg and 20 mg to placebo in patients with acute coronary syndromes. The primary safety endpoint was clinically significant bleeding [TIMI major, TIMI minor or requiring medical attention]. No significant differences were seen in the incidence of bleeding between rivaroxaban and placebo [121].

The Atlas ACS2 TIMI-51 study compared rivaroxaban 2.5 mg and 5 mg bid to placebo. Rivaroxaban increased the rates of major bleeding not related to coronary-artery bypass grafting: 2.1% vs 0.6%, $p < 0.001$ and intracranial hemorrhage [0.6% vs 0.2%, $p = 0.009$]. No significant differences were seen on other bleeding endpoints. The twice daily 2,5 mg dose resulted in fewer fatal bleeding than the 5 mg bid dosage: 0.1% vs 0.4%, $p = 0.04$ [65].

The Gemini ACS-1 study compared rivaroxaban [2.5 mg bid] to aspirin 100 mg qd in patients with ACS. All patients received background therapy with P2Y12 inhibitors [clopidogrel or ticagrelor]. Treatment was continued for one year. The primary endpoint was TIMI clinically significant bleeding. No significant differences were noted on any bleeding endpoint [C MI 66].

Meta-analyses and registry studies

An prespecified pooled analysis of the Einstein DVT and Einstein PE studies showed a lower incidence of bleeding for rivaroxaban compared to enoxaparin, followed by warfarin. The HR for bleeding in the first weeks of the study was 0.43 [95% CI 0.23 - 0.80] and 0.60 [95% CI 0.37 - 1.00] for bleeding later than 3 weeks after the start of the study [142]. Bleeding with rivaroxaban occurred less frequently and had a milder presentation than the comparator [154].

Non randomized studies

A propensity weighted nationwide cohort study from the UK showed a lower annual risk of death for apixaban [5.2%] and dabigatran [2.7%] compared to warfarin [8.5%], but the difference between rivaroxaban [7.7%] and warfarin was not statistically significant in over 60,000 patients with atrial fibrillation [106].

Reversal of bleeding

Recently a specific antidote for bleeding caused by dabigatran became available on the market: idarucizumab. Specific antidotes for the other DOACs are in development [156-158]. Recently a specific antidote for serious bleeding for apixaban and rivaroxaban became available in Europe: Andexanet alfa. This is however an extremely expensive antidote.

A German registry study showed that treatment of rivaroxaban [over 1,000 bleeding events] induced bleeding was simple and outcomes were at least as favourable as for vitamin K antagonists [159].

Myocardial infarction

Several studies have indicated an increased incidence of myocardial infarction in patients treated with dabigatran. An analysis of the Rely study showed a non significantly higher incidence of myocardial infarction with dabigatran 110 mg or 150 mg bid compared to warfarin [HR 1.29, 95% CI 0.96 - 1.75] [160].

A meta-analysis of seven randomised non-inferiority studies, including over 30,000 patients showed a significantly higher risk of myocardial infarction or acute coronary syndromes in patients treated with dabigatran than in the control groups [enoxaparin, warfarin or placebo]: 1.19% vs 0.79%, OR 1.33, 95% CI 1.03 - 1.71, $p = 0.03$]. Overall mortality was however lower in the dabigatran groups: OR 0.89, 95% CI 0.80 - 0.99, $p = 0.04$] [161].

Another meta-analysis confirmed a higher incidence of myocardial infarction for dabigatran in 14 randomised controlled studies: OR 1.34 [95% CI 1.08 - 1.65, $p = 0.007$] for dabigatran versus comparators enoxaparin, warfarin or placebo. Again all cause mortality was lower for dabigatran OR 0.89, 95% CI 0.80 - 1.00, p

= 0.041]. A higher risk of myocardial infarction was also seen compared to warfarin OR 1.41 [95% CI 1.11 - 1.80, p = 0.005] [138]. A more recent meta-analyses of randomized studies and registry data showed no increased risk of myocardial infarction of dabigatran versus comparators in data from over 580,000 patients [162], although it remains questionable whether data from clinical trials and real world data can be mixed as such.

A propensity matched cohort study showed a lower incidence of myocardial infarction in US patients treated with dabigatran compared to warfarin: HR 0.65, 95% CI 0.45 - 0.95] [163].

Liver toxicity

The effects of DOACs on liver enzymes are summarized in the Tables. No significant differences were seen regarding ALT increases or bilirubin increases compared to enoxaparin, placebo or warfarin. Liver toxicity has however been documented for all DOACs in pharmacovigilance data [164,165].

Other side-effects

The tolerability profile of dabigatran was very similar to warfarin in a direct comparative study in patients with atrial fibrillation. Dyspepsia, dizziness, dyspnoea, peripheral oedema, fatigue, cough, chest pain and back pain were observed in 5 - 12% of patients treated with either medicine [46].

Dabigatran resulted in a higher incidence of dyspepsia compared to warfarin in the Re-Ly study: 11.3% vs 5.8% [46].

Rivaroxaban and warfarin also showed a very similar tolerability profile in the Rocket AF study in patients with atrial fibrillation [50].

