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RIJKSINSTITUUT VOOR ZIEKTE- EN INVALIDITEITSVERZEKERING
DIENST GENEESKUNDIGE VERZORGING
Comité voor de evalutie van de medische praktijk inzake geneesmiddelen

The rational use of direct oral anticoagulants (DOAC) or vitamin K antagonists (VKA) in atrial fibrillation (prevention of thromboembolism) and in venous thromboembolism (treatment and secondary prevention)

Systematic literature review: full report

Consensus conference
November th 2017
Auditorium Lippens (Royal Library)
Brussels

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Abbreviations

AE	adverse events
AF	atrial fibrillation
ALT	alanine aminotransferase
AR	absolute risk
ARD	absolute risk difference
ARR	absolute risk reduction
ASA	acetyl salicylic acid
AST	aspartate aminotransferase
AT	serum alanine aminotransferase and aspartate aminotransferase
BID	twice daily
CES	compression elastic stocking
CI	confidence interval
CO	cross-over
CrCl	creatinine clearance
CRNM	clinically relevant non major
DB	double blind
DBP	diastolic blood pressure
DTI	direct thrombin inhibitor
DOAC	direct oral anticoagulant
DUS	duplex ultrasound
DVT	deep vein thrombosis
eCrCl	estimated creatinine clearance
eGFR	estimated glomerular filtration rate
FXaI	factor Xa inhibitor
GCS	graduated compression stockings
GE	gastroenteric
HIT	heparin induced thrombocytopenia
HR	hazard ratio
INR	international normalized ratio
IPC	intermittent pneumatic compression
ISTH	International Society on Thrombosis and Haemostasis
ITT	intention to treat analysis
LMWH	low molecular weight heparin
MA	meta-analysis
MI	myocardial infarct
mITT	modified intention to treat
n	number of patients
N	number of studies
NA	not applicable
NOAC	new oral anticoagulant
NR	not reported
NS	not statistically significant
NT	no statistical test
NVAF	non valvular atrial fibrillation

OA	oral anticoagulation
OL	open label
OR	odds ratio
PA	pulmonary angiogram
PE	pulmonary embolism
PG	parallel group
PO	primary outcome
PPA	per protocol analysis
PTS	post-thrombotic syndrome
RCT	randomized controlled trial
RR	relative risk
SB	single blind
SBP	systolic blood pressure
SE	systemic embolism
SS	statistically significant
THR	total hip replacement
TKR	total knee replacement
TTR	time in therapeutic range
UFH	unfractioned heparin
ULN	upper limit of the normal range
VKA	vitamin K antagonists
VTE	venous thromboembolism

1 Methodology

1.1 Introduction

This systematic literature review was conducted in preparation of the consensus conference "**The rational use of oral anticoagulants (direct (DOAC) or vitamin K antagonists (VKA)) in atrial fibrillation (prevention of thromboembolism) and in venous thromboembolism (treatment and secondary prevention)",** which will take place on the 30th of November 2017.

1.2 Questions to the jury

The questions to the jury, as they were phrased by the organising committee of the RIZIV/INAMI are:

Question – Vraag 1
Comment suivre l'observance/adhérence à un traitement anticoagulant oral et comment l'améliorer ?
Hoe moet de therapietrouw/adherentie voor een behandeling met orale anticoagulantia worden gevolgd en hoe kan die worden verbeterd?

Question – Vraag 2
En cas de FA avec indication de prise d'une anticoagulation, quel est le choix préférentiel validé entre un AVK et un AOD (efficacité/sécurité/surveillance/observance/efficience) ?
In geval van VKF met indicatie voor de inname van een anticoagulans, welke gevalideerde keuze geniet dan de voorkeur: een VKA of een DOAC (werkzaamheid/veiligheid/toezicht/therapietrouw/doeltreffendheid)?

Question – Vraag 3
En cas de FA avec indication de prise d'une anticoagulation, quels sont les arguments pour un passage des AVK à un AOD (ou l'inverse) ?
In geval van VKF met indicatie voor de inname van een anticoagulans, welke zijn de argumenten voor een overschakeling van VKA's op een DOAC (of omgekeerd)?

Question – Vraag 4
En cas de FA avec indication de prise d'une anticoagulation, en cas de choix d'un AOD, quels sont les arguments pour en préférer l'un plutôt que l'autre ?
In geval van VKF met indicatie voor de inname van een anticoagulans, indien er voor een DOAC wordt geopteerd, welke zijn de argumenten om het ene DOAC boven het andere te verkiezen?

Question – Vraag 5
En cas de FA avec indication de prise d'une anticoagulation, dans quelles circonstances faut-il suspendre un traitement anticoagulant et, si oui, faut-il assurer une substitution (temporaire) ?
In geval van VKF met indicatie voor de inname van een anticoagulans, in welke omstandigheden moet een anticoagulantiabehandeling worden opgeschort, en zo ja, moet er in een (tijdelijke) substitutie worden voorzien?

Question – Vraag 6
En cas de thromboembolie veineuse (avec ou sans embolie pulmonaire), quel est le traitement anticoagulant de premier choix à initier (efficacité/sécurité/surveillance/observance) ?
In geval van veneuze trombo-embolie (met of zonder longembolie), welke anticoagulantiabehandeling moet bij voorkeur worden opgestart (werkzaamheid/veiligheid/toezicht/therapietrouw)?

Question – Vraag 7
En cas de thromboembolie veineuse (avec ou sans embolie pulmonaire) avec indication d'un traitement anticoagulant, quelle doit être la durée de ce traitement (en fonction de quels critères) ?
In geval van veneuze trombo-embolie (met of zonder longembolie) met indicatie voor de behandeling met anticoagulantia, hoelang moet die behandeling duren (op basis van welke criteria)?

Question – Vraag 8
En cas d'embolie pulmonaire, quel est le traitement anticoagulant de premier choix (efficacité/sécurité/surveillance/observance) ?
In geval van longembolie, welke anticoagulantiabehandeling geniet de voorkeur (werkzaamheid/veiligheid/toezicht/therapietrouw)?

Question – Vraag 9
En cas d'embolie pulmonaire avec indication d'un traitement anticoagulant, quelle doit être la durée de ce traitement (en fonction de quels critères) ?
In geval van longembolie met indicatie voor een anticoagulantiabehandeling, hoelang moet die behandeling duren (op basis van welke criteria)?

Question – Vraag 10
En cas de TEV avec indication de prise d'une anticoagulation, quels sont les arguments pour un passage des AVK à un AOD (ou l'inverse) ?
In geval van VTE met indicatie voor de inname van een anticoagulans, welke zijn de argumenten voor een overschakeling van VKA's op een DOAC (of omgekeerd)?

Question – Vraag 11
En cas de TEV avec indication de prise d'une anticoagulation, dans quelles circonstances faut-il suspendre un traitement anticoagulant et, si oui, faut-il assurer une substitution (temporaire) ?
In geval van VTE met indicatie voor de inname van een anticoagulans, in welke omstandigheden moet een anticoagulantiabehandeling worden opgeschort, en zo ja, moet er in een (tijdelijke) substitutie worden voorzien?

For the members of the jury: The answers to these questions can be found in the following chapters of this document:

Question	**Chapters**
question 1 Adherence	Guidelines - Summaries chapter 3.2.1 and 3.3.1 - Details (Appendices Full Document – English) chapters 10.3.1 Studies - Summaries chapter 8 - Details (Appendices Full Document – English) chapters 20 and 21 and 22
question 2 AF - VKA or DOAC	Guidelines - Summaries chapter 3.2.2 - Details (Appendices Full Document – English) chapter 10.2.2 Studies - Summaries chapter 4 and 9 - Details (Appendices Full Document – English) chapter 11 and 12 + information from question 1
question 3 AF - Switching	Guidelines - Summaries 3.2.3 and 3.3.4 - Details (Appendices Full Document – English) 10.2.3 and 10.3.4 Studies - Summaries chapter 7 - Details (Appendices Full Document – English) chapter 19
question 4 DOAC vs DOAC	Guidelines - Summaries chapter 3.2.4 - Details (Appendices Full Document – English) chapter 10.2.4 Studies - Summaries chapter 4.3 - Details (Appendices Full Document – English) chapter 13
question 5 Bridging	Guidelines - Summaries chapter 3.4 - Details (Appendices Full Document – English) chapter 10.4 Studies - Summaries chapter 6 - Details (Appendices Full Document – English) chapter 18
question 6 and 8 VTE – VKA or DOAC	Guidelines - Summaries chapter 3.3.2 - Details (Appendices Full Document – English) chapter 10.3.2 Studies Summaries chapter 5 and 9 Details (Appendices Full Document – English) chapter 14 and 15 and 16 + information from question 1

question 7 and 9 VTE - duration	Guidelines - Summaries chapter 3.3.3 - Details (Appendices Full Document – English) chapter 10.3.3 Studies - Summaries chapter 5.9 - Details (Appendices Full Document – English) chapter 17
question 10 VTE - switching	Guidelines - Summaries 3.3.4 - Details (Appendices Full Document – English) chapter 10.3.4 Studies - Summaries chapter 7 - Details (Appendices Full Document – English) chapter 19
question 11 VTE - bridging	Guidelines - Summaries chapter 3.4 - Details (Appendices Full Document – English) chapter 10.4 Studies - Summaries chapter 6 - Details (Appendices Full Document – English) chapter 18

Table 1

1.3 Research task of the literature group

The organising committee has specified the research task for the literature review as follows:

1.3.1 Populations

The following populations are to be evaluated:

- Patients with atrial fibrillation (AF) that require anticoagulation therapy
- Patients who have experienced a venous thromboembolism (VTE), i.e. deep vein thrombosis (DVT) or pulmonary embolism (PE)

Special attention is to be given to patients with chronic kidney disease and elderly patients
Children and pregnant women will be excluded.

1.3.2 Interventions

The following anticoagulants are to be studied:

DOAC	VKA	LMWH
Apixaban Dabigatran Edoxaban Rivaroxaban	Acenocoumarol Fenprocoumon Warfarin	Dalteparin Enoxaparin Nadroparin Tinzaparin

Table 2

1.3.3 Endpoints

The following endpoints are to be reported:

Atrial fibrillation	Efficacy
	All-cause mortality[1], cardiovascular mortality Stroke, TIA, systemic embolism AMI, other relevant cardiac endpoints Hemorrhagic stroke
	Safety
	Major bleeding Clinically relevant bleeding Intracranial bleeding Gastro-intestinal bleeding Other relevant adverse events
	Adherence
	Number of doses taken TTR Other relevant adherence endpoints

Table 3

Venous thromboembolism	Efficacy
	All cause mortality Deep-vein thrombosis (DVT) symptomatic / non symptomatic Pulmonary embolism (PE) symptomatic/non-symptomatic
	Safety

[1] The endpoints that are underlined should preferably be reported in the summary document.

	Major bleeding Clinically relevant bleeding Intracranial bleeding Gastro-intestinal bleeding Post-thrombotic syndrome (PTS) Other relevant adverse events
	Adherence
	TTR Number of doses taken Premature discontinuation of study drug

Table 4

1.3.4 Specific research questions

The organising committee has asked that the literature review focuses on the following research questions.

1.3.4.1 Atrial fibrillation

DOAC versus VKA

- Information from guidelines, MAs, SRs and RCTs

DOAC versus DOAC

- Information from guidelines, MAs, SRs, RCTs and cohort studies[2]

The organizing committee is mainly interested in the information on the individual DOACs. For methodological reasons, meta-analyses that pool different DOACs are considered less important for this report.

1.3.4.2 Venous thromboembolism (DVT and PE)

DOAC versus VKA

DOAC versus LMWH

VKA versus LMWH

- Information from guidelines, MAs, SRs and RCTs

DOAC versus DOAC

- Information from guidelines, MAs, SRs, RCTs and cohort studies[2]

Comparisons of different duration of OAC

- Information from guidelines, MAs, SRs and RCTs

The organizing committee is mainly interested in the information on the individual DOACs. For methodological reasons, meta-analyses that pool different DOACs are considered less important for this report.

1.3.4.3 Adherence

How to follow-up and check adherence to OAC

- Information from guidelines

How to improve adherence to OAC:

[2] Observational studies that compare DOAC versus VKA will not be included. The physician's decision whether to give a specific patient either a DOAC or a VKA constitutes a considerable bias, making it very difficult to draw solid conclusions based on these data.

intervention versus usual care
intervention 1 versus intervention 2

- Information from guidelines and meta-analyses of RCTs

Other information on adherence to be reported

- **How many patients have an acceptable TTR or acceptable adherence to OAC in real life?**
  - Information from KCE-report, guidelines, cohort studies (if relevant for the Belgian population, i.e. European studies)
- **Does a low maintenance dose of OAC affect clinical outcomes?**
  - Information from KCE report
- **Does low adherence to OAC affect clinical outcomes? Low versus high adherence**
  - Information from KCE report, guidelines, MA, SR, RCTs, cohort studies

1.3.4.4 Switching from DOAC to VKA or from VKA to DOAC

Reasons to switch

- Information from guidelines

How to switch

- Information from guidelines, MAs, SRs and RCTs

1.3.4.5 Interrupting oral anticoagulation and bridging

What surgical procedures require temporary interruption of oral anticoagulants?

- Information from Folia Pharmacotherapeutica April 2016(1)

Substituting (bridging) versus no anticoagulation during surgical procedures

- Information from Folia Pharmacotherapeutica April 2016(1) and more recent MAs, SRs and RCTs

1.3.5 Study types

We will look at meta-analyses, systematic reviews, RCTs and observational (cohort) studies.
To be included in our review, the selected studies need to meet certain criteria.

Meta-analyses and systematic reviews

- Research question matches research question for this literature review
- Systematic search in multiple databases
- Systematic reporting of results
- Inclusion of randomised controlled trials (or observational studies for certain research questions)
- Reporting of clinically relevant outcomes (that match our selected outcomes)
- Only direct comparisons (no network meta-analyses)

RCT's

- Blinded studies are preferred, but we will not exclude unblinded trials
- Duration
  - For atrial fibrillation: a minimum duration of 6 months
  - For venous thromboembolism: any duration
- Minimum number of participants: 40 per study-arm. For studies with multiple treatment arms, we will look at the number of participants in comparisons relevant to our search.
- Phase III trials (no phase II trials)

- Post hoc (subgroup) analyses are excluded, except for the research questions about adherence, elderly patients and patients with renal impairment.

Observational (cohort) studies

- Prospective or retrospective **cohort** studies
- Only new users/naïve users of anticoagulation
- Duration at least 6 months
- Minimum number of participants: 1000

Other sources for safety and dosing

- Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI), Folia Pharmacotherapeutica, Meyler's side effects of drugs (fifteenth edition)
- The SPC (Summary of Product Characteristics) is consulted if additional information is necessary

Some publications will be excluded for practical reasons:

- Publications unavailable in Belgian libraries
- Publications in languages other than Dutch, French, German and English
- Unpublished studies

1.3.6 Guidelines

Guidelines were selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation and certain quality criteria:

- Publication date: only guidelines from 2012 onwards are to be selected.
- Quality assessment: only guidelines that report levels of evidence/recommendation are to be selected.
- Systematic review: the guideline needs to be based on a good systematic search and review of the literature.

In order to make an assessment on the rigour of development of the guidelines, guidelines will be scored according to the Agree II score, for the domain "Rigour of development". More information can be found on http://www.agreetrust.org/. [1]

This table gives an overview of the items assessed in this domain according to the Agree II score.[1]

No.	**Description of the item**
7	Systematic methods were used to search for evidence
8	The criteria for selecting the evidence are clearly described
9	The strengths and limitations of the body of evidence are clearly described
10	The methods for formulating the recommendations are clearly described
11	Health benefits, side effects, and risks have been considered in formulating the recommendations.
12	There is an explicit link between the recommendations and the supporting evidence.
13	The guideline has been externally reviewed by experts prior to its publication
14	A procedure for updating the guideline is provided

Table 5: Items assessed by the domain "Rigour of development" in AgreeII score.

Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. The domain score

“Rigour of development” can be used to assess the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them, though be careful with the interpretation because this scoring is also subjective and the resulting scores can thus be disputable.

In the section about the guidelines, the Domain scores as assessed by the literature group, are given for each guideline.

The literature group will also report whether the guideline was developed together with other stakeholders (other healthcare professionals: pharmacists, nurses,… or patient representatives) and whether these guidelines are also targeting these groups.

Similarities and discrepancies between guidelines are to be reported.

1.4 Search strategy

1.4.1 Principles of systematic search

Relevant RCTs, meta-analyses and systematic reviews were searched in a stepwise approach.

- As a start we have searched for large systematic reviews from reliable EBM-producers (NICE, AHRQ, the Cochrane library, TRIPP database) that answer some or all of our research questions. One or more systematic reviews were selected as our basic source. From these sources, all references of relevant publications were screened manually.
- In a second step, we conducted a systematic search for randomised controlled trials (RCTs), meta-analyses, systematic reviews (and sometimes observational studies) that were published after the search date of our selected systematic reviews.

The following electronic databases have been searched

- Medline (PubMed)
- Cochrane Library (CDSR)

Guidelines were searched through the link "evidence-based guidelines" on the website of vzw Farmaka asbl (www.farmaka.be) and on the website of CEBAM (www.cebam.be). These contain links to the national and most frequently consulted international guidelines, as well as links to 'guideline search engines', like National Guideline Clearinghouse and G-I-N.

1.4.2 Source documents

The following systematic reviews were selected as source documents and starting points to find relevant publications:

For atrial fibrillation – DOAC vs VKA

Van Brabandt H, San Miguel L, Fairon N, Vaes B, Henrard S, Boshnakova A, et al. Anticoagulants in non-valvular atrial fibrillation. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE), 2017 01/2017. Report No.: D/2016/10.273/101.

For venous thromboembolism – DOAC vs VKA

Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD010956. DOI: 10.1002/14651858.CD010956.pub2.

Robertson L, Kesteven P,McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. Cochrane Database of Systematic Reviews 2015, Issue 12. Art.No.: CD010957. DOI: 10.1002/14651858.CD010957.pub2.

For venous thromboembolism – VKA vs LMWH

Castellucci LA, Cameron C, Le Gal G, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: A systematic review and meta-analysis. JAMA. 2014;312(11):1122-35.

For venous thromboembolism – duration of treatment

Middeldorp S, PrinsMH, Hutten BA. Duration of treatmentwith vitamin K antagonists in symptomatic venous thromboembolism. Cochrane Database of Systematic Reviews 2014, Issue 8. Art. No.: CD001367. DOI: 10.1002/14651858.CD001367.pub3.

For adherence

Van Brabandt H, San Miguel L, Fairon N, Vaes B, Henrard S, Boshnakova A, et al. Anticoagulants in non-valvular atrial fibrillation. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE), 2017 01/2017. Report No.: D/2016/10.273/101. *No other source document found.*

For switching of treatment

No source document found.

For interrupting OAC and bridging

BCFI. Substitutietherapie bij perioperatief stoppen van orale anticoagulantia. Folia Pharmacotherapeutica 2016;43. 33-34.

For all these research questions, a search string was developed to search Medline via Pubmed from the research date of the selected source document up until 1st July 2017. If no source document could be found, a search of Medline without a starting date was performed.

1.4.3 Search strategy details

The full search strategies can be found in appendix 1.

1.5 Selection procedure

Selection of relevant references was conducted independently by two researchers. Differences of opinion were resolved through discussion. A first selection of references was done based on title and abstract. When title and abstract were insufficient to reach a decision, the full article was read to decide on inclusion or exclusion.

In– and exclusion criteria of the different types of studies are found in chapter 1.3 with relevant populations, interventions, endpoints and study criteria.
The list of articles excluded after reading of the full text can be found in the Appendix.

1.6 Assessing the quality of available evidence

To evaluate the quality of the available evidence, the GRADE system was used. In other systems that use 'levels of evidence', a meta-analysis is often regarded as the highest level of evidence. In the GRADE system, however, only the quality of the original studies is assessed. Whether the results of original studies were pooled in a meta-analysis is of no influence to the quality of the evidence.
The GRADE-system is outcome-centric. This means that quality of evidence is assessed for each endpoint, across studies.

The GRADE system assesses the following items:

Study design		+ 4	RCT
		+ 2	Observational
		+ 1	Expert opinion
Study quality		- 1	Serious limitation to study quality
		- 2	Very serious limitation to study quality
Consistency		- 1	Important inconsistency
Directness		- 1	Some uncertainty about directness
		- 2	Major uncertainty about directness
Imprecision		- 1	Imprecise or sparse data
Publication bias		- 1	High probability of publication bias
For observational studies	Evidence of association	+ 1	Strong evidence of association (RR of >2 or <0.5)
		+ 2	Very strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+ 1	Evidence of a dose response gradient (+1)
	Confounders	+ 1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

Table 6. Items assessed by the GRADE system

In this literature review the criteria 'publication bias' has not been assessed.

In assessing the different criteria, we have applied the following rules:

Study design

In this literature review RCT's and observational studies are included. RCTs start out as high quality of evidence (4 points), observational studies start out as low quality of evidence (2 points). Points can be deducted for items that are assessed as having a high risk of bias.

Study quality

To assess the methodological quality of RCT's, we considered the following criteria:

- **Randomization**: If the method of generating the randomization sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?
- **Allocation concealment:** If the method of allocation was described, was it adequately concealed (central allocation, …) or inadequate (open schedule, unsealed envelopes, etc.)?
- **Blinding**: Who was blinded? Participants/personnel/assessors. If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection with no double dummy)?
- **Missing outcome data:** Follow-up, description of exclusions and drop-outs, ITT
- **Selective outcome reporting**

If a meta-analysis or a systematic review is used, quality of included studies was assessed. It is not the quality of the meta-analysis or systematic review that is considered in GRADE assessment, but only the quality of RCTs that were included in the meta-analysis/systematic review.

Application in GRADE:
Points were deducted if one of the above criteria was considered to generate a high risk of bias for a specific endpoint.
For example:

- Not blinding participants will not decrease validity of the results when considering the endpoint 'mortality', but will decrease validity when considering a subjective endpoint such as pain, so for the endpoint pain, one point will be deducted.
- A low follow-up when no ITT analysis is done, will increase risk of bias, so one point will be deducted in this case.

Consistency

Good "consistency" means that several studies have a comparable or consistent result. If only one study is available, consistency cannot be judged. This will be mentioned in the synthesis report as "NA" (not applicable).

Consistency is judged by the literature group and the reading committee based on the total of available studies, whilst taking into account

- Statistical significance
- Direction of the effect if no statistical significance is reached. E.g. if a statistically significant effect was reached in 3 studies and not reached in 2 others, but with a non-significant result in the same direction as the other studies, these results are considered consistent.

- Clinical relevance: if 3 studies find a non-significant result, whilst a 4th study does find a statistically significant result, that has no clinical relevance, these results are considered consistent.
- For meta-analyses: Statistical heterogeneity.

Directness

Directness addresses the extent in which we can generalise the data from a study to the real population (external validity). If the study population, the studied intervention and the control group or studied endpoint are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

A point can be deducted for imprecision if the 95%-confidence interval crosses both the point of appreciable harm AND the point of appreciable benefit (e.g. RR 95%CI ≤0.5 to ≥1.5).

Additional considerations for observational studies

For observational studies, when no points are deducted for risk of bias in one of the above categories, a point can be added if there is a large magnitude of effect (high odds ratio), if there is evidence of a dose-response gradient or (very rarely) when all plausible confounders or other biases increase our confidence in the estimated effect.

Application of GRADE when there are many studies for 1 endpoint:

Points are only deducted if the methodological problems have an important impact on the result. If 1 smaller study of poor quality confirms the results of 2 large good quality studies, no points are deducted.

More information on the GRADE Working Group website: http://www.gradeworkinggroup.org

1.7 Synopsis of the study results

The complete report contains per research question:

- (Comprehensive) summary of selected guidelines.
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system (English).
- Evidence tables (English) of systematic reviews or RCTs on which the answers to the study questions are based.

The synopsis report contains per research question:

- (Brief) summary of selected guidelines.
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system.

The conclusions have been discussed and adjusted through discussions between the authors of the literature search and the reading committee of the literature group.

2 Critical reflections of the reading committee and the literature group

2.1 Remarks on the guidelines

- Most guidelines base their conclusions on the same handful of DOAC trials (there is usually only 1 (or 2) major trial per DOAC).
- Adherence is mentioned as an issue with anticoagulant medication. However little attention is paid in the guidelines as to how a medical professional can help to improve a patient's adherence.
- Guidelines recommend switching when a patient's TTR is unsatisfactory. Of course, it is good practice to first investigate what could cause too high/low TTR (interactions, diet, poor adherence…).
- Some guidelines were written before DOAC antidotes were put on the market. Sometimes a DOAC is advised against due to there not being any antidote, which is no longer correct for dabigatran, that now has an antidote available on the market (for the others, an antidote has been developed but has not been released on the market).
- None of the guidelines take into account the possible interactions when considering warfarin over DOAC, or when making a choice between DOACs. They all have a different profile. For example, apixaban, dabigatran, edoxaban and rivaroxaban are metabolized by P-gp, warfarin by CYP2C9, apixaban and rivaroxaban by CYP3A4[3]... For the DOACs, not all interactions have been studied yet. Interactions with warfarin are 'detected' and adjusted for by measuring the INR and adapting the doses, but interactions with DOACs are not.
  Especially in the case of older patients or polymedication, possible interactions should be taken into account.
- For some guidelines, a lot of the authors have strong ties with the industry.

2.2 Risk of stroke vs risk of bleeding with OAC in atrial fibrillation

Before discussing the relative benefits and risks of DOAC compared to VKA, it is important to consider the risk/benefit ratio of treatment with OAC. The (decreased) risk of stroke when taking OAC must of course be weighed against the risk of bleeding.
In patients with a high risk of stroke (CHA2DS2-VASC>=2), guidelines will generally recommend OAC treatment, because the benefits are considered to be greater than the risks (when properly taking into account the patient's bleeding risk).
In patients with a lower risk of stroke (CHA2DS2-VASC=1), there is some debate. To clarify the competing risks, the term 'net clinical benefit' is sometimes used. Some authors define this as the net difference between the ischemic strokes that are prevented and the hemorrhagic strokes that are caused by OAC ((2), (3), (4)). When the risk of ischemic stroke without OAC is comparable to the risk of haemorrhagic stroke with OAC, there does not seem to be much reason to start anticoagulation. The KCE report on anticoagulants in non-valvular AF (2) argues that this may be the case in patients with CHA2DS-VASc=1.

[3] Information from BCFI/CBIP website. This is not a complete list. For more information on this subject, BCFI/CBIP, the SmPC and also EMA (EPAR – European Public Assessment Reports) will provide valuable information.

In the AF trials comparing DOAC to VKA, the primary endpoint of stroke/systemic embolism also includes haemorrhagic stroke. However, because of lack of a placebo arm (for ethical reasons), the rate of stroke (ischemic and haemorrhagic) without OAC in these populations is not known. In these trials, the term 'net clinical benefit' is often used to describe other composite endpoints, such as stroke/systemic embolism plus major bleeding (with or without mortality).

Apart from haemorrhagic stroke and any other intracranial bleeding, which are feared adverse events, the risk of other major bleeding events will also influence the risk/benefit balance of OAC treatment.

The reading committee also wants to point out that for a patient, a (fatal) bleeding event with OAC will quite likely be perceived differently than a (fatal) ischemic stroke. We assume that for a patient (and for a doctor), it is often easier to accept an event that could not be prevented than to accept an event that is (possibly) caused by the preventive treatment.

2.3 Risk of recurrent VTE vs risk of bleeding with OAC in VTE

In VTE, the same arguments can be made: the risk of a VTE without treatment must be weighed against the risk of bleeding with treatment.

2.4 Do trial data represent a real life situation?

2.4.1 Age

When we consider anticoagulant treatment in AF to be a life-long treatment, we need to know whether a certain OAC will be efficient in reducing stroke risk, without an excessive risk of bleeding, throughout a patient's life. This includes very old age, frailty due to old age, declining renal function, multimorbidity…

The mean age in the AF trials was 70-73y. The AF studies include a fair amount of patients >75y, but information is lacking on the higher age groups (number of patients >80 or >85 not reported or low numbers).

The mean age in the VTE trials was 55-57y. 7% to 14% of patients was >75y.

2.4.2 Renal function

The calculation of the creatinine clearance in the phase III trials was based on the Cockroft-Gault formula.

Patients with an estimated creatinine clearance <30ml/min (or <25ml/min for apixaban) were excluded from the trials. We have no information on the efficacy and safety of DOACs in these patients.

Renal function decreases with age. We need to establish how to properly deal with patients on DOACs throughout their ageing process and throughout the decline in renal function and what to do when they reach a creatinine clearance <30ml/min. VKA treatment is constantly monitored and adjusted to reach a therapeutic INR and thus also adjusts for declining renal function and altering of physiology with age. For DOACs, no monitoring of anticoagulation is done (But see also 1.5 Monitoring, for information on the monitoring of renal function).

2.4.3 Other risk factors/other specific populations

For this review, we were asked to take a closer look at 2 specific subgroups, i.e. older patients and patients with declining renal function.

There are other risk factors that predispose to bleeding and other specific populations that may or may not be properly represented in the trials. For some of these subgroups, like patients at risk of falls (e.g. edoxaban (5)), or patients with polypharmacy(e.g. rivaroxaban (6) or apixaban (7), some analyses have been published. These publications, although very interesting, were not included in our review.
In very specific circumstances, like patients in palliative care with a very short life expectancy, the choice on whether or not to anticoagulate and the choice of anticoagulant will probably be based more on ethical discussion and patient preference than evidence based arguments.

2.4.4 $CHADS_2$

In the AF trials with apixaban and dabigatran, 1/3 of patients had a CHADS2 score = 1. There is some debate whether these patients benefit from anticoagulant treatment (see 1.2: risk of stroke vs risk of bleeding).
In the current guidelines, CHA2DS2-VASC scores are mostly used, which makes it more difficult to compare a patient to the trial population.

2.4.5 VTE

Trials include either patients with acute DVT (excluding patients with PE), patients with acute PE (with or without DVT) or patients with acute VTE (DVT and/or PE).

DVT and PE are manifestations of the same disease process. There may however be a difference in risk of mortality or even in risk of recurrent VTE in patients with only DVT compared to patients presenting with PE, because DVT and PE represent a different degree of severity of the same disease process.

2.4.6 Risk of bleeding

The clinical trials did not admit patients with a high risk of bleeding to enter the study. It is not clear how this risk is defined. Patients with a high CHA2DS2-VASC score usually also have a high HASBLED score, so it is also not clear how such an exclusion criterion would have been applied.

The KCE report (2) discusses some factors that may have influenced the risk of bleeding (and consequently – the difference in bleeding risk between DOAC and VKA) in the pivotal AF trials.
- questions about data integrity in the RE-LY trial (dabigatran)
- use of aspirin in 30-40% of participants (which increases warfarin bleeding risk two-fold when combined)
- quality of INR control in the trials
- standards of care in participating countries/study centers
- deficient INR measuring device in the rivaroxaban trial (ROCKET AF)[4]

2.4.7 INR

The mean time in the therapeutic range (TTR) in the warfarin arm of the AF trials ranged from 55% (rivaroxaban) to 65% (edoxaban). In the VTE trials, mean TTR ranged from 57% (dabigatran- RE-COVER 2) to 64% (edoxaban).

[4] See also the final report of the EMA concerning this topic.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000944/WC500201726.pdf

2.4.8 Follow-up in the trials

Patients in a clinical trial generally receive a high-quality follow-up. If follow-up in real life is less rigorous, a higher rate of problems may occur. For example, poor adherence may go unnoticed for longer, adverse events may not be picked up in time…
Discontinuation rates in the AF trials were high (20-30%). It is unclear how this affects the study results.

2.5 Monitoring

VKA requires frequent INR control and dose adjustments, which may be perceived as a burden and is often used as an argument against VKA. DOACs do not require monitoring of anticoagulation (but **do** require **monitoring of renal function**, and regular follow-up visits are equally necessary, to check for adherence, adverse events, interactions...).
However, there is some evidence that monitoring of anticoagulation with DOACs is not only possible, but may also be beneficial in terms of reduced major bleeding ((2, 8, 9)). We need more evidence to determine whether monitoring of anticoagulation with DOACs may be a useful part of a standard follow-up, or may be helpful in certain clinical conditions such as detection of drug accumulation in (acute) renal/liver failure, planning the timing of urgent surgery, special patient characteristics such as obesity or malabsorption, guiding the physician in the administration of reversal agents…

2.6 Adherence and persistence

To estimate patient adherence and persistence to/with OAC, different parameters are used throughout the literature. Each of them shows us part of the picture, but each of them is also influenced by other factors, so they need to be interpreted with caution.

- **Discontinuation rates**. The percentage of patients that stops taking OAC. The reason for stopping is not always clear. It can be a patient's decision or doctor's decision, due to adverse events, due to switching to another OAC. The discontinuation rates in the AF trials are quite high for both DOACs and VKA. In observational studies, discontinuation is often defined by exceeding a certain time-frame of interruption of OAC (e.g. more than 2 or 3 months interruptions = discontinuation).

- **Percentage of days covered**, percentage of pills taken. Based on prescription data (in observational studies, % days covered by the prescription) or on pill counts (% of doses taken, in RCTs), this number gives us an idea of how accurately the patient takes his/her medication on a day-to-day basis. This number is difficult to estimate for VKA, because the dose of VKA will vary and data on dose are often not available.

- **TTR**. For VKA, the Time in the therapeutic range of the INR is influenced by many factors, including patient adherence. The TTR is often the only parameter that is reported in clinical trials that may give us information on 'adherence'. For VKA, a patient does not only need to adhere to the VKA treatment, but also to the monitoring regimen.

DOACs have a short half-life. This makes adherence extremely important, because missing just one dose may increase thrombo-embolic risk. The question whether once daily DOACs result in better adherence than twice daily DOACs is a very interesting one, but was not part of our literature review.

2.7 Quality of life, patient preference

Our literature search did not include patient preference or difference in quality of life between treatment with DOAC or treatment with warfarin (because this was not a research question for this report).

2.8 Cost effectiveness

Our literature review does not include a cost-effectiveness assessment. The recent KCE report 'Anticoagulants in non-valvular atrial fibrillation' covers this topic and will be discussed during the Consensus Conference.

2.9 Switching

We did not find RCTs that examined the best way of switching from VKA to DOAC or reversed. Several authors have remarked that switching between OAC is a high-risk period for patients, with a higher risk of thrombo-embolism (and a higher risk of bleeding), most likely due to inadequate anticoagulation. It seems wise to avoid switching anticoagulants when there is no clinical need. It is also important that great care is taken to maintain an adequate anticoagulation when switching.

2.10 Study quality and methodological problems

2.10.1 Trial design

A lot of the RCTs use a non-inferiority design but often the analyses are incompletely reported (for example they only report an analysis of the ITT (intention to treat) population, or the authors planned a sensitivity analysis but did not report the results). The choice of non-inferiority margin, especially in the VTE trials, is quite wide. For more information, see 1.11.3 Number Needed to treat.

2.10.2 Sponsoring

Most studies in this report are industry-sponsored. All efficacy studies with DOACs were sponsored studies.

2.10.3 Comparisons

There are no RCTs comparing efficacy and safety between different DOACs. The only comparisons we have between DOACs are indirect or from observational studies; both are bias sensitive.

2.10.4 Heterogeneity

We present a lot of individual trials in this report, sometimes followed by a meta-analysis. A reason for this choice is that significant heterogeneity exists between trials, so sometimes pooling isn't adequate.

2.10.5 DOAC vs VKA

Trials with DOACs compare the new anticoagulant to 'conventional treatment' (LMWH followed by VKA). All these trials are constructed as non-inferiority trials. Some of the trials with apixaban and rivaroxaban are designed to compare interventions in both the initial phase and continuation phase of treatment. However, in these trials, the majority of patients had received up to 24 or 48 hours of initial treatment with LMWH, heparin or fondaparinux prior to randomization. Therefore, no conclusions can be drawn as to the efficacy of apixaban and rivaroxaban compared to 'standard' treatment in the first two days of treatment. Outcomes are also often only reported for the entire follow up period, not specifically for the initial phase. This is of interest especially if there is an initial phase where one group receives the DOAC at a higher dose (usually 7 days) while the other group

receives LMWH and a VKA until they have an INR in therapeutic range on VKA. Sometimes subgroup analyses will look at this specifically.

2.10.6 Duration of DOAC treatment

Studies examining the optimal duration of treatment with a DOAC in the prevention of recurrent VTE include patients that had been in the earlier trial comparing DOAC to warfarin. This can raise questions as to the population sample, since it may select a potentially 'healthier' population, i.e. one that had no major adverse events during the first trial.

2.11 Some methodological issues explained

2.11.1 GRADE

GRADE is a method that is usually applied to the result of a meta-analysis, or to a 'body of evidence', consisting of multiple studies for a certain comparison. Our review focusses mostly on the individual DOACs, as per the request of the organizing committee. Because of this, we usually have only 1 study for each comparison.

It is more difficult to make firm conclusions about the benefit or harm of a drug based on 1 study. And of course GRADE scoring based on a single trial is not ideal. For example, we cannot score for consistency. On top of that, the classic criteria for study quality (allocation concealment, randomization, describing drop-out) are usually well described in the included studies, which could lead to high GRADE scores. However, the applicability of these results to a real-life population is not always straightforward (because of patient selection, trial conditions, duration…), which should lower the GRADE scoring.

The GRADE process requires not only an evaluation of the methodological problems in a study, but also an estimate on whether a specific methodological problem in a study is likely to create a relevant bias. Only when there is high risk of bias, the GRADE score is lowered.

2.11.2 Primary endpoint – secondary endpoint

Studies are designed around a primary endpoint. Secondary endpoint can be considered as supportive evidence of the primary outcome, if the result of the primary outcome is statistically significant. When there is a large number of secondary outcomes, there is a higher risk that some secondary outcomes become false positive, due to chance. In a trial design, adjustments should be made for dealing with multiple comparisons.

2.11.3 Number needed to treat

A number needed to treat is always specific to a study. The number is affected by the initial risk of the study population and by the study duration. As a general rule, NNTs from different studies should not be compared. A correct presentation of the NNT should also include the confidence interval for this NNT.

2.11.4 Non-inferiority trials

Non-inferiority trials are constructed to test whether the newer drug is 'not inferior' (i.e. not unacceptably worse) than an active 'conventional' treatment. To test this, a margin of non-inferiority is chosen: a threshold below which it can be established that the new drug is not (markedly) worse than its comparator.

Conducting and reporting of non-inferiority trials should done be according to certain standards (10-13):

- The **comparator** treatment should have a proven efficacy in the population that is studied. In the non-inferiority trial, this comparator should be used in the same fashion as in the historical trials in which its efficacy versus placebo was established.
- The choice of the non-inferiority **margin** is important: a very wide margin will prove statistical non-inferiority more easily but casts doubt on the actual efficacy and clinical benefit. A valid choice of margin should be based on previous placebo-controlled trials of the comparator.
In studies on AF and VTE, very few placebo-controlled trials exist. Treating patients with placebo would not be considered ethical nowadays. It is therefore difficult to establish a reliable non-inferiority margin. In the AF trials, the non-inferiority margins for the treatment difference for stroke/systemic embolism were chosen to preserve at least 50% of the benefit of warfarin over placebo (the effect of warfarin was based on a number of historical trials). This means that the upper boundary of the confidence interval of the relative risk of DOAC vs VKA would have to be lower than 1.38 (or 1.46, depending on the calculation method or chosen width of the CI) to prove statistical non-inferiority.
In the VTE trials, the non-inferiority margins vary. In some trials, a margin was chosen to preserve at least 70% of the risk reduction of warfarin vs placebo, in other trials, 50% preservation was chosen. As a consequence, to prove statistical non-inferiority, the upper boundaries of the 95% confidence interval of the hazard ratio of DOAC vs VKA range from 1.5 (edoxaban), to 2 (rivaroxaban), to even 2.85 (dabigatran). It is difficult to find a sound clinical argument for selecting such a high non-inferiority margin. For example, dabigatran would be considered non-inferior to the current standard of care even if the upper limit of the 95% CI indicated almost tripling of the incidence of symptomatic recurrent VTE.
-The **statistical analysis** is also a matter of consideration and subject to debate. It is often advised to perform a per-protocol analysis as well as an intent-to treat (ITT) analysis. This is because it is assumed that non-inferiority is more easily proven in an ITT analysis because of the dilution of the treatment effect due to non-compliance, treatment cross-over, drop out etc.
In a lot of the non-inferiority trials in this review, only an ITT analysis (or modified ITT) was performed.

2.11.5 Observational studies

To compare one DOAC to another, we included observational studies (cohort studies).
We did not include observational studies comparing DOACs to VKA. Starting a VKA versus a DOAC can be motivated by several patient-related factors (causing selection bias); this is less the case when starting DOAC1 versus DOAC2.
To further minimize selection bias, we only included cohort studies that analyzed OAC naive users.
An observational study cannot prove a causal link, it can merely establish an association between the treatment and a specific outcome. The quality of evidence in the GRADE approach for observational studies is LOW by default, although upgrading or downgrading according to certain rules is possible.