Rivaroxaban has been associated with severe skin reactions [Stevens Johnson syndrome]. It is unclear whether its incidence is higher than that of other DOACs [5].

Discussion on safety

Two meta-analyses showed a lower incidence of bleeding with apixaban compared to the other medicines.

Apixaban has the lowest incidence of major bleeding, which is best documented in atrial fibrillation.

Apixaban is awarded 80%.

Dabigatran also shows a higher incidence of GI side-effects compared to other DOACs. An advantage of dabigatran is the availability of a reasonably priced antidote.

This results in a 10% lower score for dabigatran compared to apixaban: 70%.

Rivaroxaban has a relatively high incidence of major bleeding in an analysis of studies in atrial fibrillation. The study population of the Rocket A study had the highest baseline CHADS/ CHADS-VASc score and thus the highest baseline HAS-BLED score of all NOAC AF-registration trial populations. High CHADS/CHADS-VASc scores drive embolic events and also high HAS-BLED scores drive bleeding.

Rivaroxaban is awarded 70% as well.

Relatively limited data are available for edoxaban. Edoxaban also scores 70%.

The scores for side-effects are as follows.

Apixaban	80%
Dabigatran	70%
Edoxaban	70%
Rivaroxaban	70%

Dosage frequency

Scoring

Criterion	Api	Dab	Edo	Riv
Treatment and prevention of deep venous thrombosis	10 mg bid for 7 days followed by 5 mg bid for 6 months followed by 2.5 mg bid for long time prophylaxis	150 mg bid 110 mg bid in the elderly	60 mg qd	15 mg bid for 3 weeks Followed by 20 mg qd
Prevention of stroke during atrial fibrillation	5 mg bid	150 mg bid 110 mg bid in low risk patients or in patients at high risk of bleeding	60 mg qd	20 mg qd followed by 10 mg qd

Criterion	Weighting	Api	Dab	Edo	Riv
Treatment and prevention of venous thromboembolism	50%	40%	40%	100%	90%
Prevention of stroke during atrial fibrillation	50%	40%	40%	100%	100%
Score	100%	80%	80%	100%	95%

Adherence to DOACs is not optimal [166]. Medication adherence was better for rivaroxaban than for dabigatran [167] or apixaban [168] in patients with atrial fibrillation. A Danish study also showed a better compliance for rivaroxaban compared to dabigatran and apixaban [169].

Documentation

The documentation of DOACs is summarised below.

Prevention of DVT and pulmonary embolism after orthopaedic surgery.

	Studies	Patients	Years	Patient days	Ref
Apixaban	4	>1000	7	>100 million	[26-29]
Dabigatran	6	>1000	>10	>100 million	[30-34,68]
Edoxaban	4	>1000	3	>100 million	[35-38]
Rivaroxaban	5	>1000	>10	>100 million	[39-43]

Prevention of stroke during atrial fibrillation.

	Studies	Patients	Years	Patient days	Ref
Apixaban	2	>1000	7	>100 million	[44,45]
Dabigatran	3	>1000	>10	>100 million	[46-48]
Edoxaban	2	>1000	3	>100 million	[49,94]
Rivaroxaban	2	>1000	9	>100 million	[50,51]

Treatment and prevention of deep venous thrombosis.

	Studies	Patients	Years	Patient days	Ref
Apixaban	4	>1000	7	>100 million	[52-54,114]
Dabigatran	4	>1000	>10	>100 million	[55-57]
Edoxaban	2	>1000	3	>100 million	[58,59]
Rivaroxaban	5	>1000	>10	>100 million	[60-63]

Acute coronary syndromes.

	Studies	Patients	Years	Patient days	Ref
Apixaban	2	>1000	7	>100 million	[64,119]
Dabigatran	1	743	>10	>100 million	[120]
Edoxaban	0	>1000	3	>100 million	
Rivaroxaban	2	>1000	>10	>100 million	[65,66]

Overall score for documentation.

	Studies	Patients	Years	Patient days	Score
Apixaban	12	>1000	7	>100 million	83%
Dabigatran	14	>1000	>10	>100 million	93%
Edoxaban	8	>1000	3	>100 million	68%
Rivaroxaban	14	>1000	>10	>100 million	93%

SOJA score.

	Weight	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Approved indications	40	28	28	20	40
Number of formulations	20	16	16	16	16
Variability of the AUC	40	30	19	30	30
Drug Interactions	60	27	27	30	27
Clinical efficacy	400	280	280	252	268
Side effects	220	176	154	154	154
Dosage frequency	120	96	96	120	114
Documentation	100	83	93	68	93
Total	1000	736	713	690	742

Discussion

Applied methodology

Drug selection was performed by means of the SOJA method, which is a well-established rational and transparent way of selecting medicines [or in this case inhalation devices] within a therapeutic class from a formulary perspective. The evaluation of the criteria in the SOJA method is highly standardized in order to promote unbiased judgement of drugs from various pharmacological

categories based on clinically relevant criteria. Of course, there is potential debate on the correct scoring system with respect to each criterion and individual decisions are highly subjective. This is the case with any method used to quantify properties of drugs. The SOJA method is intended as a tool for rational drug decision making, enabling clinicians and pharmacists to include all relevant aspects of a certain group of drugs, thereby preventing formulary decisions being based on only one or two criteria. Besides this, possible "hidden criteria" [such as personal financial interest] are excluded from the decision making process. The outcome of this study should be seen as the basis for discussions within formulary committees and not as the absolute truth.