2.11.6 Statistically significant versus clinically relevant

A study may show non-inferiority of a certain drug, or superiority, when compared to another treatment. A point estimate and a confidence interval around this estimate are usually provided. The confidence interval gives us an idea of the (im)precision of the estimate and of the range in which the true effect plausibly lies (14). It is important to realize that the true effect can be anywhere within this confidence interval.
The GRADE score reflects how certain we are that this estimate is close to the true effect.

This is how the results in this document are reported.
Whether a difference found in a study is also clinically relevant (i.e. will make a noticeable difference to the patient), is another matter. Some authors have tried to propose thresholds for clinical relevance. The point estimate, as well as the upper and lower boundary of the confidence interval is then examined in relation to this threshold. For hard endpoints, usually a relative risk reduction of 25% is proposed.
It will be up to the jury to consider the results of the trials in this report in the light of clinical relevance.

3 Guidelines

This is a summary of the selected guidelines. A more detailed description can be found in the appendices.

3.1 General information on the selected guidelines

3.1.1 For atrial fibrillation

Abbreviation	Guideline
AHA/ACC/HRS 2014 (15)	American Heart Association / American College of Cardiology / Heart Rhythm Society Guideline for the management of patients with atrial fibrillation
CCS 2016/2014/2012 (16) (17) (18)	Canadian Cardiovascular Society - Focused 2012 update of the CCS atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control - 2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation - 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation
ESC 2016 AF (19)	European Society of cardiology /Guidelines for the management of atrial fibrillation developed in collaboration with EACTS
NICE 2014 (20)	National Institute for health and Care Excellence / Atrial Fibrillation

Table 7: selected guidelines for atrial fibrillation and their abbreviations as used in this report

The recent KCE report on anticoagulants in non-valvular atrial fibrillation (Van Brabandt, 2017(2) will be reported alongside these guidelines (see appendices).

3.1.2 For venous thromboembolism

Abbreviation	Guideline
ACCP 2016 (21)	American College of Chest Physicians / Antithrombotic therapy for VTE disease: CHEST Guideline and Expert 2016
ESC 2014 -VTE (22)	European Society of Cardiology / Acute pulmonary embolism (diagnosis and management) 2014

Table8: selected guidelines for venous thromboembolism and their abbreviations as used in this report

3.2 Atrial Fibrillation

3.2.1 Adherence

The CCS, ESC and NICE guideline mention patient adherence to therapy outright, albeit briefly. The first two speak of the need to discuss the importance of adherence to therapy with the patient and to put the patient in a central role in decision-making. Checking adherence is considered an important part of the follow-up of the patient. Knowledge (about disease, about treatment, about management goals) and capabilities (what to do if…) are considered to be an integral part of follow-up with the aim to improve adherence, according to ESC.
ESC mentions tailored patient education throughout AF management, although not (solely) in the context of adherence.

NICE mentions evaluating adherence if anticoagulation control (as shown by deficient INR or TTR) is poor. ESC advises to check adherence if a patient has a stroke despite anticoagulant therapy. There are no mentions of adherence in the context of DOACs.

3.2.2 First treatment choice: starting with VKA or DOAC?

Note from the literature group: comparisons of VKA or DOACs with ASA / antiplatelet and combinations thereof are done by some guidelines but aren't within the scope of this review.

The following table summarizes recommendations once it has been established that anticoagulation was necessary. How this need is established depends on guidelines, scales (CHA_2DS_2-VAsc for example) and thresholds used by the guideline. How to make the decision to start anticoagulation falls outside of the scope of this literature review.

The first three guidelines in this table agree that in the case of nonvalvular atrial fibrillation, a DOAC is preferable as a first treatment.

AHA/ACC/HRS 2014 gives a higher QoE for their recommendation of using warfarin after a stroke or previous TIA in NVAF, compared to a lower QoE for DOACS. Warfarin is also recommended for patients with end-stage CKD. Dabigatran and rivaroxaban are not recommended and dabigatran is even recommended against in CKD patients.

NICE 2014 mentions that choice of OAC therapy must be discussed with the patient, but that with NVAF and in the presence of certain risk factors, a DOAC is recommended.

	Warfarin	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
AHA/ACC/HRS 2014 (LoE)	For AF patients with mechanical heart valves (I,B) NVAF with prior stroke, TIA or CHA2DS2VASc ≥2 (I, A) NVAF and CHA2DS2VASc ≥2 and end-stage CKD (IIb, B)	NVAF with prior stroke, TIA or CHA2DS2VASc ≥2 (I, B)	NVAF with prior stroke, TIA or CHA2DS2VASc ≥2 (I, B) Should NOT be used in patient with a mechanical heart valve (III harm, B) Not recommended for patients with end-stage CKD (III no benefit, C)		NVAF with prior stroke, TIA or CHA2DS2VASc ≥2 (I, B) Not recommended for patients with end-stage CKD (III no benefit, C)
CCS 2016/2014/2012	AF and mechanical heart valves, rheumatic mitral stenosis, or moderate and severe non-rheumatic mitral stenosis (strong, mod quality)	A DOAC is preferred for NVAF (strong, high QoE) also in the case of CAD + risk factors (stroke, TIA, DM, hypertension, heart failure) a DOAC is preferred (conditional recommendation, low QoE)			
ESC 2016	for AF patients with moderate to severe mitral stenosis (QoE: C) or mechanical heart valves (QoE: B)	A DOAC is preferred to VKA in patient eligible for DOACS (IA)			
NICE 2014		Recommended in NVAF and risk factor(s): -prior stroke or TIA -≥75y -hypertension -diabetes mellitus -symptomatic heart failure	Recommended in patients with NVAF and risk factor(s): -previous stroke, TIA or systemic embolism -LV ejection fraction <40% -symptomatic HF (NYHA ≥2) -≥75 y -≥65y and CAD, DM or hypertension		Recommended in patients with NVAF and risk factor(s): -prior stroke or TIA -congestive heart failure -hypertension -≥75 y -diabetes mellitus

Table9: choice of OAC medication

3.2.3 Switch from VKA to DOAC or reversed

Three guidelines discuss the switch to DOACs: AHA/ACC/HRS 2014, ESC 2016 and NICE 2014. The first two mention that switching to a DOAC is recommended if the TTR is not well controlled. The ESC 2016 guideline also mentions adherence (in the sense that this switch should be considered only when the unsatisfactory TTR is not due to poor adherence).

The AHA/ACC/HRS 2014 mentions the choice should be reevaluated “at periodic intervals” in the light of stroke and bleeding risks.

The strength of recommendation is weak for both guidelines. Level of evidence is low according to AHA/ACC/HRS 2014 but high for the ESC 2016.

NICE 2014 is more precise as to what constitutes a poor anticoagulation control: 2 INR values higher than 5 or one higher than 8 within the past 6 months, 2 INR less than 1.5 in the past 6 months, or a TTR <65%. In those cases, discussion of alternative stroke prevention strategies with the patient is recommended, as well as the potential risks and benefits of apixaban, dabigatran or rivaroxaban. No guideline mentions a situation a case in which a switch from a DOAC to warfarin would be indicated.

3.2.4 Choice between DOACS

The ESC 2016 guideline does not mention any difference between the DOACs.

The AHA/ACC/HRS 2014 guideline does not make a difference between DOACs except on the subject of end-stageend-stage CKD. Warfarin is the recommended treatment (see First treatment choice: starting with VKA or DOAC?), but dabigatran is advised against due to possible harm, while rivaroxaban is not recommended.

CCS 2016/2014/2012 does not make a differing recommendation for any of the DOACs, but mentions dosage adjustment for dabigatran in patients ≥75y.

NICE 2014 lists the risk factors mentioned in the marketing authorization, here summarized in a table:

	Apixaban	Dabigatran	Rivaroxaban
Prior stroke or TIA	X	X	X
Prior systemic embolism		X	
≥75 y	X	X	X
Hypertension	X	≥65y	X
Diabetes mellitus	X	≥65y	X
Symptomatic/congestive heart failure	X	NYHA class 2 or above	X
Left ventricular ejection fraction <40%		X	
≥65y and 1 risk factor such as: diabetes mellitus, hypertension, CAD		X	

Table10: different risk factors in market authorization of the DOACs

3.3 Deep vein thrombosis and pulmonary embolism

3.3.1 Adherence

None of the guidelines mention adherence outright.

3.3.2 First treatment choice: DOACs or VKA?

ACCP 2016 guideline makes recommendations for both DVT and PE, ESC 2014 only for PE. However ESC 2014 states that the studies it bases its recommendations on often include patients with both patients with DVT or with PE.

Both guidelines make a difference between patients with or without cancer. In those with cancer, LMWH are to be preferred, it's only in patients without cancer that the choice must be made between a DOACs or a VKA.

The ACCP guideline suggests a DOAC over VKA therapy for the first three months of anticoagulant therapy, but it is not a strong recommendation. The ESC 2014 guideline does not recommend one above the other. Rather, it says that the DOACs are proven non-inferior and presents them as alternatives. All are recommended with the same strength and quality of evidence.
The guidelines differ in which use of parenteral anticoagulation they recommend before initiating the different DOACs.

Choice of treatment also depends on how long the treatment should continue, which itself depends on the kind of thrombo-embolism that befell the patient. In long term treatment ESC 2014 recommends DOACs over VKA (see also item "duration of treatment"), which can influence the first treatment of choice.

DOACs are recommended against by both guidelines in the case of renal disease or creatinine clearance <30 mL/min, in which case VKA is preferred. Quality of evidence is low for these recommendations.
ACCP 2016 guideline recommends VKA or apixaban also in the case of dyspepsia or history of gastro-intestinal bleeding.

3.3.3 Duration of treatment

The two guidelines are in agreement for the duration of treatment (of a proximal DVT, PE or isolated distal DVT) when due to a **transient risk factor or surgery**: **3 months** are preferred over shorter or longer duration. The recommendations are usually strong with moderate levels of evidence.

They also agree for the treatment of **unprovoked DVT or PE**. Both **recommend at least 3 months**, with ACCP 2016 stating longer treatment being preferable.

For a **first unprovoked VTE**, and in the case of low (or even moderate for ACCP 2016) bleeding risk, **extended therapy (with no scheduled stop date)** is recommended by both, though the recommendation is not a strong one ***('we suggest'***). ACCP 2016 recommends 3 months for patients with a high bleeding risk.

In the case of **a second unprovoked VTE**, **extended therapy (with no scheduled stop date)** is recommended but more strongly ***('we recommend'***). Here however ACCP 2016 recommends only a 3 month therapy in people with high risk of bleeding.

In the case of **cancer**, therapy should be **extended** (with no stop date) or until the cancer is cured (strong recommendation in ACCP 2016, weak recommendation ('**considered**') in ESC 2014).

In case of extended therapies ESC 2014 suggests DOACs over VKA.

In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals.

3.3.4 Switch from VKA to DOAC or reversed

There are no formal recommendations on switching from one to the other. However the ESC 2014 guideline recommends DOACs for long-term anticoagulation. This implies a possible switch from VKA to DOAC if therapy is extended beyond three months.

3.4 Bridging

CCS 2016/2014/2012, ESC 2016 and AHA/ACC/HRS 2014 make statements about bridging in atrial fibrillation.

Interrupting or not
The decision on whether or not to interrupt OAC should be made by weighing the risk of stroke when interrupting against the risk of bleeding when continuing the OAC (CCS 2016).
Interrupting is not deemed necessary for interventions with low risk of bleeding, including cardiovascular procedures such as cardiac device implantation and percutaneous interventions (CCS 2016, ESC 2016).
CCS has provided a list of surgical procedures and associated bleeding risk (see appendices).

Bridging or not
The decision on whether or not to bridge with LMWH when interrupting OAC should also balances the risk of stroke against the risk of bleeding (CCS 2016, AHA/ACC/HRS 2014).
The guidelines agree that patients with mechanical heart valves require bridging therapy (AHA/ACC/HRS 2014, CCS 2016)

CCS 2016 suggests bridging for patients at high risk of stroke. (CHADS2, score >= 4, mechanical heart valve, stroke/transient ischemic attack within 3 months, rheumatic heart disease). AHA/ACC/HRS 2014 and ESC 2016 make no formal recommendation on who exactly should receive bridging.
CCS 2016 and ESC 2016 both refer to the BRIDGE trial, in which interruption of anticoagulation was non-inferior to bridging, and led to a lower rate of major bleeding.

CCS recommends no bridging for NVAF patients receiving DOACs who undergo elective surgery or invasive procedures requiring interruption of anticoagulation.

4 Atrial fibrillation. Summary and conclusions

4.1 DOACs vs VKA. Information from RCTs

4.1.1 Apixaban 5mg 2x/d vs warfarin in atrial fibrillation

Apixaban 2x5mg/x vs warfarin (INR 2-3) in non-valvular atrial fibrillation			
Bibliography: Granger 2011 ARISTOTLE *(23)*			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Stroke or systemic embolism	18207 (1 study) median 1.8y	Apixaban 1.27%/y Warfarin 1.60%/y **HR= 0.79 (95%CI 0.66-0.95)** **p<0.001 for non-inferiority** **p = 0.01 for superiority** *estimated NNT/2y=152 (92 to 625)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok, but incomplete testing for non-inferiority Consistency: NA Directness: -1 34% CHADS=1 Imprecision: OK
All-cause mortality	18207 (1 study) median 1.8y	Apixaban 3.52%/y Warfarin 3.94%/y **HR 0.89 (95%CI 0.80-0.998)** **p=0.047** *estimated NNT/2y=119(64 to 6345)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok, but incomplete testing for non-inferiority Consistency: NA Directness: -1 Imprecision: OK
Major bleeding	18207 (1 study) median 1.8y	Apixaban 2.13%/y Warfarin 3.09%/y **HR 0.69 (95%CI 0.60–0.80)** **SS less major bleedings with apixaban** **p <0.001** *estimated NNT/2y=52(41 to 81)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok, but incomplete testing for non-inferiority Consistency: NA Directness: -1 Imprecision: OK
Intracranial bleeding	18207 (1 study) median 1.8y	Apixaban 0.33%/y Warfarin 0.80%/y **SS less intracranial bleedings with apixaban** **HR 0.42 (95%CI 0.30-0.58)** **p<0.001** *estimated NNT/2y=107(83 to 149)**	⊕⊕⊕⊖ **MODERATE** Study quality: ok, but incomplete testing for non-inferiority Consistency: NA Directness: -1 Imprecision: OK
Gastro-intestinal bleeding	18207 (1 study) median 1.8y	Apixaban 0.76%/y Warfarin 0.86%/y NS, p = 0.37	⊕⊕⊕⊖ **MODERATE** Study quality: ok, but incomplete testing for non-inferiority Consistency: NA Directness: -1 Imprecision: OK

** NNT calculations by the literature group, based on event rate per 100 person-years. Confidence interval based on Hazard ratio. This is an approximation, because we have insufficient data to perform a correct NNT assessment based on actual survival at any given time point.*

In this double blind, non-inferiority RCT, apixaban 2x5mg/d was compared to warfarin in 18207 patients with non-valvular atrial fibrillation. The mean age was 70y, mean $CHADS_2$ 2.1. Patients with eGFR< 25 ml/min were excluded from the trial.
The median follow-up was 1.8y.

The interpretation of these results is somewhat limited by the study population: 34% of included patients had a CHADS2 score of 1, which is a lower score than most guidelines recommend to initiate oral anticoagulant treatment.

Apixaban was **non-inferior and superior** to warfarin in the prevention of **stroke or systemic embolism**.
In a similar population, approximately 152 people would need to be treated with apixaban instead of warfarin for 2 years to prevent 1 additional stroke (95%CI 92 to 625).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Apixaban was associated with a **lower** rate of **all-cause mortality** compared to warfarin.
In a similar population, approximately 119 people would need to be treated with apixaban instead of warfarin for 2 years to prevent 1 extra death (95%CI 64 to 6345).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Apixaban treatment resulted in **less major bleeding** compared to warfarin treatment.
In a similar population, approximately 52 people would need to be treated with apixaban instead of warfarin for 2 years to prevent 1 major bleeding (95%CI 41 to 81).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Apixaban treatment resulted in **less intracranial bleeding** compared to warfarin treatment.
In a similar population, approximately 107 people would need to be treated with apixaban instead of warfarin for 2 years to prevent 1 intracranial bleeding (95%CI 83 to 149).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **gastro-intestinal bleeding** rates between apixaban and warfarin.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

No statistical analysis was performed for non-bleeding adverse events.

4.1.2 Dabigatran 110mg 2x/d vs warfarin in atrial fibrillation

Dabigatran 110mg 2x/d vs warfarin (INR 2-3) in nonvalvular atrial fibrillation			
Bibliography: Connolly 2009 RE-LY(24) + revisions *Connolly 2010(25),Hohnloser 2012(26),Connolly 2014 (27)**			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Stroke or systemic embolism	18113 (1 study) median 2y	Dabigatran 110mg: 1.54%/y Warfarine: 1.72%/y **RR 0.89 (0.73–1.09)** **p<0.001 for non-inferiority** Not superior (p=0.27)	⊕⊕⊕⊖ **MODERATE** Study quality: open label, reporting inconsistencies Consistency: NA Directness:-1 32% $CHADS_2$=1 Imprecision: OK
All-cause mortality	18113 (1 study) median 2y	Dabigatran 110mg: 3.75%/y Warfarine: 4.13%/y NS: RR 0.91 (95%CI 0.80-1.03) p=0.13	⊕⊕⊕⊖ **MODERATE** Study quality: open label, reporting inconsistencies Consistency: NA Directness:-1 32% $CHADS_2$=1 Imprecision: OK
Major bleeding	18113 (1 study) median 2y	Dabigatran 110mg 2.92%/y Warfarin 3.61%/y **SS less major bleeding with dabigatran 110 mg** **RR 0.80 (0.70–0.93)** **P = 0.003** *estimated NNT/2y=73 (47 to 198)**	⊕⊕⊕⊖ **MODERATE** Study quality: open label, reporting inconsistencies Consistency: NA Directness:-1 32% $CHADS_2$=1 Imprecision: OK
Intracranial bleeding	18113 (1 study) median 2y	Dabigatran 110mg 0.23%/y Warfarine 0.74%/y **SS less intracranial bleedings with dabigatran 110mg:** **RR 0.31 (95%CI 0.20-0.47)** **p<0.001** *estimated NNT/2y=98 (85 to 128)**	⊕⊕⊕⊖ **MODERATE** Study quality: open label, reporting inconsistencies Consistency: NA Directness:-1 32% $CHADS_2$=1 Imprecision: OK
Gastro-intestinal bleeding	18113 (1 study) median 2y	1.12%/y vs 1.02/y RR1.10 (95%CI 0.86-1.41) p=0.43 NS	⊕⊕⊕⊖ **MODERATE** Study quality: open label, reporting inconsistencies Consistency: NA Directness:-1 32% $CHADS_2$=1 Imprecision: OK
Myocardial infarction	18113 (1 study) median 2y	Revised data(26) 0.82%/y vs 0.64%/y RR 1.29 (95%CI 0.96–1.75) p=0.09	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label, reporting inconsistencies Consistency: NA Directness: Imprecision: -1 wide CI

In this non-inferiority open label RCT, dabigatran 110 mg 2x/d was compared to dabigatran 150 mg 2x/d and to warfarin (INR 2-3) in 18113 patients with non-valvular atrial fibrillation. The mean age was 71y, mean $CHADS_2$ 2.1. Patients with eGFR < 30 ml/min were excluded from the trial. The median follow-up was 2y.

The interpretation of these results is somewhat limited by the study population: 32% of included patients had a CHADS2 score of 1, which is a lower score than most guidelines recommend to initiate oral anticoagulant treatment.
The unblinded design of this study and some reporting inconsistencies also impacts our confidence in these results.

We report here the results of the comparison of dabigatran 110 mg vs warfarin.

Dabigatran 110 mg was **non-inferior** to warfarin in the prevention of **stroke or systemic embolism**. Dabigatran was not superior to warfarin.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **mortality** rates between dabigatran 110 mg and warfarin.
GRADE: MODERATE or LOW quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Dabigatran 110 mg treatment resulted in **less major bleeding** compared to warfarin treatment.
In a similar population, approximately 73 people would need to be treated with dabigatran 110 mg instead of warfarin for 2 years to prevent 1 extra major bleeding (95%CI 47 to 198).
GRADE: MODERATE or LOW quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Dabigatran 110 mg treatment resulted in **less intracranial bleeding** compared to warfarin treatment.
In a similar population, approximately 98 people would need to be treated with dabigatran 110 mg instead of warfarin for 2 years to prevent 1 extra intracranial bleeding (95%CI 85 to 128).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **gastro-intestinal bleeding** rates between dabigatran 110 mg and warfarin.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **rates of myocardial infarction** between dabigatran 110 mg and warfarin. (See also chapter 'Dabigatran and myocardial infarction')
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflect the true effect.

There were more patients with dyspepsia with dabigatran110 mg compared to warfarin. (11.8% vs 5.8%; p<0.001)

4.1.3 Dabigatran 150mg 2x/d vs warfarin in atrial fibrillation

Dabigatran 150mg 2x/d vs warfarin (INR 2-3) in nonvalvular atrial fibrillation			
Bibliography: Connolly 2009 RE-LY(24) + revisions *Connolly 2010(25),Hohnloser 2012(26),Connolly 2014 (27)**			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Stroke or systemic embolism	18113 (1 study) median 2y	Dabigatran 150mg: 1.12%/y Warfarin: 1.72%/y **RR 0.66 (95%CI 0.52-0.81)** **p<0.001 for non-inferiority** **p<0.001 for superiority** *estimated NNT/2y=84 (61 to 153)**	⊕⊕⊕⊖ **MODERATE** Study quality: open label, reporting inconsistencies Consistency: NA Directness:-1 32% $CHADS_2$=1 Imprecision: OK
All-cause mortality	18113 (1 study) median 2y	Dabigatran 150mg: 3.64%/y Warfarin: 4.13%/y NS: RR 0.88 (95%CI 0.77-1.00) (p=0.051)	⊕⊕⊕⊖ **MODERATE** Study quality: open label, reporting inconsistencies Consistency: NA Directness:-1 32% $CHADS_2$=1 Imprecision: OK
Major bleeding	18113 (1 study) median 2y	Dabigatran 150mg 3.4%/y warfarin 3.61%/y RR 0.94 (0.82–1.08) P = 0.41 NS	⊕⊕⊕⊖ **MODERATE** Study quality: open label, reporting inconsistencies Consistency: NA Directness:-1 32% $CHADS_2$=1 Imprecision: OK
Intracranial bleeding	18113 (1 study) median 2y	Dabigatran 150mg 0.30%/y warfarin 0.74%/y **SS less intracranial bleedings with dabigatran:** **RR 0.40 (95%CI 0.27-0.60),** **p<0.001** *estimated NNT/2y=114 (93 to 169)**	⊕⊕⊕⊖ **MODERATE** Study quality: open label, reporting inconsistencies Consistency: NA Directness:-1 32% $CHADS_2$=1 Imprecision: OK
Gastro-intestinal bleeding	18113 (1 study) median 2y	1.51%/y vs 1.02%/y **SS more GI-bleedings with dabigatran:** **RR 1.50 (95%CI 1.19-1.89),** **p<0.001** *estimated NNH/2y=103 (258 to 55)**	⊕⊕⊕⊖ **MODERATE** Study quality: open label, reporting inconsistencies Consistency: NA Directness:-1 32% $CHADS_2$=1 Imprecision: OK
Myocardial infarction	18113 (1 study) median 2y	**Revised data** *(26)- total MI* Dabigatran 150mg: 97/6067 0.81%/y Warfarin: 75/6022 ; 0.64%/y RR 1.27 (95%CI 0.94–1.71) NS p = 0.12	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label, reporting inconsistencies Consistency: NA Directness:ok Imprecision: wide CI

** NNT calculations by the literature group, based on event rate per 100 person-years. Confidence interval based on relative risk.*

In this non-inferiority open label RCT, dabigatran 110 mg 2x/d was compared to dabigatran 150 mg 2x/d and to warfarin (INR 2-3) in 18113 patients with non-valvular atrial fibrillation. The mean age was 71y, mean $CHADS_2$ 2.1. Patients with eGFR < 30 ml/min were excluded from the trial.

The median follow-up was 2y.

The interpretation of these results is somewhat limited by the study population: 32% of included patients had a CHADS2 score of 1, which is a lower score than most guidelines recommend to initiate oral anticoagulant treatment.
The unblinded design of this study and some reporting inconsistencies also impacts our confidence in these results.

We report here the results of the comparison of dabigatran 150 mg vs warfarin.

Dabigatran 150 mg was **non-inferior and superior** to warfarin in the prevention of **stroke or systemic embolism**.
In a similar population, approximately 84 people would need to be treated with dabigatran 150 mg instead of warfarin for 2 years to prevent 1 stroke (95%CI 61 to 153).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in rates of **mortality** between dabigatran 150 mg and warfarin.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in rates of **major bleeding** between dabigatran 150 mg and warfarin.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Dabigatran 150 mg treatment resulted in **less intracranial bleeding** compared to warfarin treatment.
In a similar population, approximately 114 people would need to be treated with dabigatran 150 mg instead of warfarin for 2 years to prevent 1 extra intracranial bleeding (95%CI 93 to 169).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Dabigatran 150 mg treatment resulted in **a higher rate of gastro-intestinal bleeding** compared to warfarin treatment.
In a similar population, approximately 102 people would need to be treated with dabigatran 150 mg instead of warfarin for 2 years to cause 1 additional gastro-intestinal bleeding (95%CI 258 to 55).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.
There was **no statistically significant difference** in **rates of myocardial infarction** between dabigatran 150 mg and warfarin. (See also chapter 'Dabigatran and myocardial infarction')
GRADE: LOW quality of evidence

We have low confidence that the results of the study reflect the true effect.

There were more patients with dyspepsia with dabigatran150 mg compared to warfarin. (11.3% vs 5.8%; p<0.001)

4.1.4 Edoxaban 60 mg/d vs warfarin in atrial fibrillation

Edoxaban 60 mg versus warfarin (INR 2-3) in non-valvular atrial fibrillation			
Bibliography: Giugliano 2013 ENGAGE AF-TIMI 48(28)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Stroke or systemic embolism	21105 (1 study) median 2.8y	Edoxaban 60: 1.18% pt/y Warfarin: 1.50% pt/y **HR 0.79 (97.5% CI 0.63 – 0.99)** **p for non-inferiority <0.001** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 high discontinuation, confusing calculations Consistency: NA Directness: OK Imprecision: OK
All-cause mortality	21105 (1 study) median 2.8y	Edoxaban 60: 3.99 % pt/y Warfarin: 4.35 % pt/y HR 0.92 (0.83–1.01) p<0.08 NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: NA Directness: OK Imprecision: OK
Major bleeding	21105 (1 study) median 2.8y	Edoxaban 60: 2.75% pt/y Warfarin: 3.43% pt/y **HR 0.80 (95%CI 0.71-0.91)** **p<0.001** **SS less major bleeding with edoxaban 60 mg** *estimated NNT/2y=74 (51 to 161)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: NA Directness: OK Imprecision: OK
Intracranial bleeding	21105 (1 study) median 2.8y	Edoxaban 60: 0.39 % pt/y Warfarin: 0.85 % pt/y **HR 0.47 (95%CI 0.34–0.63)** **p <0.001** **SS less intracranial bleeding with edoxaban 60** *estimated NNT/2y=109 (90 to 159)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: NA Directness: OK Imprecision: OK
Gastro-intestinal bleeding	(1 study)	Edoxaban 60: 1.51 % pt/y Warfarin: 1.23 % pt/y **HR 1.23 (1.02–1.50)** **p=0.03** **SS more GI bleeding with edoxaban 60** *estimated NNH/2y=179 (2033 to 82)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: NA Directness: OK Imprecision: OK

** NNT calculations by the literature group, based on event rate per 100 person-years. Confidence interval based on Hazard ratio. This is an approximation, because we have insufficient data to perform a correct NNT assessment based on actual survival at any given time point.*

In this double blind, non-inferiority RCT, edoxaban 60mg was compared to edoxaban 30mg and to warfarin (INR2-3) in 21105 patients with non-valvular atrial fibrillation. The mean age was 72y. 77.5% of participants had a $CHADS_2$ score of 2 or 3 (the remaining participants had a $CHADS_2$ score >3 Patients with eGFR < 30 ml/min were excluded from the trial. The median follow-up was 2.8y.

The interpretation of these results is somewhat limited by the high rate of discontinuations throughout the trial (1/3 of participants discontinued) and the numerous analyses of different populations and treatment periods. An ITT analysis was also performed on the data.

We report here the results of edoxaban 60 mg vs warfarin.

Edoxaban 60 mg was **non-inferior** to warfarin in the prevention of **stroke or systemic embolism**.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **mortality** rates between edoxaban 60 mg and warfarin.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect

Edoxaban 60 mg treatment resulted in **less major bleeding** compared to warfarin treatment.
In a similar population, approximately 74 people would need to be treated with edoxaban 60 mg instead of warfarin for 2 years to prevent 1 extra major bleeding (95%CI 51 to 161).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect

Edoxaban 60 mg treatment resulted in **less intracranial bleeding** compared to warfarin treatment.
In a similar population, approximately 109 people would need to be treated with edoxaban 60 mg instead of warfarin for 2 years to prevent 1 extra intracranial bleeding (95%CI 90 to 159).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect

Edoxaban 60 mg was associated with a **higher** rate of **gastro-intestinal bleeding** compared to warfarin.
In a similar population, approximately 179 people would need to be treated with edoxaban 60 mg instead of warfarin for 2 years to cause 1 extra gastro-intestinal bleeding (95%CI 2033 to 82).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect

No statistical analysis was performed for non-bleeding adverse events.

4.1.5 Edoxaban 30 mg/d vs warfarin in atrial fibrillation

Edoxaban 30 mg versus warfarin (INR 2-3) in non-valvular atrial fibrillation			
Bibliography: Giugliano 2013 ENGAGE AF-TIMI 48(28)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Stroke or systemic embolism	21105 (1 study) median 2.8y	Edoxaban 30: 1.61% pt/y Warfarin: 1.50% pt/y **HR 1.07 (97.5% CI 0.87 – 1.31)** **p for non-inferiority 0.005** **SS**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: NA Directness: OK Imprecision: OK
All-cause mortality	21105 (1 study) median 2.8y	Edoxaban 30: 3.80 % pt/y Warfarin: 4.35 % pt/y **HR 0.87 (95%CI 0.79–0.96)** **p<0.006** **SS lower mortality with edoxaban 30 mg** *estimated NNT/2y=91 (55 to 288)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: NA Directness: OK Imprecision: OK
Major bleeding	21105 (1 study) median 2.8y	Edoxaban 30: 1.61% pt/y Warfarin: 3.43% pt/y **HR 0.47 (95%CI 0.41 - 0.55)** **p<0.001;** **SS less major bleeding with edoxaban 30 mg** *estimated NNT/2y=28 (25 to 33)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: NA Directness: OK Imprecision: OK
Intracranial bleeding	21105 (1 study) median 2.8y	Edoxaban 30: 0.26 % pt/y Warfarin: 0.85 % pt/y **HR 0.30 (95%CI 0.21–0.43)** **p<0.001** **SS less intracranial bleeding with edoxaban 30 mg** *estimated NNT/2y=85 (75 to 104)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: NA Directness: OK Imprecision: OK
Gastro-intestinal bleeding	(1 study)	Edoxaban 30: 0.82 % pt/y Warfarin: 1.23 % pt/y **HR 0.67 (95%CI 0.53–0.83)** **p <0.001** **SS less GI bleeding with edoxaban 30** *estimated NNT/2y=122 (87 to 239)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: NA Directness: OK Imprecision: OK

** NNT calculations by the literature group, based on event rate per 100 person-years. Confidence interval based on Hazard ratio. This is an approximation, because we have insufficient data to perform a correct NNT assessment based on actual survival at any given time point.*

In this double blind, non-inferiority RCT, edoxaban 60 mg was compared to edoxaban 30 mg and to warfarin (INR2-3) in 21105 patients with non-valvular atrial fibrillation. The mean age was 72y. 77.5% of participants had a $CHADS_2$ score of 2 or 3 (the remaining participants had a $CHADS_2$ score >3). Patients with eGFR < 30 ml/min were excluded from the trial.
The median follow-up was 2.8y.

The interpretation of these results is somewhat limited by the high rate of discontinuations throughout the trial (1/3 of participants discontinued) and the numerous analyses of different populations and treatment periods.

We report here the results of edoxaban 30 mg vs warfarin.

Edoxaban 30 mg was **non-inferior** to warfarin in the prevention of **stroke or systemic embolism**. However, the upper limit of the non-inferiority margin is quite wide.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Edoxaban 30 mg was associated with a **lower mortality** rate compared to warfarin.
In a similar population, approximately 91 people would need to be treated with edoxaban 30 mg instead of warfarin for 2 years to prevent 1 extra death (95%CI 55 to 288).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Edoxaban 30 mg treatment resulted in **less major bleeding** compared to warfarin treatment.
In a similar population, approximately 28 people would need to be treated with edoxaban 30 mg instead of warfarin for 2 years to prevent 1 extra major bleeding (95%CI 25 to 33).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect

Edoxaban 30 mg treatment resulted in **less intracranial bleeding** compared to warfarin treatment.
In a similar population, approximately 85 people would need to be treated with edoxaban 30 mg instead of warfarin for 2 years to prevent 1 extra intracranial bleeding (95%CI 90 to 159).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect

Edoxaban 30 mg was associated with a **lower** rate of **gastro-intestinal bleeding** compared to warfarin.
In a similar population, approximately 122 people would need to be treated with edoxaban 30 mg instead of warfarin for 2 years to prevent 1 gastro-intestinal bleeding (95%CI 87 to 239).
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect

No statistical analysis was performed for non-bleeding adverse events.

4.1.6 Rivaroxaban 20mg/d vs warfarin in atrial fibrillation

rivaroxaban 20mg/d vs warfarin (INR 2-3) in nonvalvular atrial fibrillation			
Bibliography: Patel 2011(29) (ROCKET AF trial)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Stroke or systemic embolism	14264 (1 study) mean 707 days	Per-protocol analysis Rivaroxaban: 1.7%/y Warfarin:2.2%/y **HR 0.79 (95%CI 0.66 – 0.96) SS; p<0.001 for non-inferiority** (not superior in ITT analysis)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 low TTR in warfarin group, questions about point of care device Consistency: NA Directness: OK Imprecision: OK
All-cause mortality	14264 (1 study) mean 707 days	Rivaroxaban 1.87% Warfarin 2.21% HR 0.85 (95%CI 0.70 – 1.02) p=0.073 NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: NA Directness: OK Imprecision: OK
Major or non-major clinically relevant bleeding (PO)	14264 (1 study) mean 707 days	rivaroxaban 14.9%/y Warfarin 14.5%/y HR 1.03 (0.96–1.11) p=0.44 NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: NA Directness: OK Imprecision: OK
Major bleeding	14264 (1 study) mean 707 days	3.6%/y vs 3.4%/y 1.04 (0.90–1.20) (NS: p=0.58)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: NA Directness: OK Imprecision: OK
Intracranial bleeding	14264 (1 study) mean 707 days	Rivaroxaban 0.5%/y vs warfarin 0.7%/y **HR 0.67 (95%CI 0.47–0.93) p=0.02** **SS less intracranial bleeding with rivaroxaban** *estimated NNT/2y=250 (135 to 1021)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: NA Directness: OK Imprecision: OK
Gastro-intestinal bleeding	14264 (1 study) mean 707 days	**3.15%/y vs 2.16%/y (SS: p<0.001)** *estimated NNH/2y=51*	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: NA Directness: OK Imprecision: OK

** NNT calculations by the literature group, based on event rate per 100 person-years. Confidence interval based on Hazard ratio. This is an approximation, because we have insufficient data to perform a correct NNT assessment based on actual survival at any given time point.*

In this double blind, non-inferiority RCT, rivaroxaban 20 mg was compared to warfarin (INR2-3) in 14264 patients with non-valvular atrial fibrillation. The mean age was 73 y, mean $CHADS_2$ 3.5 (100% of patients had $CHADS_2$>=2). Patients with eGFR < 30 ml/min were excluded from the trial.
The median follow-up was 707 days.

The interpretation of these results is somewhat limited by the low TTR in the warfarin group and by the reports that a defective point of care device was used in the warfarin arm of the trial (Cohen 2016 (30)).

Rivaroxaban was **non-inferior** to warfarin in the prevention of **stroke or systemic embolism**.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **mortality** rates between rivaroxaban and warfarin.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **major and clinically relevant non-major bleeding** rates between rivaroxaban and warfarin.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

There was **no statistically significant difference** in **major bleeding** rates between rivaroxaban and warfarin.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Rivaroxaban treatment resulted in **less intracranial bleeding** compared to warfarin treatment.
In a similar population, approximately 250 people would need to be treated with rivaroxaban instead of warfarin for 2 years to prevent 1 intracranial bleeding (95%CI 135 to 1021)
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Rivaroxaban treatment resulted in **more gastro-intestinal bleeding** compared to warfarin treatment.
In a similar population, approximately 51 people would need to be treated with rivaroxaban instead of warfarin for 2 years to cause 1 extra gastro-intestinal bleeding.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

No statistically significant differences were observed for non-bleeding adverse events.

A smaller trial, comparing rivaroxaban 15mg/d in 1280 Japanese patients(31), found that rivaroxaban 15mg was non-inferior to warfarin for the safety endpoint major and clinically relevant non-major bleeding (HR 1.11 (95% CI 0.87–1.42). However, the chosen margin for non-inferiority was wide.

4.1.7 Comparison of populations in DOAC trials

Study	ARISTOTLE Granger 2011	RE-LY Connolly 2009	ENGAGE AF Giugliano 2013	ROCKET AF Patel 2011
Mean age	70	71	72	73
CHADS2 score	Score 1: 34%	Score 1: 32%	Score 1: 0	Score 1: 0
	Score 2: 35.8%	Score 2: 35.5%	Score 2-3: 77.5%	Score 2: 13%
	Score ≥3: 30.2%	Score ≥3: 32.5%	Score 4-6: 22.5%	Score 3: 44% Score 4: 29% Score 5: 13%
Previous use of VKA	57%	50%	59%	62%
CrCl ≤50 ml/min	16.6%	NR	19%	NR
Prior stroke	19.5%	20%	28%	55%
Congestive heart failure	35.5%	32%	57%	62%
Hypertension	87.5%	79%	94%	91%
Type 2 diabetes	25%	23%	36%	40%

4.2 DOAC vs VKA. Information from meta-analyses

Several meta-analyses have been performed on the efficacy and safety of the DOACs compared to warfarin, by pooling the trial with the individual DOACs. The results vary slightly, depending on the inclusion criteria (with or without ximelagatran, with or without J-rocket AF, separating high dose from low dose…) (Ruff 2014(32), Jia 2014(33), Providencia 2014(34)).
In a lot of comparisons that reach statistical significance, the 95% confidence interval of the results (relative risk) is very close to 1 (representing no difference). This means that the clinical relevance of the observed differences may be low.

For some comparisons (e.g. major bleeding), a high statistical heterogeneity is observed. This may reflect a difference in treatment effect of the drugs, or a difference in the included populations in the studies.

4.2.1.1 Stroke/systemic embolism

For stroke/systemic embolism, DOACs as a group resulted in a **lower risk of stroke/systemic embolism** compared to warfarin. (Jia 2014(33), Providencia 2014(34)).
When considering only the 'high dose' treatment arms (excluding the treatment arms of dabigatran 110 mg and edoxaban 30 mg), the difference remained statistically significant (Ruff 2014(32), Jia 2014(33)).
Pooling of all Factor Xa inhibitors also revealed a statistically significant reduction in risk of stroke compared to warfarin.
The lower risk of total stroke/SE with the DOACs was mainly driven by a **lower risk of hemorrhagic stroke** with the DOACs. **No statistically significant difference in risk of ischemic stroke** was observed (Ruff 2014(32), Jia 2014(33), Providencia 2014(34)).
When pooling the **lower doses** of dabigatran and edoxaban and comparing them to warfarin, the difference in risk of stroke/SE was **not statistically significant**. This too was influenced by the reduced risk of hemorrhagic stroke with the low-dose DOACs; **the risk of ischemic stroke was increased** with low dose DOACs (dabigatran/edoxaban) compared to warfarin (Ruff 2014(32), Jia 2014(33)).

4.2.1.2 Mortality

In all meta-analyses, treatment with DOACs resulted in a **lower mortality rate** compared to warfarin (Ruff 2014(32), Jia 2014(33), Providencia 2014(34)).

4.2.1.3 Major bleeding

For major bleeding, **DOACs as a group caused less major bleeding** compared to warfarin (Providencia 2014(34)).
Pooling only the '**high dose'** regimens, the lower rate of major bleeding with DOACs only reached **borderline** statistical significance (Ruff 2014(32), Jia 2014(33)).
Pooling of the **lower dose** treatment arms (dabigatran/edoxaban) did **not** result in a statistically significant difference in major bleeding compared to warfarin (Ruff 2014(32), Jia 2014(33)).