Outcome

Relatively limited differences in score are seen between the DOACs [about 10% between the highest and lowest score]. Of course, the present scoring is based on the weights assigned by the authors. The essence of the SOJA method is that users of the method may assign their own relative weight to each selection criterion. This interactive program is available on the internet: www.tablet.sojaonline.nl. Other relative weights will of course affect the relative scores for the medicines.

The present score is an overall score for all approved indications. It could be argumented that a different selection should be made for each indication, because of differences in documented efficacy between DOACs for the various applications.

It should be stressed that one single DOAC will not be suitable for all patients. All DOACs have advantages and disadvantages.

The relatively high score for rivaroxaban is caused by a favourable score for the number of approved indications, dosage frequency and documentation.

Apixaban shows the highest score for safety. Dabigatran and rivaroxaban show the highest scores for documentation, whereas edoxaban is given once daily for all approved indications and shows few relevant drug interactions.

Dabigatran does not score well for variability of AUC [a criterion that is usually not very relevant for most physicians]. The documentation of edoxaban [as well as the number of approved indications] is more limited than that of the other DOACs. The incidence of side-effects of rivaroxaban and dabigatran appears to slightly higher than that of apixaban, although direct comparative studies are lacking.

Strength and limitations of the methodology

Selection criteria

Of course, other selection criteria could be applied as well. We did not include Contra-indications and Warnings and Precautions in the matrix. There were no relevant differences between the DOACs in this respect. Differences in the incidence of bleeding or drug interactions were accounted for in the current selection criteria.

Variability of the AUC is a standard criterion for SOJA. Its relevance for DOACs is unclear. That is why a low weight was assigned tot his criterion. When one considers this criterion to be completely irrelevant,a zero weight can be given to this criterion in the interactive program.

Clinical efficacy and safety are the most important selection criteria for all groups of medicines. Unfortunately these criteria are difficult to score for DOACs because of the lack of direct comparative studies and differences in patient populations, study design and applied endpoints. Meta-analyses and registry data may be of value in the judgement of efficacy and safety. All data sources have specific strenghts and weaknesses.

Acquisition cost was not included as a selection criterion to make the score internationally applicable. The present matrix can be used as a pre selection tool of the most suitable DOACs from a quality point of view. Because prices may different institutions and in different healthcare systems, individual procurement procedures should lead to a selection of the best options.

The acquisition cost of the DOACs included in this analysis is relatively high, especially compared to vitamin K antagonists, such as acenocoumarol and warfarin. INR monitoring costs, as well as patients' discomfort of these determinations must be taken into account regarding vitamin K antagonists. On the other hand, detemining INR values also contributes to good compliance in users of vitamin K antagonists, whereas such a check is lacking for DOACs. This should be taken into consideration before preferring DOACs over vitamin K antagonists.

Of course, other selection criteria could be applied as well. There are some differences in the suitability of DOACs to be included in Baxter rolls or whether or not specific DOACs can be swallowed irrespective of food intake. We did not include these selection criteria.

Judgement of properties of DOACs

Double-blind comparative studies are the most important source of information of the determination of clinical efficacy and tolerability. These studies usually have limitations in the selection of patients and a limited duration of the study. No direct comparative studies are available, which makes it possible to reliably evaluate the DOACs on the most important selection criteria, clinical efficacy and safety. This score should therefore be considered as preliminary. On the other hand, it seems quite unlikely that large scale direct comparative studies with more than 2 DOACs will be published in the near future, so we will have to deal with indirect comparisons.

Because of the lack of direct comparative studies, the results of meta-analyses and registries were also taken into consideration. These kind of studies also have limitations. The quality of meta-analyses is as good as the quality of the studies which are included. Patient populations may be quite different for patients treated with the individual DOACs in registry studies.

Formulary choices versus decisions in treatment of individual patients

It should be stated that formulary selection is a different process than decision making in individual patients. Selection criteria like variability in AUC, number of approved indications and documentation are typical criteria that may be relevant from a formulary perspective, but not for the selection of a DOAC in individual patients.

The above described differences in properties of DOACs may lead to drug and dosage choices based on the specific situation of the patient, such as comedication [risk of interactions], bleeding risk, personal preference for once daily or twice daily dosing, renal or hepatic function and individual tolerability.

Conclusion

We found limited differences in the scores of the available DOACs. The scores for the top 3 DOACs [rivaroxaban, apixaban and dabigatran] were less than 5% different from each other, using the relative weights applied by the authors. A different follow-order may result when other weightings are given to the selection criteria.

All these DOACs are suitable for formulary inclusion, followed by a selection oft he most suitable for a DOAC in individual patients, based on patient characteristics.