Pooling of all **Factor Xa inhibitors** revealed **no statistically significant difference** in major bleeding compared to warfarin (Providencia 2014(34)).
The lower risk of major bleeding with the DOACs was influenced by a **lower risk of intracranial hemorrhage** with the DOACs (Ruff 2014(32), Jia 2014(33), Providencia 2014(34)).

4.2.1.4 Gastrointestinal bleeding

No statistically significant difference in gastro-intestinal bleeding was observed when comparing all DOACs to warfarin.
Considering only the '**high dose'** regimens, risk of gastro-intestinal bleeding was **higher with DOACs**.
Pooling the **lower dose** DOAC treatment arms (dabigatran/edoxaban), differences in gastro-intestinal bleeding rates did **not** reach statistical significance.

4.2.1.5 Myocardial infarction

No statistically significant difference in rates of myocardial infarction was observed when comparing all DOACs to warfarin. The results were similar when considering only the high dose treatment arms or when considering only the Factor Xa-inhibitors. When pooling the **low dose treatment arms** (dabigatran/edoxaban), a **higher rate** of myocardial infarction was observed with the DOACs.

4.3 DOAC vs DOAC in atrial fibrillation. Information from observational studies

Observational cohort studies comparing different DOACs may give us an indication of how the DOACs perform in real-world situations. However, in an observational study, one cannot assume a causal relationship between the drugs used and the clinical outcomes that are observed. Other factors, associated with the use of these drugs, may cause or may contribute to the observed effect.
Observational studies comparing different DOACs in AF are starting to emerge in the last couple of years. The (lower) quality of the data are influenced by the following factors:
- The follow-up time in these studies is still quite short (usually <1 year).
- Most data are derived from electronic prescription databases. The accuracy and completeness of the databases (e.g. about patient characteristics) may influence the results.
-As for all prescription information: the prescribing of a drug does not mean that the drug is actually taken (correctly) by the patient.
In the GRADE classification, observational studies start out as LOW quality of evidence. This score can be lowered to VERY LOW if there are problems with study quality, directness, precision…

We assess the quality of evidence from these observational studies to be VERY LOW, mainly due to the short follow-up time.

4.3.1 Apixaban vs dabigatran

4.3.1.1 Stroke

In 1 retrospective cohort study in 13 048 AF patients in the USA, **no statistically significant difference in stroke rate** was found between apixaban and dabigatran (Noseworthy 2016(35)).

4.3.1.2 Major bleeding

For major bleeding, the results are unclear.
In a Danish retrospective cohort study of 54 321 new OAC users, a **lower rate of major bleeding of borderline statistical significance** was observed with apixaban compared to dabigatran (Lamberts 2017(36)).
In a USA cohort study of 12 099 new OAC users, **no statistically significant difference** was observed (Lip 2016(37)).
In another USA cohort study of 13 084 new DOAC users, a **lower rate of major bleeding** was observed with apixaban compared to dabigatran (Noseworthy 2016(35)).
A systematic review found 5 additional cohort studies (conference abstracts) that reported no statistically significant difference in major bleeding rates between apixaban and dabigatran, although in 4 of these cohorts, apixaban had a numerically lower rate of major bleeding compared to dabigatran (Deitelzweig 2017(38)).

4.3.2 Apixaban vs rivaroxaban

4.3.2.1 Stroke

In 1 retrospective cohort study of 13 130 new DOAC users in the USA, **no statistically significant difference in stroke rates** was found between apixaban and rivaroxaban (Noseworthy 2016(35)).

4.3.2.2 Major bleeding

In 1 Danish and 2 American retrospective cohort studies of new OAC/DOAC users, **a higher rate of major bleeding was observed with rivaroxaban** compared to apixaban (Lamberts 2017(36), Lip 2016(37); Noseworthy 2016(35)).
A systematic review found 5 additional cohort studies (conference abstracts) that also reported a higher rate of major bleeding with rivaroxaban compared to apixaban (Deitelzweig 2017(38).

4.3.3 Dabigatran vs rivaroxaban

4.3.3.1 Stroke/SE

A meta-analysis of 6 observational cohort studies comparing found a **similar risk of stroke/systemic** embolism in rivaroxaban-users compared to dabigatran users (Bai 2017-175(39)).
Similar results were found in a more recent Taiwanese retrospective cohort study (Lai 2017(40)). (However, dosages used were low, and some patients in this cohort may have already been included in the meta-analysis).

4.3.3.2 Mortality

In the meta-analysis of 4 observational cohort studies, a **higher mortality** rate was observed in rivaroxaban users compared to dabigatran users (Bai 2017-175(39)).
Similar results were found in a more recent Taiwanese retrospective cohort study (Lai 2017(40)). (However, dosages used were low, and some patients in this cohort may have already been included in the meta-analysis).

4.3.3.3 Myocardial infarction

No statistically significant difference in rates of myocardial infarction was observed between rivaroxaban and dabigatran-users, in a meta-analysis of 2 observational cohort studies (Bai 2017-175(39)).
Similar results were found in a more recent Taiwanese retrospective cohort study (Lai 2017(40)). (However, dosages used were low, and some patients in this cohort may have already been included in the meta-analysis).

4.3.3.4 Bleeding

In a meta-analysis of 5 observational cohort studies in patients with atrial fibrillation, a **higher rate of major bleeding** was observed with rivaroxaban compared to dabigatran.
A systematic review found 1 additional cohort study (conference abstract) that also reported a higher rate of major bleeding with rivaroxaban compared to dabigatran (Deitelzweig 2017(38).
Similar results were also found in a more recent Taiwanese retrospective cohort study (Lai 2017(40)). (However, dosages used were low, and some patients in this cohort may have already been included in the meta-analysis).

Gastro-intestinal bleeding was also observed more frequently with rivaroxaban compared to dabigatran. For int**racranial bleeding, no statistically significant difference** was observed (Bai 2017-175(39)).
Similar results were found in a more recent Taiwanese retrospective cohort study (Lai 2017(40)). (However, dosages used were low, and some patients in this cohort may have already been included in the meta-analysis).

A Danish cohort study in 22 358 patients with NVAF reported **higher rates of any bleeding with rivaroxaban 20 mg** compared to dabigatran 150 mg. The difference for rivaroxaban 15 mg versus dabigatran 110 mg was not statistically significant (Gorst-Rasmussen 2016(41)).

4.4 DOACs in elderly patients with atrial fibrillation

Atrial fibrillation is a chronic condition. Anticoagulants to prevent stroke or systemic embolism will often be taken 'for life', or until a very advanced age. This means that it is important to examine the efficacy and safety of anticoagulants in older age groups. Physiological changes with advancing age, comorbidities, declining renal function, frailty… all these factors may influence the efficacy and safety of anticoagulants and alter the risk/benefit balance.
In this chapter, we take a closer look at the information that is available on the use of DOACs in elderly patients with atrial fibrillation (with special attention to those >75y). In the next chapter, we will focus on the use of DOACs in patients with impaired renal function.
We advise to compare the information in this chapter to the Summary of the Product Characteristics of each DOAC.

4.4.1 Information from RCTs

In all the RCTs, rates of stroke, major bleeding and mortality were higher in the older age groups.

4.4.1.1 Apixaban

In the ARISTOTLE trial (Granger 2011(23)), apixaban 5 mg 2x/d was compared to warfarin (INR 2-3). In this trial, participants with 2 or more risk factors for major bleeding (>80y, serum creatinine >1.5mg/dl or <60 kg) were given a reduced dose of apixaban of 2.5mg 2x/d.
5678 participants were >=75y.
A prespecified subgroup analysis for 3 age groups (<65y, 65 to 75y, >=75y) was performed (Granger 2011(23) and Halvorsen 2014(42)).

The results of the comparison of apixaban to warfarin in the different age groups were **consistent** with the overall trial results. In the two highest age groups, there were **lower rates of stroke and lower rates of major bleeding with apixaban** compared to warfarin; in participants <65 y, there were no statistically significant differences (possibly due to lack of power). No statistically significant difference between age groups was found.

4.4.1.2 Dabigatran

In the RE-LY trial ((24) dabigatran 110mg 2x/d was compared to dabigatran 150 mg 2x/d and to warfarin (INR 2-3)..
Post hoc subgroup analyses for different age groups were performed (<75y vs >=75y; >65y vs 65-75y vs >=75y; >75 vs 75-79 vs 80-85 vs >=85). (Eikelboom 2011(43) and Lauw 2017(44)). 7258 participants were >=75y.

For dabigatran 110mg 2x/d compared to warfarin, the results were as follows.
- For **stroke/systemic embolism** in participants <75y and participants >=75y the results were **consistent** with the overall trial results. There was **no statistically significant difference** in treatment effect for stroke/systemic embolism between both age groups (Eikelboom 2011(43))
-For **major bleeding,** the **younger age groups** (<75y) **had lower rates with dabigatran** 110 mg compared to warfarin, whereas similar rates were seen in the participants >=75y. The difference between both age groups **was statistically significant** (Eikelboom 2011(43)).

For dabigatran 150mg 2x/d compared to warfarin, the results were as follows.
- For stroke/systemic embolism in participants <75y and participants >=75y the results were **consistent** with the overall trial results. There were **lower rates of stroke/systemic embolism** with dabigatran 150 mg compared to warfarin in both age groups. No statistically significant difference between age groups was found.
-For **major bleeding**, with dabigatran 150 mg, **lower rates of major bleeding were seen in the younger** age groups (<75y), whereas similar rates were observed in patients >=75y (Eikelboom 2011(43)). When further dividing the patients >= 75y in different age segments, **similar (75-79y) or even higher rates** (80-85y) of major bleeding were seen **with dabigatran 150 mg compared to warfarin**. The difference in treatment effect between the different age groups **was statistically significant** (Lauw 2017(44)).

4.4.1.3 Edoxaban

In the ENGAGE AF-TIMI 48 trial ((28)), edoxaban 60 mg/d was compared to edoxaban 30mg/d and to warfarin (INR 2-3).
In this trial, 25.3% of participants were given a reduced dose (edoxaban 30mg /d instead of 60mg/d or 15mg/d instead of 30mg/d) if the eGFR was 30-50ml/min, if they were <= 60 kg or if there was concomitant use of verapamil, quinidine or dronedarone.
8474 participants were >=75y.

A prespecified subgroup analysis for 3 age groups (<65y, 65 to 75y, >=75y) was performed (Giugliano 2013(28) and Kato 2016(45)).
The results of the comparison of edoxaban to warfarin in the different age groups were **consistent** with the overall trial results. There were no statistically significant differences between the age groups **on stroke/systemic embolism and on risk of major bleeding**.

Whether edoxaban 60 mg and edoxaban 30 mg were analysed separately or together, there was **no age-dependent effect on stroke/systemic embolism or on risk of major bleeding** compared to warfarin.

4.4.1.4 Rivaroxaban

In the ROCKET AF trial ((29)) rivaroxaban 20 mg/d was compared to warfarin (INR 2-3). Dose reduction of rivaroxaban to 15mg/d was required for patients with CrCl 30-49ml/min.
6229 participants were >=75y.

A pre-specified subgroup analysis for 2 age groups (<75y, >=75y) was performed (Halperin 2014(46)).
The results of the comparison of rivaroxaban to warfarin in the different age groups are **consistent** with the overall trial results. **No statistically significant difference for stroke/systemic embolism or for major bleeding** was seen between rivaroxaban and warfarin**, in both age groups.** No statistically significant difference between age groups was found.

4.4.2 Information from meta-analyses

4.4.2.1 Stroke/systemic embolism

In a meta-analyses in patients >=75y, pooling the 4 pivotal trials comparing DOACs to VKA in atrial fibrillation showed **a lower risk of stroke/systemic embolism** with DOACs compared to VKA.
When only the **low dose of dabigatran and edoxaban** were considered, the difference was **not statistically significant** (Sadlon 2016 2016(47)).

A subgroup analysis comparing the DOACs to VKA in the age groups <75y and >=75y found no statistically significant difference in treatment effect between both age groups (Ruff 2014(32)).

4.4.2.2 Bleeding outcomes

In a meta-analysis in patients >= 75 y, **no statistically significant difference in risk of major and clinically relevant non-major bleeding** was found when comparing **the 4 DOACs** to VKA, if considering only the **high dose** treatment arms for dabigatran and edoxaban (Sadlon 2016(47)).

When pooling the **low dose** treatment arms of dabigatran and edoxaban together with apixaban and rivaroxaban, a **lower rate of major and clinically relevant non-major bleeding** was seen with the DOACs compared to VKA (Sadlon 2016(47)).
In both analyses, a **high heterogeneity** was found, that could not be explained by several sensitivity analyses. A difference in population in the included studies (different bleeding risk) or a difference in treatment effect between the DOACs may be the cause of the heterogeneity (Sadlon 2016(47), Sharma 2015(48)).
A subgroup analysis comparing the DOACs to VKA in the age groups <75y and >=75y found **no statistically significant difference** in treatment effect for major bleeding **between both age groups** (Ruff 2014(32)).

4.5 DOACs in patients with impaired renal function and atrial fibrillation

In this chapter, we examine the available data with DOACs in patients with impaired renal function. Some patients with AF may have impaired renal function when starting OAC, others may develop renal impairment with advancing age. In both cases, it is important to examine the risk/benefit ratio of DOACs compared to warfarin.

4.5.1 Information from RCTs: analyses according to baseline renal function

Overall, patients with a lower eGFR had higher rates of stroke and major bleeding.

4.5.1.1 Apixaban

In the ARISTOTLE trial (Granger 2011(23)), apixaban 5 mg 2x/d was compared to warfarin (INR 2-3). In this trial, participants with 2 or more risk factors for major bleeding (>80y, serum creatinine >1.5mg/dl or <60 kg) were given a reduced dose of apixaban of 2.5mg 2x/d. 3017 participants had an eGFR ≤50 mL/min. Patients with eGFR < 25 ml/min were excluded from the trial.

A pre-specified subgroup analysis according to baseline renal function (Cockroft-Gault) was performed (>80 mL/min vs 50–80 mL/min vs ≤50 mL/min) (Granger 2011(23) and Hohnloser 2012(49)).
The results were as follows.
-**For stroke/systemic embolism,** the effect of apixaban was consistent with the overall trial results and there were no differences between the groups with different degrees of renal impairment.
- For **major bleeding,** the results were not uniform across subgroups: apixaban resulted in **lower rates of major bleeding** compared to warfarin but the difference was more pronounced in the **lower eGFR range** (eGFR<=50ml/min) and was not significant in eGFR >80ml/min. The difference between the subgroups was statistically significant.
Similar results were found when eGFR was calculated according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).

4.5.1.2 Dabigatran

In the RE-LY trial ((24) dabigatran 110mg 2x/d was compared to dabigatran 150 mg 2x/d and to warfarin (INR 2-3). 3554 participants had an eGFR ≤50 mL/min. Patients with eGFR < 30 ml/min were excluded from the trial.

A pre-specified subgroup analysis according to baseline renal function (Cockroft-Gault) was performed (>=80 mL/min vs 50–79 mL/min vs ≤50 mL/min) (Hijazi 2014(50)).

For dabigatran 110mg 2x/d compared to warfarin, the results were as follows.
- For **stroke/systemic embolism,** the results across the different subgroups were **consistent** with the overall trial results and there were no statistically significant differences between groups with different degrees of renal impairment.
-For **major bleeding**, the results were **not uniform across subgroups: dabigatran 110mg was associated with lower bleeding rates** compared to warfarin in patients **with eGFR 50-79 and eGFR >=80ml/min,** while in patients with eGFR < 50 ml no difference was observed.

The difference in treatment effect between subgroups was not statistically significant when eGFR was calculated with Cockroft-Gault, but was statistically significant when calculated with CKD-EPI and with MDRD.

For dabigatran 150mg 2x/d compared to warfarin, the results were as follows.
-For **stroke/systemic embolism,** the results across the different subgroups were **consistent** with the overall trial results.
-For **major bleeding**, the results were **not consistent**. When calculated with Cockroft-Gault, renal function appeared to have no impact on the treatment effect of dabigatran 150 compared to warfarin. However, when eGFR was calculated with CKD-EPI or with MDRD, a statistically significant difference between subgroups was observed: **dabigatran 150mg was associated with lower bleeding rates** compared to warfarin in patients **with eGFR>=80ml/min,** while this was not the case in the two other groups.

4.5.1.3 Edoxaban

In the ENGAGE AF-TIMI 48 trial ((28)), edoxaban 60 mg/d (high dose treatment arm) was compared to edoxaban 30mg/d (low dose treatment arm) and to warfarin (INR 2-3).
25.3% of participants were given a reduced dose (edoxaban 30mg/d instead of 60mg/d in the high dose treatment arm or 15mg/d instead of 30 mg/d in the low dose treatment arm) if the eGFR was 30-50ml/min, if they were <= 60 kg or if there was concomitant use of verapamil, quinidine or dronedarone.
2740 participants had an eGFR <=50ml/min. Patients with eGFR < 30 ml/min were excluded from the trial.

A pre-specified subgroup analysis according to baseline renal function (Cockroft-Gault) was performed in the high dose treatment arm edoxaban (60mg or reduced to 30 mg if any of the above risk factors). Subgroups were >50ml/min vs ≤50 mL/min. (Bohula 2016(51))
The results were as follows.
-For **stroke/systemic embolism,** the results of the comparison of edoxaban to warfarin according to baseline renal function was **consistent** with the overall trial results: in both subgroups, there was no statistically significant difference between 'high dose' edoxaban and warfarin and there were no differences between the groups with different degrees of renal impairment.
Rates of **major bleeding** were lower with 'high dose' edoxaban compared to warfarin in both subgroups. No statistically significant difference between subgroups was found.

4.5.1.4 Rivaroxaban

In the ROCKET AF trial ((29)) rivaroxaban 20 mg/d was compared to warfarin (INR 2-3). Dose reduction of rivaroxaban to 15mg/d was used for 2950 patients with CrCl 30-49ml/min.

A pre-specified subgroup analysis according to baseline renal function (<eGFR 30-49ml/min vs eGFR>=50ml/min) was performed (Fox 2011(52)).
The results of the comparison of rivaroxaban to warfarin in the groups with different degrees of renal impairment concerning **stroke/systemic embolism** and **major bleedings** are **consistent** with the overall trial results and there were no differences between the groups.

4.5.2 Information from RCTs: change of renal function throughout trial

For 2 of the major DOAC trials (apixaban, rivaroxaban), we found a post-hoc **subgroup analysis according to worsening (versus stable) renal function over time**. The treatment effect of DOAC versus warfarin was compared in patients who experienced a declining renal function of >20%CrCl throughout the trial and patients without such decline.
The results in patients with worsening renal function over time was consistent with the overall trial results and there were no differences between subgroups (Bohm 2014(53), Fordyce 2016(54)).

The evolution of the **renal function throughout time** (and the possible influence of the OAC on the decline in renal function) was compared between patients on DOACs and patients on warfarin in 3 trials (apixaban, dabigatran, rivaroxaban) (Hijazi 2016(55); Bohm 2014(53); Fordyce 2016(54)). Throughout the trials with dabigatran and rivaroxaban, patients taking warfarin had a small but statistically significant stronger decline in renal function, compared to patients taking the DOAC (absolute difference of 1 ml/min) (Bohm 2014(53); Fordyce 2016(54)). In the apixaban trial, no numbers were given, but differences in decline of renal function were described as small and possibly affected by confounding factors (Hijazi 2016(55)).

Since these are all post hoc analysis, using observational data from the trials, with complete loss of randomization and causality, more research is needed to make any firm statements.

4.5.3 Information from meta-analyses

4.5.3.1 Stroke/systemic embolism

A meta-analysis comparing DOACs to VKA in AF patients, according to different levels of creatinine clearance found **no evidence of a difference in treatment effect** for stroke/SE between the different subgroups (Ruff 2014(32)).

4.5.3.2 Bleeding outcomes

A meta-analysis comparing DOACs to VKA in patients with AF and an estimated creatinine clearance (eCrCl) of 50-80 mL/min or <50mL/min reported a **lower risk of hemorrhagic stroke with DOACs** in both subgroups (Raccah 2016(56)). This is consistent with the overall trial results.

For **major bleeding**, a **lower risk** was observed with DOACs in patients with an **eCrCl of 50-80mL/min** compared to VKA. For patients with an **eCrCl<50mL/min**, the difference between DOACs and VKA was **not statistically significant** and a high heterogeneity was observed (Raccah 2016(56)). Another meta-analysis comparing DOACs to VKA in AF patients, according to different levels of creatinine clearance found **no evidence of a difference in treatment effect** for stroke/SE or major bleeding between the different subgroups (Ruff 2014(32)).

4.6 Dabigatran and the risk of myocardial infarction

Some questions have been raised about a possible increased risk of myocardial infarction with the use of dabigatran (compared to warfarin). In this chapter, we discuss some of the literature concerning this issue. Note: for apixaban, edoxaban and rivaroxaban this apparent increased risk was not observed.

4.6.1 RCTs

RE-LY dabigatran 150 vs warfarin in AF	
Myocardial infarction	**Original article** Dabigatran 150mg: 89/6076; 0.74%/y Warfarin: 63/6022; 0.53%/y **RR 1.38 (95%CI 1.00-1.91)** **SS more MI in dabigatran group** **p = 0.048** **NNH (2y): 238 (95%CI ∞ to 104)** **After revision** *(26)- total MI* Dabigatran 150mg: 97/6067 0.81%/y Warfarin: : 75/6022 ; 0.64%/y RR 1.27 (95%CI 0.94–1.71) NS p = 0.12

In the original publication of the RE-LY trial that compared dabigatran to warfarin in non-valvular atrial fibrillation, a higher rate of myocardial infarction was found with dabigatran 150 mg (RR 1.38; 95%CI 1.00-1.75) compared to warfarin. Later, a revision of these data was published: after adding some MIs that were previously overlooked (both silent MI and clinical MI), the difference between dabigatran 150 mg and warfarin was no longer statistically significant (RR 1.27; 95%CI 0.94 – 1.71). If we look at the **absolute risk** in the **original data,** dabigatran 150 mg was associated with a **0.21%** risk increase per patient per year compared to warfarin. In this scenario 238 similar patients would have to be treated with dabigatran for 2 years, to cause 1 additional MI compared to warfarin (95% CI ∞ to 104).

RE-LY dabigatran 110 vs warfarin in AF	
Myocardial infarction	Original article Dabigatran 110mg: 86/6015; 0.82%/y Warfarin: 63/6022 0.53%/y RR 1.35 (95%CI 0.98–1.87) p=0.07 After revision (26)- *total MI* Dabigatran 110mg: n=98/6015 0.82%/y Warfarin: 75/6022 ; 0.64%/y RR 1.29 (95%CI 0.96–1.75) p=0.09

For dabigatran 110 mg, in the original data as well as the revised data of the RE-LY trial, the difference in the rate of MI was not statistically significant compared to warfarin.

RE-MEDY dabigatran 150 vs warfarin after at least 3 months of continuous anticoagulation	
Acute coronary syndrome:	Dabigatran: 13/1430 (0.9%) Warfarin: 3/1426 (0.2%) **p= 0.02 in favour of warfarin** **NNH (1y)= 143**

In the RE-MEDY trial that compared dabigatran to warfarin in the extended treatment of VTE (after at least 3 months of oral anticoagulation), a higher rate of acute coronary syndrome was also observed with dabigatran (0.9% vs 0.2%; p=0.02).

RE-COVER I and II dabigatran 150 vs warfarin in VTE	
Acute coronary syndrome	Dabigatran:9/2553; 0.4% Warfarin:5/2554; 0.2% NS

No statistically significant difference between dabigatran and warfarin was found in the RE-COVER I and II trials, that compared dabigatran to warfarin in the treatment of VTE.

4.6.2 Meta-analyses

The production company of dabigatran performed a meta-analysis with individual participant data from all phase II and III trials that compared dabigatran to any other comparator (Clemens 2013(57)). In the pooled analysis of **individual patient data comparing dabigatran with warfarin** (in the indications of atrial fibrillation and VTE, i.e. the trials mentioned above**), a higher rate of myocardial infarction was observed with dabigatran 150 mg**, which was statistically significant OR 1.42, (95% CI 1.07–1.88). For dabigatran 110 mg, the difference was not statistically significant (OR1.30; 95% CI 0.96–1.76).
The authors found no difference in MI rates in the trials that compared dabigatran to enoxaparin (in the prevention of VTE during surgery) or in the trials that compared dabigatran to placebo (either for the long-term secondary prevention of VTE or for acute coronary syndrome). However, our confidence in these estimates is limited by the wide confidence interval, the short follow-up times and the pooling of different indications. *(GRADE for dabigatran vs enoxaparin and dabigatran vs placebo VERY LOW quality of evidence).*
Based on all the above analyses, the authors of this patient-level meta-analysis conclude that well-controlled warfarin may have a protective effect against MI, while dabigatran may not necessarily increase the risk of MI.

Another meta-analysis (Uchino 2012(58)) pooled all the (seven) trials comparing dabigatran to any comparator (warfarin, enoxaparin, placebo) and concluded that **dabigatran (any dose) was associated with an increased risk of MI when compared to any other treatment** (1.19%) vs (0.79%); OR 1.33; 95% CI 1.03-1.71. Sensitivity analysis using the revised RE-LY data or excluding short-term trials had similar results. No analysis was done for each separate comparator, or for the separate indications.
A third meta-analysis of 12 RCTs, by Douxfils 2014 ((59) had wider inclusion criteria, and stratified the analyses by comparator and by dose of dabigatran. This analysis comes to mostly similar conclusions.
- **Dabigatran (any dose) was associated with an increased risk of MI when compared to any other treatment** (warfarin, enoxaparin, placebo) (OR 1.34; 95%CI 1.08—1.65).
- **Dabigatran was associated with an increased risk of MI when compared to warfarin** (Dabigatran any dose: OR 1.41; 95%CI 1.11—1.80; dabigatran 150 mg: OR 1.43; 95%CI 1.08 - 2.47).

We would like to point out that all of the above analyses were mostly driven by the large weight of a small number of trials (e.g. large weight for RE-LY for the comparison vs warfarin).

4.6.3 Observational studies

This increased risk of MI with dabigatran compared to VKA was not found in a meta-analysis of **observational data (Darwiche 2016(60)).**

Note: *According to our inclusion criteria, this reference should not have been included in our review, because this is an observational comparison between DOACs and VKA (and therefor subject to considerable bias). However, the organizing committee asked us to look at the MI issue with dabigatran. This is why we briefly mention this publication.*

When pooling of all the observational studies comparing dabigatran to VKA in atrial fibrillation, no statistically significant difference was found for MI (RR 0.98; 95%CI 0.86-1.13). In OAC naïve users, the risk of MI was lower with dabigatran 150 mg than with VKA (RR 0.82; 95%CI 0.71–0.96). In dabigatran 110 mg users that had switched from VKA, a higher risk of MI was found (RR 1.40; 95%CI 1.04–1.88).

Of course we need to consider the observational setting: **no causality between the drug and the observed endpoint can be inferred** – it may be the different patient characteristics that are responsible for the effect. In this meta-analysis, it is also not clear how MI was diagnosed/defined in each of the included observational studies. Another important limitation is a possible selection bias: the choice between prescribing dabigatran or a VKA will be influenced by a lot of factors, not all of which can be measured or predicted.

The data do suggest, according to the authors of the meta-analysis, that the way in which dabigatran is currently selected in clinical practice is not associated with an increased risk of MI, compared to the current use and selection of warfarin (Darwiche 2016(60)).

4.6.4 GRADE and additional remarks

The quality of evidence concerning a possible increased risk with dabigatran compared to warfarin is influenced by the quality of the included trials, by some inconsistencies in the results and by the relative short follow-up times in some of the included studies. It is also important to note the boundaries of the confidence interval of the above results: the confidence interval ranges from no (clinically relevant) difference between dabigatran and warfarin, and ranges towards a clinically relevant benefit of warfarin.

More data are needed to make a definitive statement.

GRADE: LOW quality of evidence.

The whole debate about a possible risk increase of myocardial infarction with dabigatran must of course be weighed against other risks and benefits of both dabigatran and warfarin in the indication for which they are used; a wider risk-benefit profile of all the major clinical endpoints will give us a more nuanced perspective.

5 VTE. Summary and conclusions

5.1 DOAC versus standard treatment in the (initial and) extended treatment of VTE. RCTs

5.1.1 Apixaban versus enoxaparin/warfarin for acute VTE

Apixaban 10mg bid, followed by 5mg bid versus enoxaparin followed by warfarin (INR 2-3) for acute VTE			
Bibliography: Agnelli 2013-AMPLIFY(61)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	5395 (1 study) 6m	Apixaban: 1.5% Enox+warf: 1.9% RR=0.79 (0.53 to 1.19) NS	⨁⨁⨁⨀ **MODERATE** Study quality:-1 unclear allocation concealment and assessor blinding, low event rates, incomplete ITT Consistency:NA Directness: OK Imprecision: OK
Recurrent symptomatic VTE or death related to VTE (PO)	5395 (1 study) 6m	2.3% vs 2.7% RR= 0.84 (0.60 to 1.18), **p-value for non-inferiority < 0.001**	⨁⨁⨁⨀ **MODERATE** Study quality:-1 incomplete non-inferiority testing, and unclear allocation concealment and assessor blinding Consistency:NA Directness: OK Imprecision: OK
Major bleeding (PO)	5395 (1 study) 6m	0.6% vs 1.8% **RR=0.31 (95%CI 0.17 to 0.55)** **SS in favour of apixaban** *estimated NNT/6m: 84 (67-124)*	⨁⨁⨁⨀ **MODERATE** Study quality:-1 non-inferiority design, and unclear allocation concealment and assessor blinding Consistency:NA Directness: OK Imprecision: OK
Clinically relevant non-major bleeding	5395 (1 study) 6m	3.8% vs 8.0% **RR=0.48 (95%CI 0.38 to 0.60)** **SS in favour of apixaban** *estimated NNT/6m: 24 (21-32)*	⨁⨁⨁⨀ **MODERATE** Study quality:-1 Consistency:NA Directness: OK Imprecision: OK

In this trial, patients with acute VTE (DVT or PE) were randomized to treatment with apixaban (10mg twice daily for 7 days, followed by 5mg twice daily) or conventional treatment (enoxaparin 1mg/kg/12h for at least 5 days, and warfarin begun concomitantly – INR target 2-3).
About 86% of patients had received treatment with LMWH, heparin or fondaparinux prior to randomization (about 55% up to 24 h, about 30% up to 48 h). This means that we have insufficient data about the efficacy of apixaban compared to enoxaparin in the first 24-48 hours of treatment.
Duration of treatment and follow-up was 6 months. This was a non-inferiority trial.
Patients with CrCl<25 ml/min were excluded from the trial.

Our confidence in the results of this trial is somewhat impaired by the incomplete testing for non-inferiority (no per-protocol testing) and the exclusion of a number of patients from the ITT population without a clear explanation.

Mortality was not significantly different between treatment groups.
GRADE: MODERATE quality of evidence

Apixaban was found to be non-inferior to conventional treatment for the composite endpoint of recurrent symptomatic VTE or death related to VTE.
GRADE: MODERATE quality of evidence

Rates of major bleeding and clinically relevant non-major bleeding were significantly lower with apixaban compared to conventional treatment.
GRADE: MODERATE quality of evidence

Additional study:
A small Japanese RCT (AMPLIFY-J) in 80 patients with acute VTE that compared apixaban to UFH/warfarin (INR 1.5 – 2.5) found a higher rate of a composite endpoint of major and clinically relevant non-major bleeding with warfarin (Nakamura 2015(62)).

5.1.2 Dabigatran versus warfarin for acute VTE after 5-9 days of initial treatment

Dabigatran 150mg bid versus warfarin (target INR 2.0 to 3.0) for VTE, after initial parenteral anticoagulation for 5-9 days			
Bibliography: Schulman 2014 (63): included RE-COVER I(64) and RE-COVER II(65)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	5107 (2 studies) 6m	1.8% vs 1.8% RR: 1.00 (95%CI, 0.67 to 1.51) NS	⊕⊕⊕⊖ **MODERATE** Study quality:-1 >10% drop-out, no ITT, Consistency: OK Directness: OK Imprecision: OK
Recurrent VTE	5107 (2 studies) 6m	2.4% vs 2.2% RR: 1.09 (95%CI, 0.76 to 1.57) NS p<0.001 for non-inferiority	⊕⊕⊕⊖ **MODERATE** Study quality:-1 wide margin Consistency: OK Directness: OK Imprecision: OK
Major bleeding	5107 (2 studies) 6m	2.4% vs 2.2% RR: 1.09 (95%CI, 0.76 to 1.57) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 Consistency: OK Directness: OK Imprecision:-1 wide CI
Major or clinically relevant non-major bleeding	2564 (1 study) 6m	Schulman 2009 only **5.6% vs 8.8%** **HR: 0.63(95%CI 0.47 to 0.84)** **SS in favor of dabigatran** *estimated NNT/6m: 32 (22-71)*	⊕⊕⊕⊖ **MODERATE** Study quality:-1 non-inferiority trial, >10% exclusion, no ITT Consistency: OK Directness: OK Imprecision: OK
Acute coronary syndrome		Dabigatran:9/2553; 0.4% Warfarin:5/2554; 0.2% NS	⊕⊕⊖⊖ **LOW** Study quality:-1 non-inferiority trial, >10% exclusion, no ITT Consistency: OK Directness: OK Imprecision:-1 low event rate

Two trials (Schulman 2009 – RE-COVER I and Schulman 2011 – RE-COVER II) compared dabigatran 150 mg twice daily to warfarin treatment (INR target 2-3), after initial parenteral anticoagulation for 5-9 days in patients with acute VTE. A meta-analysis of both trials was performed. Both trials were non-inferiority trials.
Patients with CrCl<30 ml/min were excluded from the trial.

Please note that we have no information on the use of dabigatran in the initial treatment (5-9 days) of VTE.
Our confidence in the results is lowered by the incomplete non-inferiority testing and a wide non-inferiority margin.

There is **no significant difference in mortality** between dabigatran treatment and warfarin treatment.

GRADE: MODERATE quality of evidence

Rates **of recurrent VTE** were not significantly different between both treatments. Dabigatran is found to be **non-inferior** to warfarin in the prevention of recurrent VTE. Pre-specified margins for non-inferiority were high.
GRADE: MODERATE quality of evidence

There is **no significant difference in major bleeding events** between both treatments.
GRADE: LOW quality of evidence

Treatment with dabigatran resulted in lower rates of all bleeding events and lower rates of the composite of major and clinically relevant non-major bleeding events, compared to warfarin.
GRADE: MODERATE quality of evidence

There is **no significant difference in rates of myocardial infarction** between both treatments. (See also chapter 'Dabigatran and myocardial infarction')
GRADE: LOW quality of evidence

Additional analyses:
A pre-specified subgroup analysis of these trials according to whether the index event was a DVT or a PE, found results in both subgroups that were comparable to the overall trial results; no statistically significant difference in treatment effect (for efficacy as well as safety) between patients with DVT and patients with PE were found (Goldhaber 2016(66)).

5.1.3 Edoxaban versus enoxaparin/warfarin for acute VTE after at least 5 days of initial treatment

Edoxaban 60 mg 1x/d vs warfarin for VTE			
Bibliography: Hokusai-VTE 2013 (67)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	8292 (1 study) 12m	3.2% vs 3.1% no analysis	not applicable
Recurrent symptomatic VTE (PO)	8292 (1 study) 12m	3.2% vs 3.5% HR: 0.89 (0.70 – 1.13) **p<0.001 for non-inferiority**	⨁⨁⨁⨀ **MODERATE** Study quality:-1 incomplete non-inferiority testing Consistency:NA Directness: OK Imprecision: OK
Major bleeding	8292 (1 study) 12m	1.4% vs 1.6% HR: 0.84 (0.59 – 1.21) NS	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency:NA Directness: OK Imprecision:-1
Major or clinically relevant bleeding event	8292 (1 study) 12m	8.5% vs 10.3% HR: 0.81 (0.71 – 0.94) p=0.004 **SS more bleeding with warfarin** *estimated NNT/treatment duration: 56(34-162)*	⨁⨁⨁⨀ **MODERATE** Study quality:-1 unclear description of blinding concealment, only 1 trial Consistency:NA Directness: OK Imprecision: OK

In this non-inferiority RCT, edoxaban 60 mg was compared to warfarin (INR 2-3) in patients with acute symptomatic VTE. Patients with CrCL <50 ml/min and body weight <60kg received 30mg of edoxaban. The mean age was 55.8y. Follow-up was 12 months.
Patients with CrCl<30 ml/min were excluded from the trial.
All patients received initial therapy with open-label enoxaparin or unfractionated heparin for at least 5 days.
Duration of treatment was 3, 6 or 12 months, decided by the treating physician before randomization.

Please note that we have no information on the use of edoxaban in the first 5 days of treatment of VTE.

Our confidence in the results is lowered by the incomplete non-inferiority testing (no per-protocol analysis).

There was no statistical analysis done for mortality rates.

Edoxaban was **non-inferior to warfarin in the prevention of recurrent symptomatic VTE**.

GRADE: MODERATE quality of evidence

No statistically significant **difference in major bleeding** rates was found between edoxaban and warfarin.
GRADE: MODERATE quality of evidence

A **lower rate of major or clinically relevant non-major bleeding** was found with edoxaban compared to warfarin.
GRADE: MODERATE quality of evidence

5.1.4 Rivaroxaban versus enoxaparin/vitamin K antagonist for acute VTE

Rivaroxaban 15mg bid, then 20mg/d versus standard therapy with enoxaparin1mg/kg bid followed by adjusted dose VKA (warfarin or acenocoumarol) in patients with symptomatic DVT or PE			
Bibliography: Einstein DVT 2010(68), Einstein PE 2012(69)			
Outcomes	**N° of participants (studies) Follow up**	**Relative effect (95% CI)** ***Absolute effect***	**Quality of the evidence (GRADE)**
Mortality	8281 (2 studies) 3, 6 or 12m	Einstein 2010 (DVT patients) 2.2% vs 2.9% HR: 0.67 (95% CI 0.44 to 1.02) Einstein PE 2012 (PE patients) 2.4% vs 2.1% HR=1.13 (95%CI 0.77 to 1.65)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 open label, non-inferiority design, low TTR in VKA group Consistency: OK Directness: OK Imprecision: OK
Symptomatic recurrent VTE (PO)	8281 (2 studies) 3, 6 or 12m	Einstein 2010 (DVT patients) 2.1% vs 3.0% **HR: 0.68 (95 % CI 0.44 to 1.04); SS,** p<0.001 for non-inferiority Einstein PE 2012 (PE patients) 2.1% vs 1.8% **HR= 1.12 (95% CI 0.75 to 1.68) SS,** p=0.003 for non-inferiority	⊕⊕⊕⊖ **MODERATE** Study quality:-1 open label, unclear non-inferiority reporting Consistency: OK Directness: OK Imprecision: OK ⊕⊕⊖⊖ **LOW** Study quality:-1 open label, unclear non-inferiority reporting Consistency: OK Directness: OK Imprecision:-1 very wide non-inferiority margin…
Major or clinically relevant non-major bleeding (PO)	8281 (2 studies) 3, 6 or 12m	Einstein 2010 (DVT patients) 8.1% vs 8.1% HR: 0.97 (95% CI 0.76 to 1.22) Einstein PE 2012 (PE patients) 10.3% vs 11.4% HR= 0.90 (95% CI 0.76 to 1.07)	⊕⊕⊕⊖ **MODERATE** Study quality:-1 open label, low TTR in VKA group Consistency: OK Directness: OK Imprecision: OK
Major bleeding	8281 (2 studies) 3, 6 or 12m	Einstein 2010 (DVT patients) 0.8% vs 1.2% HR: 0.65 (95% CI 0.33 to 1.30) Einstein PE 2012 (PE patients) 1.1% vs 2.2% **HR: 0.49 (95% CI 0.31 to 0.79)** **SS in favour of rivaroxaban** *estimated NNT/treatment duration: 91(66-217)*	⊕⊕⊖⊖ **LOW** Study quality:-1 Consistency:-1 Directness: OK Imprecision: OK

Two non-inferiority open label RCTs compare oral rivaroxaban to standard treatment with enoxaparin followed by adjusted dose vitamin K antagonist (warfarin or acenocoumarol) in the treatment of symptomatic VTE. One trial (Einstein DVT 2010) includes only patients with

symptomatic DVT (excluding symptomatic PE), the other trial (Einstein PE 2012) includes patients with symptomatic PE (with or without DVT).
In the Einstein DVT trial, about 72% of patients had received 1 or 2 days of treatment with LMWH, heparin or fondaparinux prior to randomization. In the Einstein PE trial, about 92% of patients had received 1 or 2 days of pre-randomization treatment. This means that we have insufficient data about the efficacy of rivaroxaban compared to enoxaparin in the first 24-48 hours of treatment.
Duration of treatment was 3, 6 or 12 months, decided by the treating physician before randomization.
Patients with CrCl<30 ml/min were excluded from the trial.
The mean age was 56 y for DVT and 58y for PE.

Our confidence in the results is lowered by the incomplete non-inferiority testing (no per-protocol analysis) and a very wide non-inferiority margin.

No significant difference in mortality is observed between both treatment regimens.
GRADE: MODERATE quality of evidence

Rivaroxaban is non-inferior to standard treatment with enoxaparin and VKA in preventing recurrent symptomatic VTE.
GRADE: MODERATE quality of evidence for DVT
GRADE: LOW quality of evidence for PE

No significant difference in total major or clinically relevant non-major bleeding is observed between both treatment groups.
GRADE: MODERATE quality of evidence

In patients with PE, there is significantly less major bleeding with rivaroxaban compared to standard treatment. In patients with DVT, this difference is not significant.
GRADE: LOW quality of evidence

5.2 DOACs versus standard treatment in the (initial and) extended treatment of VTE. Meta-analyses

Several meta-analyses comparing DOACs to LMWH followed by BKA in the prevention of recurrent VTE have been published. The results vary according to the inclusion criteria. It is advisable to interpret these results with caution and to take the results in the individual trials into account.

Also note that in some RCTs (RE-COVER and HOKUSAI), patients received a DOAC only after (5-9 days) initial parenteral anticoagulation. This is another argument against pooling of all the DOAC trials in VTE.

5.2.1 Recurrent VTE

A meta-analysis that pools the results of all the trials comparing DOACs (apixaban, dabigatran, edoxaban, rivaroxaban) to standard therapy in the initial/extended treatment of VTE (Dentali 2015(70)) found **no statistically significant** difference in recurrent VTE or VTE related death between **DOACs and standard therapy** when analyzing all patients, or when analyzing only patients with PE or with DVT.

A meta-analysis that compared **factor Xa inhibitors** (apixaban, edoxaban, rivaroxaban) to **standard therapy** in **patients with PE** also found **no statistically significant difference** in recurrent VTE or recurrent PE (Cochrane Robertson 2015(71)).

Another meta-analysis, comparing the factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) to standard therapy in **patients with DVT** found no statistically significant difference in recurrent VTE, but did **find a lower rate of recurrent DVT** with the Factor Xa inhibitors (OR 0.75; 95%CI 0.57, 0.98) (Cochrane Robertson 2015 (72)).

5.2.2 Bleeding outcomes

DOACs as a group (apixaban, dabigatran, edoxaban, rivaroxaban) showed **a lower risk of major/clinically relevant non-major bleeding** compared to standard therapy when **analyzing all patients** (RR 0.64; 95%CI 0.47-0.86), or when **analyzing only patients with PE**. For patients with **DVT**, the difference was **not statistically significant**. A high heterogeneity was observed in the analysis of PE patients (Dentali 2015(70)).

A meta-analysis that compared **factor Xa inhibitors** (edoxaban, rivaroxaban) to standard therapy in **patients with PE** found **no statistically significant difference in major bleeding** rates between both treatments (Robertson 2015(71))**.**

However, another meta-analysis comparing the factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) to standard therapy in **patients with DVT** found **a lower rate of major bleeding with factor Xa inhibitors (OR 0.57;95%CI 0.43, 0.76) (**Cochrane Robertson 2015 (72)).

5.3 DOACs versus standard treatment in elderly patients with acute VTE. Information from RCTs

5.3.1 Apixaban

In the RCT comparing apixaban to enoxaparin/warfarin for VTE, 759 patients were >=75y.
When comparing the treatment effect for recurrent VTE and major bleeding across different age subgroups, no statistically significant difference between these subgroups was found (AMPLIFY(61)).

5.3.2 Dabigatran

In the 2 RCTs comparing dabigatran to enoxaparin/warfarin for VTE, 529 patients were >=75y.
In subgroup analyses according to age, no difference in treatment effect for recurrent VTE was found between the subgroups. Subgroup analyses for bleeding outcomes were not reported. (63)

5.3.3 Edoxaban

In the RCT comparing edoxaban to enoxaparin/warfarin for VTE, 1104 patients were >=75y.
When comparing the treatment effect for recurrent VTE or major bleeding across different age subgroups, no statistically significant difference between these subgroups was found (67).

5.3.4 Rivaroxaban

For rivaroxaban, no statistical tests were reported for subgroup analyses.

5.4 DOACs versus standard treatment in patients with renal impairment and acute VTE. Information from RCTs

5.4.1 Apixaban

In the RCT comparing apixaban to enoxaparin/warfarin for VTE, 338 patients had a CrCl <=50ml/min. Patients with a CrCl <25 ml/min were excluded.

In subgroup analyses according to renal function, **no difference** in treatment effect for recurrent VTE or major bleeding was found between the subgroups (AMPLIFY(61)).

5.4.2 Dabigatran

In the RCT comparing dabigatran to enoxaparin/warfarin for VTE, 267 patients had a CrCl <50ml/min. Patients with a CrCl <30ml/min were excluded.
In subgroup analyses according to renal function, **no difference** in treatment effect for recurrent VTE was found between the subgroups. Subgroup analyses for bleeding outcomes were not reported (63).

5.4.3 Edoxaban

In the RCT comparing edoxaban to enoxaparin/warfarin for VTE, 541 patients had a CrCl <=50ml/min. Patients with a CrCl <30ml/min were excluded.
In subgroup analyses according to renal function, **no difference** in treatment effect for recurrent VTE or major bleeding was found between the subgroups (67).

5.4.4 Rivaroxaban

In the 2 RCTs comparing rivaroxaban to enoxaparin/VKA for VTE, 636 patients had a CrCl <50ml/min. Patients with a CrCl <30ml/min were excluded.
In subgroup analyses according to renal function, **no difference** in treatment effect for **recurrent VTE** was found between the subgroups.
For major bleeding, there was a difference between subgroups. In patients with normal renal function, rates of major bleeding were not different between rivaroxaban and VKA, but a benefit of rivaroxaban was observed in patients with mild renal impairment (CrCl 50-79ml/min) and an even larger benefit with moderate renal impairment (CrCl<50ml/min). This is because the rates of major bleeding increased with decreasing renal function in the VKA-treated group, but remained stable in rivaroxaban-treated patients.
For **clinically relevant major or non-major bleeding**, however, no such differences between subgroups were observed (Bauersachs 2014(73)).

5.5 DOACs versus warfarin for acute VTE, according to cTTR (center's time in the therapeutic range)

5.5.1 Apixaban

In the RCT comparing apixaban vs enoxaparin/warfarin for VTE, no statistical tests were reported for the subgroup analyses according to cTTR (AMPLIFY(61)).

5.5.2 Dabigatran

For dabigatran, we found no subgroup analyses according to cTTR.

5.5.3 Edoxaban

In the RCT comparing edoxaban to enoxaparin/warfarin for VTE, a subgroup analysis according to cTTR was peformed (<60% vs >=60%).

There was **no** statistically significant difference in treatment effect for **recurrent VTE** across different subgroups of cTTR.

There was however a statistically significant difference in **major bleeding** between the subgroups; in patients with a cTTR <60%, there was less major bleeding with edoxaban compared to warfarin. In patients with a cTTR>=60%, there was no statistically significant difference between edoxaban and warfarin. (67).

5.5.4 Rivaroxaban

For rivaroxaban, no statistical tests were reported for subgroup analyses.

5.6 Switching in VTE

We found no concrete information on switching from VKA to DOAC (or reverse) in VTE.

5.7 Low molecular weight heparin versus vitamin K antagonist for acute VTE

We found no new trials since our literature review for the Consensus Conference on VTE in 2014. In this chapter we will present the results that were reported in the previous report.

5.7.1 LMWH vs VKA in all patients with VTE

Long term LMWH versus VKA for patients with VTE			
Bibliography: meta-analysis Nice 2012 (74)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
All-cause mortality	2953 (16 studies) 3m-6m	16.5% vs 16.4% RR: 0.99 (95%CI 0.85 to 1.15)	⨁⨁⨁⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment, open label Consistency: OK Directness: OK Imprecision: OK
All-cause mortality – subgroup DVT	1872 (11 studies) 3m-6m	7.4% vs 6.7% RR: 1.1 (95%CI 0.79 to 1.51)	⨁⨁⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 wide CI
All-cause mortality – subgroup PE	162 (2 studies) 3m-6m	4.3% vs 0% RR: 3.28 (95%CI 0.38 to 28.33)	⨁⨁⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 wide CI
Recurrent VTE	2916 (16 studies) 3m-6m	7.8% vs 11.6% **RR: 0.68 (95%CI 0.54 to 0.85)** **SS in favour of LMWH** Absolute effect: 37 fewer per 1000 (95% CI 17 fewer to 53 fewer)	⨁⨁⨁⊖ **MODERATE** Study quality: -1 Consistency: OK Directness: OK Imprecision: OK
Recurrent VTE – subgroup DVT	1845 (11 studies) 3m-6m	8.6% vs 11.6% **RR: 0.74 (95%CI 0.56 to 0.97)** **SS in favour of LMWH** Absolute effect: 30 fewer per 1000 (95% CI 3 fewer to 51 fewer)	⨁⨁⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 wide CI
Recurrent VTE – Subgroup PE	162 (2 studies) 3m-6m	4.3% vs 0% RR: 3.28 (95%CI 0.38 to 28.33)	⨁⨁⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 wide CI
Major bleeding	2762 (15 studies) m-6m	3.3% vs 4.1% RR: 0.79 (95%CI 0.55 to 1.16)	⨁⨁⊖⊖ **LOW** Study quality: -1 Consistency: OK Directness: OK Imprecision: -1 wide CI

A systematic review and meta-analysis that was conducted for the 2012 NICE guideline on venous thromboembolic disease compares low molecular weight heparin (LMWH) to vitamin K antagonists (VKA) for the continuation phase of the treatment of venous thromboembolism. 16 RCTs of patients with either acute DVT (excluding PE), acute PE or acute VTE (both DVT or PE) were included. Trials with cancer patients were also included.
Results for all trials (non-cancer and cancer) are reported here.

No significant difference in mortality was observed between treatment with LMWH and treatment with VKA for all studies.
GRADE: MODERATE quality of evidence

There is also no significant difference in mortality when only RCTs of patients with DVT are considered (exclusion of patients with PE).
Nor is there a significant difference in mortality in 2 studies that include only patients with PE.
GRADE: LOW quality of evidence

For all studies, there is **significantly less recurrence of VTE with LMWH** compared to VKA (RR: 0.68; 95%CI 0.54 to 0.85).
GRADE: MODERATE quality of evidence

For studies that include only patients with DVT (excluding patients with PE), there is significantly less recurrence of VTE with LMWH compared to VKA (RR: 0.74; 95%CI 0.56 to 0.97).
GRADE: LOW quality of evidence

There is no significant difference in recurrence rates of VTE in 2 trials that include only patients with PE.
GRADE: LOW quality of evidence

No significant difference in major bleeding is observed when comparing LMWH to VKA in all studies.
GRADE: LOW quality of evidence

Our search yielded another result: a Cochrane collaboration review on vitamin K antagonists or low molecular-weight heparin for the long term treatment of symptomatic venous thromboembolism by Andras et al.(75). 10 of the 16 studies in the NICE 2012 review are also included. Different selection criteria were used (e.g. trials with 100% cancer patients were excluded, and the diagnosis of VTE had to be confirmed with (contrast) venography or another visual method). The way data was analysed also differs from the NICE 2012 review.

They found that there was a non-significant difference in VTE recurrence in favour of LMWH (OR: 0.80; 95% CI 0.59 to 1.13), and that the difference in bleeding significantly favoured LMWH (OR 0.50; 95% CI 0.31 to 0.79).
They saw no difference in mortality.

These results are comparable to the NICE analysis in non-cancer patients (see below).

5.7.2 Low molecular weight heparin versus vitamin K antagonist in non-cancer patients

Long term LMWH versus VKA for non-cancer patients with VTE			
Bibliography: meta-analysis Nice 2012 (74)			
Outcomes	**N° of participants (studies) Follow up**	**Results***	**Quality of the evidence (GRADE)**
All-cause mortality	2953 (16 studies) 3m-6m	5.4% vs 4.3% RR: 1.23 (95%CI 0.8 to 1.9) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment, open label Consistency: OK Directness: OK Imprecision: OK
Recurrent VTE	2916 (16 studies) 3m-6m	8.4% vs 9.9% RR: 0.85 (95%CI 0.63 to 1.13) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: OK Directness: OK Imprecision: OK
Major bleeding	2762 (15 studies) m-6m	**1.2% vs 2.6%** **RR: 0.48 (95%CI 0.24 to 0.97)** **SS in favour of LMWH** Absolute effect: **14 fewer per 1000 (95% CI 1 fewer to 20 fewer)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 Consistency: OK Directness: OK Imprecision: OK

A systematic review and meta-analysis that was conducted for the 2012 NICE guideline on venous thromboembolic disease compares low molecular weight heparin (LMWH) to vitamin K antagonists (VKA) for the continuation phase of the treatment of venous thromboembolism. 16 RCTs of patients with either acute DVT (excluding PE), acute PE or acute VTE (both DVT or PE) were included. A separate analysis was also performed in non-cancer patients.

No significant difference in mortality was observed between treatment with LMWH and treatment with VKA for studies in non-cancer patients.
GRADE: MODERATE quality of evidence

For **non-cancer patients, there is no statistically significant difference in recurrence of VTE** with LMWH compared to VKA.
GRADE: MODERATE quality of evidence

For **non-cancer patients, LMWH were associated with a lower rate of major bleeding** compared to VKA.
GRADE: MODERATE quality of evidence

5.8 DOACs vs VKA in the extended treatment prevention of recurrent VTE

5.8.1 Dabigatran versus warfarin after at least 3 months of continued anticoagulant treatment

Dabigatran 150mg bid versus warfarin (INR 2-3) after >3m long term treatment, for the prevention of recurrent VTE			
Bibliography: Schulman 2013-RE-MEDY*(76)*			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	2866 (1 study) 36m	1.2% vs 1.3% HR= 0.90 (95%CI 0.47 to 1.72) NS	⨁⨁⨀⨀ **LOW** Study quality:-1 non-inferiority, protocol alterations Consistency: NA Directness: OK Imprecision:-1 low event rates
Recurrent or fatal VTE (PO)	2866 (1 study) 36m	**1.8% vs 1.3%** **HR= 1.44 (95 CI 0.78 to 2.64)** **p for non-inferiority=0.01**	⨁⨁⨁⨀ **MODERATE** Study quality:-1 non-inferiority poor reporting. Wide margin! Consistency: NA Directness: OK Imprecision: see study quality
Major bleeding	2866 (1 study) 36m	0.9% vs 1.8% HR= 0.52 (95%CI 0.27 to 1.02) NS	⨁⨁⨀⨀ **LOW** Study quality:-1 Consistency: NA Directness: OK Imprecision:-1
Major or clinically relevant bleeding event	2866 (1 study) 36m	5.6% vs 10.2% **HR= 0.54 (95%CI 0.41 to 0.71)** **SS in favour of dabigatran** *estimated NNT/mean study duration: 22(17-34)*	⨁⨁⨁⨀ **MODERATE** Study quality:-1 Consistency: NA Directness: OK Imprecision: OK
Acute coronary syndrome	2866 (1 study) 36m	0.9% vs 0.2% **p= 0.02 in favour of warfarin** *estimated NNH/mean study duration: 143*	⨁⨁⨀⨀ **LOW** Study quality:-1 Consistency: NA Directness: OK Imprecision:-1 low event rates

This trial recruited patients with a previous VTE-event, who had received long-term anticoagulant treatment for 3-12 months and were considered to be at increased risk for recurrent venous thromboembolism on the basis of the site investigator's assessment (not further defined). These patients were randomized to receive either dabigatran 150mg bid or warfarin (INR target 2-3) for a maximum of 36 months. This was a non-inferiority trial.

There was no significant difference in mortality between the dabigatran group and the warfarin group.
GRADE: LOW quality of evidence

Dabigatran was found to be non-inferior to warfarin in preventing recurrent of fatal VTE. The trial quality and choice of non-inferiority margin however is somewhat debatable.

GRADE: MODERATE quality of evidence

There was no significant difference in symptomatic DVT or symptomatic nonfatal PE between both treatment arms.
GRADE: LOW quality of evidence

There was no significant difference in major bleeding between both treatments.
GRADE: LOW quality of evidence

There was significantly less major or clinically relevant bleeding with dabigatran compared to warfarin.
GRADE: MODERATE quality of evidence

There were significantly more cases of acute coronary syndrome with dabigatran than with warfarin treatment
GRADE: LOW quality of evidence

5.9 Duration of treatment after VTE

5.9.1 Duration of treatment with VKA or DOAC. Meta-analyses

VKA 'longer' vs 'shorter' treatment in the prevention of recurrent VTE			
Bibliography: Cochrane Middeldorp 2014(77); Marik 2015(78)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Recurrent VTE	3536 (10 studies) 3 m – 4y	All indications (77) **RR 0.20 (95% CI 0.11 to 0.38)**	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: NA Directness: OK Imprecision: OK
	533 (2 studies) 12 m - 24 m	Unprovoked first VTE (78) **OR 0.09 (95%CI 0.03 to 0.25)** **SS less recurrent VTE with long term treatment**	
	2639 (7 studies) up to 1 y	After cessation of long-term treatment RR 1.28 (95% CI 0.97 to 1.70) NS	
Mortality	1049 (4 studies) 3m - 24m	All indications RR 0.89 (95% CI 0.66 to 1.21) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 wide CI
	533 (2 studies) 24m	Unprovoked first VTE OR 0.86 (95%CI 0.20 to 3.61) NS	
Major bleeding	1350 (6 studies)	All indications **RR 2.60 (95% CI 1.51 to 4.49)** **SS more bleeding with longer**	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 wide CI/-2 very wide CI ⊕⊕⊖⊖ **LOW** for unprovoked first VTE)
	533 (2 studies)	Unprovoked first VTE OR 5.13(95%CI 0.87—30.15) NS	

DOAC 'longer' vs 'shorter' treatment in the prevention of recurrent VTE			
Bibliography: Marik 2015(78)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Recurrent VTE	5021 (3 studies) 18 m - 24 m	**OR 0.16 (95%CI 0.11 to 0.24)** **SS less recurrent VTE with long term treatment**	⊕⊕⊕⊕ **HIGH** Study quality: OK Consistency: OK Directness: OK Imprecision: OK
Mortality	5021 (3 studies) 18 m -24 m	All indications OR 0.52 (95%CI 0.10 to 2.66) NS	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: OK Imprecision: -1 wide CI
Major bleeding	5021 (3 studies) 18 m -24 m	OR 1.88 (95%CI 0.19 to 18.06) NS	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: OK Imprecision: -2 very wide CI

We found several meta-analyses that examined long duration versus short duration anticoagulants in the prevention of recurrent VTE Cochrane Middeldorp 2014(77); Marik 2015(78); Sindet Pedersen 2015(79)). The in- and exclusion criteria of these meta-analyses differed, but more importantly, the trials included in these meta-analyses were also quite diverse: different treatments, treatment durations, inclusion criteria (first, second, provoked, unprovoked, DVT, PE…).
In Cochrane Middeldorp 2014, all treatment indications and treatment durations were included. The treatment durations in the 'longer' treatment arm ranged from 3 months to 4 years and in the 'shorter' treatment arms from 1 month to 6 months.
In Marik 2015, only patients with a first unprovoked VTE were included. Long-term treatment of the 2 included trials was 24 m, short term treatment was 3-6m. .

In spite of these complexities, some conclusions can be made.

The following comparisons were made in different meta-analyses:
- Longer vs shorter treatment with VKA (see table above and detailed tables in full document)
- Longer vs shorter treatment with DOAC (see table above and detailed tables in full document)
- 6m vs 3 m with VKA (see detailed tables in full document)
- 12 m vs 3m with VKA (see detailed tables in full document)

For all the above comparisons, during prolonged OAC treatment we see **less recurrence of VTE** compared to placebo or no treatment.
After cessation of prolonged treatment, the recurrence rate of VTE is not significantly different from the rate in the shorter treatment group. This indicates that the protection against recurrent VTE is only evident for as long as the OAC treatment is continued.
GRADE: HIGH quality of evidence
We have high confidence that the results of the study reflects the true effect.

No difference in mortality rates was observed in any of the meta-analyses or individual trials between a longer OAC treatment and a shorter one.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflects the true effect.

In a meta-analysis of 6 RCTs with vitamin K antagonists, a **higher rate of major bleeding** was observed in patients with longer treatment compared to patients with shorter treatment. However, smaller meta-analyses with VKA or a meta-analysis comparing longer and shorter duration of DOACs did find a higher rate of major bleeding, but it was **not statistically significant**. A low event rate is probably to blame.
GRADE: MODERATE quality of evidence (LOW for unprovoked first VTE with VKA)
We have moderate confidence that the results of the study reflects the true effect.

5.9.2 Duration of treatment with DOACs. RCTs

It is important to remark that the patients that are included in the RCTs comparing DOACs to placebo in the extended treatment of VTE, are different form the average VTE patient in daily life. When compared to VTE patients in the general population, patients included in these studies are on average younger (56y), have less comorbidities, present a lower risk of bleeding and have, for the most part, less risk factors that would make them eligible for continued treatment (e.g. cancer, antiphospholipid syndrome, recurrent VTE…) (Connors 2013(80)).

5.9.2.1 Apixaban versus placebo after at least 6 months of anticoagulant treatment

Apixaban 2.5mg bid or 5mg bid versus placebo after long term treatment (6-12m) for VTE, for the prevention of recurrent VTE			
Bibliography: Agnelli 2013-AMPLIFY-EXT(81)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Recurrent VTE or death from any cause (PO)	2486 (1 study) 12m	Apix 2.5 vs apix 5 vs pla 3.8% vs 4.2% vs 11.6% Apix 2.5 vs pla: **RR=0.33 (95% CI 0.22 to 0.48)** **SS in favour of apixaban 2.5** *estimated NNT/12m: 13 (11-17)* Apix 5 vs pla: **RR=0.36 (95% CI 0.25 to 0.53)** **SS in favour of apixaban 5** *estimated NNT/12m:14 (12-19)*	⊕⊕⊕⊖ **MODERATE** Study quality:-1 discontinuation unbalanced between groups, extension trial Consistency: NA Directness: OK Imprecision: OK
Major bleeding	2486 (1 study) 12m	0.2% vs 0.1% vs 0.5% Apix 2.5 vs pla: RR= 0.49 (95%CI 0.09 to 2.64) NS Apix 5 vs pla: RR=0.25 (95%CI 0.03 to 2.24) NS	⊕⊕⊖⊖ **LOW** Study quality:-1 Consistency: NA Directness: OK Imprecision:-1 very wide CI; low event rates
Clinically relevant non-major bleeding	2486 (1 study) 12m	3.0% vs 4.2% vs 2.3% Apix 2.5 vs pla: RR= 1.29 (95% CI 0.72 to 2.33) NS Apix 5 vs pla: **RR= 1.82 (95%CI 1.05 to 3.18)** **SS (more bleeding with apixaban 5 mg)** *estimated NNH/12m: 53 (870-20)*	⊕⊕⊖⊖ **LOW** Study quality:-1 Consistency: NA Directness: OK Imprecision:-1 wide CI

This trial recruited patients that had experienced a recent VTE (index event, 65% DVT, 35% PE) and had been treated for 6-12 months with standard anticoagulant treatment or apixaban and for whom there was 'clinical equipoise' regarding the continuation or cessation of anticoagulation therapy (no criteria provided). The patients were randomized to either apixaban 2.5mg bid, 5mg bid or placebo, for an additional 12 months.
An average of 13% of these patients had already experienced a previous VTE event (before the index event).

The inclusion of patients that had been included in the AMPLIFY trial may cause a selection bias.
The 'clinical equipoise' regarding continuing or stopping anticoagulation was not defined. With regards to an increased risk of recurrent VTE, about 1/5 of the included population had a risk factor that *may* have made them eligible for continued treatment, such as cancer (1.1 to 2.2%), permanent immobilization (2.3 to 3.6%), antecedent of VTE (11.8 to 14.5%), know prothrombotic genotype (3.2 to 4.3%).

Mortality was not reported as a separate outcome.

The rate of **recurrent VTE or death from any cause (**as a composite endpoint) was significantly lower in the apixaban treatment groups compared to placebo.
GRADE: MODERATE quality of evidence

The rate of major bleeding was low. There was **no significant difference in major bleeding** between the apixaban treatment groups and placebo, but precision for this outcome is weak.
GRADE: LOW quality of evidence

There was **no** significant difference in **clinically relevant non-major bleeding** when comparing apixaban 2.5 mg bid to placebo. There was however a significant difference for this outcome when comparing apixaban 5mg bid to placebo.
GRADE: LOW quality of evidence

5.9.2.2 Dabigatran versus placebo after at least 6 months of anticoagulant treatment

Dabigatran 150mg bid versus placebo after long term treatment, for the prevention of recurrent VTE			
Bibliography: Schulman 2013-RE-SONATE(76)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Recurrent or fatal VTE or unexplained death (PO)	1353 (1study) 6m	0.4% vs 5.6% **HR= 0.08 (95%CI 0.02 to 0.25)** **SS in favour of dabigatran** *estimated NNT/6m: 20 (19-24)*	⊕⊕⊕⊖ **MODERATE** Study quality:-1 unclear blinding, extension, modified ITT Consistency: NA Directness: OK Imprecision: OK
Major bleeding	1353 (1study) 6m	0.3% vs 0% HR= not estimable	NOT APPLICABLE
Major or clinically relevant bleeding event	1353 (1study) 6m	5.3% vs 1.8% **HR= 2.92 (95%CI 1.52 to 5.60)** **SS in favour of placebo** *estimated NNH/6m: 29 (107-12)*	⊕⊕⊕⊖ **LOW** Study quality:-1 Consistency: NA Directness: OK Imprecision:-1
Acute coronary syndrome	1353 (1study) 6m	0.1% vs 0.2% NT	Not applicable

This trial recruited patients with a previous VTE-event (= index VTE event), who had received long-term anticoagulant treatment for 6 to 18 months. Patients in whom anticoagulant therapy 'should be continued' were excluded from this study (no further definition provided).
The patients were randomized to receive either dabigatran 150mg bid or placebo, for an additional 6 months.
It is not reported whether any patients had experienced a VTE prior to the index event.

The inclusion of patients that had been included in the RE-COVER trials may cause a selection bias.

Mortality was not reported as a separate endpoint.

The rate of **recurrent VTE** (fatal or non-fatal) or unexplained death (as a composite endpoint) was **significantly higher in the placebo** group. Most of the events were VTE-events.
GRADE: MODERATE quality of evidence

The rates of **major bleeding were very low** in both groups (0 event in the placebo group).

Major bleeding or clinically relevant non-major bleeding (as a composite endpoint) was observed **more** frequently in the dabigatran group. This difference was statistically significant.
GRADE: LOW quality of evidence

5.9.2.3 Rivaroxaban versus placebo after at least 6 months of anticoagulant treatment

Rivaroxaban 20mg/d versus placebo for VTE, in patients who had completed 6-12 m of treatment			
Bibliography: EINSTEIN-extension 2010(68)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mortality	1197 (1 study) 6m-12m	0.2% vs 0.3% No statistical test	**NOT APPLICABLE**
Symptomatic recurrent VTE (PO)	1197 (1 study) 6m-12m	1.3% vs 7.1% **HR: 0.18 (95% CI 0.09 to 0.39)** **SS in favour of rivaroxaban** *estimated NNT/mean study duration: 18 (16-23)*	⨁⨁⨁⊖ **MODERATE** Study quality:-1 extension Consistency: NA Directness: OK Imprecision: OK
Major or clinically relevant non-major bleeding (PO)	1197 (1 study) 6m-12m	6.0% vs 1.2% **HR: 5.19 (95% CI 2.3 to 11.7)** **SS in favour of placebo** *estimated NNH/mean study duration:21 (65-8)*	⨁⨁⨁⊖ **MODERATE** Study quality:-1 extension Consistency:NA Directness: OK Imprecision: OK
Major bleeding	1197 (1 study) 6m-12m	0.7% vs 0% NS	⨁⨁⊖⊖ **LOW** Study quality -1 Consistency: NA Directness: OK Imprecision:-1 low event rates

This trial includes patients that had been treated for 6 to 12 months with a VKA or with rivaroxaban for a VTE episode (the index event: DVT or PE) and for whom there was 'clinical equipoise' with respect to the need for continued anticoagulation.
For 14.1% to 17.9% of these patients, the index event was not the first VTE event.
The patients were randomized to receive either rivaroxaban 20mg daily or a matching placebo.
Treatment duration in the trial was 6 or 12 months.

The inclusion of patients that had been included in the EINSTEIN trials may cause a selection bias. The authors expected a placebo event rate for VTE of 3.5%, but the actual event rate in the placebo group was 7.1%. This higher-than-expected event rate in the placebo group makes us question the (non-existent) criteria in this study for continuing or discontinuing anticoagulant treatment.

Mortality rates were very low in both groups. No statistical test was done.
GRADE: NOT APPLICABLE

There was significantly **fewer recurrent symptomatic VTE in patients treated with rivaroxaban** compared to patients treated with placebo (HR: 0.18; 95% CI 0.09 to 0.39).
GRADE: HIGH quality of evidence

There was significantly **more major or clinically relevant non-major bleeding** in rivaroxaban-treated patients (HR: 5.19 95% CI 2.3 to 11.7).
GRADE: HIGH quality of evidence

Rates of **major bleeding** were very low. The difference between rivaroxaban and placebo was **not statistically significant.**
GRADE: LOW quality of evidence

6 Bridging. Summary and conclusions

6.1 Systematic review

A systematic review, Daniels 2015(82), searched for publications (controlled trials, observational studies and guidelines) related to the management of anticoagulants in the peri-procedural period.

It found one meta-analysis (Siegal 2012(83)) of observational studies that compared the clinical outcomes of bridging with LMWH versus no bridging in patients with an interruption of VKAs (mostly warfarin) because of an elective surgery or procedure.
This meta-analysis suggests there is no change of risk of **thromboembolic events** (8 cohort studies, 5184 patients) with bridging therapy versus no bridging. However, bridging therapy was associated with an increased risk of **major bleeding events** (5 cohort studies, 3501 patients) compared to no bridging.

A subsequent RCT, Douketis 2015, BRIDGE(84), was also reported by SR Daniels 2015(82).

6.2 Information from RCTs

Bridging with LMWH versus placebo after interruption of warfarin in AF			
Douketis 2015(84) BRIDGE Trial			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Stroke, systemic embolism, or TIA (PO)	1884 (1 study) 30 days	Bridging: 3/895 (0.3%) Placebo: 4/918 (0.4%) MD: 0.1% (95%CI -0.6 to 0.8) **p=0.01 for non-inferiority** p=0.73 for superiority	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 patients with high risk of thromboembolism excluded Imprecision: ok
All-cause mortality	1884 (1 study) 30 days	Bridging: 4/895 (0.4%) Placebo: 5/918 (0.5%) p = 0.88 for superiority NS	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 patients with high risk of thromboembolism excluded Imprecision: ok
Major bleeding (PO)	1884 (1 study) 30 days	Bridging: 1/895 (3.2%) Placebo: 0/918 (1.3%) **RR (pla vs bridging): 0.41 (95%CI 0.20 to 0.78)** **SS in favour of placebo** **p = 0.005 for superiority** *estimated NNT(for not bridging): 53(39 to 142)*	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 patients with high risk of thromboembolism excluded Imprecision: ok

Table 11

In this double blind, non-inferiority and superiority RCT(84), bridging with the LMWH dalteparin (100 IU/kg body weight) was compared to no bridging (placebo delivered subcutaneously), in 1884 NVAF patients with an interruption of warfarin because of an elective invasive procedure. The patients were followed for 30 days after the procedure.

Patients with a high risk of thromboembolic events (mechanical heart valve, stroke, systemic embolism or TIA within previous 12 weeks) were excluded from this study.

In NVAF patients interrupting warfarin for an elective surgery or procedure, no bridging therapy was **non-inferior** to bridging therapy for risk of **stroke, systemic embolism or TIA**.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

In NVAF patients interrupting warfarin for an elective surgery or procedure, no bridging therapy resulted in a statistically significant **decreased risk of major bleeding** compared to bridging therapy.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflect the true effect.

Additional information from other RCTs:

In the RE-LY trial (24) dabigatran 110mg 2x/d was compared to dabigatran 150 mg 2x/d and to warfarin (INR 2-3) in patients with non-valvular atrial fibrillation.

A pre-specified subanalysis (85) compared bridging therapy (LMWH or unfractioned heparin) versus no bridging therapy in patients whose anticoagulation therapy was interrupted because of an elective procedure.

In 1415 patients, warfarin therapy was interrupted. Bridging was not associated with a change in **stroke and systemic embolism** risk compared to no bridging therapy. However, bridging therapy was associated with **more major bleeding** and **more thromboembolism**. These results further support the results of RCT Douketis 2015(84).

In 2691 patients, dabigatran therapy was interrupted. Bridging was not associated with a change in **stroke and systemic embolism** risk, nor with **any thromboembolism**, compared to no bridging therapy. However, bridging therapy was associated with more **major bleeding**.

7 Switching. Summary and conclusions

7.1 Caution when switching

Several authors have commented on the risk (thrombo-embolic risk as well as bleeding risk) that seems to accompany the switch from one anticoagulant to another (Caldeira 2014(86); Mahaffey 2013(87); Ruff 2014(88)). This aspect of switching is outside the scope of our literature review. However, it is important to realise that switching constitutes a high risk period for patients and that extra care needs to be taken as to the manner of switching, the instructions to the patient and the follow-up, to minimize the risks due to inadequate anticoagulation.

7.2 Reasons to switch

See guidelines

7.3 How to switch

There are no RCTs that compare different switching methods, so we don't actually have any strong evidence as to what the best method may be.

After reports of a higher risk of stroke and bleeding in patients transitioning from a DOAC to VKA at the end of 2 trials comparing DOACs to warfarin in AF (Mahaffey 2013(87), Granger 2012(89)) the authors of ENGAGE AF TIMI developed an end-of-trial transition strategy aimed at minimizing these risks (Ruff 2014(88)).
A detailed description of this strategy can be found in the annex.

For more information on how to switch, we suggest consulting the Summary of Product Characteristics.

8 Adherence and persistence to oral anticoagulants. Summary and conclusions

8.1 Definitions

Adherence: active,voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result(90)

Persistence: the duration of time from the initiation to discontinuation of therapy(90)

Adherence and persistence can be classified as medication-taking behaviour

Time in the therapeutic range (TTR): duration of time in which the patient's International Normalized Ratio (INR) values were within a desired range

8.2 Adherence and persistence in atrial fibrillation: RCTs

In the trials comparing DOACs to warfarin, there is no information on how many doses of the study drugs were actually taken. There is however some other information:
- The mean time in the therapeutic range (TTR) in the warfarin group was reported.
- The rates of discontinuation of the study drug were also reported.

The TTR in the different DOAC trials is reported in the table below.
For rivaroxaban, this was rather low (55%). Later reports point out that the device used to measure INR in the rivaroxaban-trial was 'defective' (Cohen 2016(30)).

DOAC in the trial	mean TTR in warfarin arm (INR 2-3)	Remarks
Apixaban (23)	62.2%	
Dabigatran (24)	64%	not blinded
Edoxaban (28)	65%	
Rivaroxaban (29)	55%	inaccurate measuring device

The discontinuation rates in the trials were quite high (see table below). Given that participants in clinical trials may be more motivated and may receive stricter follow-up than patients in a real-world setting, it is possible that discontinuation in real life is even higher ((2)).

DOAC in the trial	discontinuation		Mean duration of trial
	DOAC	warfarin	
Apixaban (23)	25.3%	27.5%	1.8y
Dabigatran (24)	20.7%-21.2%	16.6%	2y
Edoxaban (28)	33.0%-34.4%	34.5%	2.8y
Rivaroxaban (29)	23.7%	22.2%	1.9y

Two **meta-analyses** (Chatterjee 2014(91); Caldeira 2015 (92))
compared discontinuation rates between DOACs and warfarin in all the atrial fibrillation trials. **No difference in discontinuation rates** between DOACs and warfarin was found, although heterogeneity was very high.

In the next chapter we will look at discontinuation in observational studies.

8.3 Adherence and persistence in atrial fibrillation: observational studies

We included 6 European cohort studies with >1000 newly anticoagulated participants.
Detailed tables can be found in the appendices.
Different durations of follow-up, different care-settings and different definitions of persistence or non-persistence make it very difficult to compare these results and to draw conclusions for the Belgian practice.

8.3.1 Persistence, non-persistence, discontinuation

The definition of persistence varied between studies. Usually a prescription gap exceeding 1 month or 2 months was considered as 'non-persistence'. In some studies, switching to another OAC was considered to be non-persistence, whilst in other studies it was not.
The reasons for non-persistence are usually not reported. Since these are observational studies, no causal relationship can be assumed between the OAC that is used and the adherence rates that are observed.

1 **Swedish** prospective cohort study (Forslund 2016(93)) in 17.741 participants reported persistence rates after **1 year** with **warfarin (85.0%), apixaban (85.9%), dabigatran (74.4%) and rivaroxaban (77.4%).**
Comparing the DOACs, **persistence was higher with apixaban** compared to rivaroxaban or to dabigatran. The use of apixaban was relatively new in this population.

1 **UK** retrospective cohort study (Johnson 2016(94)) in 13.089 OAC naïve primary care patients, reported persistence rates after a follow-up of maximum **22 months, with warfarin (70.6%), apixaban (82.8%), dabigatran (62.5%), rivaroxaban (67.6%).**
Using the same patient database, another author (Martinez 2016 (95)) reported persistence rates at 1 y for VKA (63.6%) and for DOACs (79.2%) (the definition of persistence in Martinez 2016 was more strict than for Johnson 2016).
Comparing the DOACs (Johnson 2016(94)), **persistence was higher with apixaban**, compared to dabigatran and rivaroxaban over the total follow-up time. However, there was a very low number of apixaban users, especially at longer follow-up times.

1 **Danish** retrospective cohort study (Lamberts 2017(36)) in 54.321 OAC naïve patients, reported **persistence rates of 72.2%** over a mean follow up time of 403 days (total study duration >3y).
Persistence at +/-3y was 40% with warfarin, 85% with apixaban, 70% with dabigatran and 85% with rivaroxaban.
Comparing the DOACs at +/-3 years, **persistence was higher with apixaban** compared to dabigatran. There was **no statistically significant difference between apixaban and rivaroxaban**. Again, the number of apixaban users at 3y follow-up was low.

1 **German** retrospective cohort study (Beyer-Westendorf 2016(96))
in **7265** OAC naïve primary care patients, reported persistence rates at **6 months of 58.1% for VKA (mostly phenprocoumon); 60.3% for dabigatran and 66.0% for rivaroxaban.**
After **1 year**, persistence rates were **25.5% for VKA, 47.3% for dabigatran and 53.1% for rivaroxaban**.

Comparing the DOACs **at 6 months, a higher persistence with rivaroxaban compared to dabigatran** was seen**. At 1 year, no statistically significant difference between rivaroxaban and dabigatran** was seen.

8.3.2 Percentage of days covered

Adherence was derived from prescription data and described as a percentage of days covered (PDC) by the prescription of a specific OAC.

1 **Swedish** prospective cohort study (Forslund 2016(93)) reported the adherence to newly prescribed **DOACs after 1 year**. **>92% of patients had a good adherence** (defined as PDC>80%). >71% of patients had a seemingly full adherence (PDC=100%). **Good adherence was more likely with rivaroxaban** compared to dabigatran. Full adherence was higher with rivaroxaban compared to apixaban and dabigatran.

1 **Danish** retrospective cohort study (Gorst-Rasmussen 2015(97)) reported the adherence to 2960 OAC naïve **dabigatran** users, who remained on **dabigatran for 1 year**. **76.8% of patients had good adherence** (PDC>80%). The total PDC at 1 y was 83.9%.

8.3.3 Medication possession ratio

The medication possession ratio is defined as the proportion of days that the patient should be in possession of medication that was supplied, within a defined time period.
1 **German** retrospective cohort study (Beyer-Westendorf 2016(96)) in **7265** OAC naïve primary care patients, reported the adherence to rivaroxaban and dabigatran at 6 months. A **good adherence** (MPR>80%) was seen in **61.4% of rivaroxaban users and 49.5% of dabigatran users.** Good adherence was **more likely with rivaroxaban** compared to dabigatran.

8.4 Impact of adherence and persistence on clinical outcomes in AF: observational studies

2 retrospective cohort studies in the USA provide data on the risk of stroke/systemic embolism in NVAF patients that are non-adherent to anticoagulant treatment. (YAO 2016 (98); Shore 2014 USA(99))

- In 1 retrospective cohort the risk of stroke when not taking anticoagulants **increased with the duration of the treatment interruption.** In patients with **higher CHA2DS2VASc scores**, the risk becomes apparent after a shorter interruption compared to patients with lower CHADS2VASC scores. In patients with a CHA2DS2VASC score of 0 or 1, treatment interruption was not associated with increased risk of stroke/systemic embolism. (YAO 2016 (98);)

- In another retrospective cohort, patients who were non-adherent (PDC<80%) to dabigatran had a **higher combined rate of all-cause mortality and stroke, compared to adherent patients** (PDC>=80%). (Shore 2014 USA(99))

8.5 Impact of time in the therapeutic range (TTR) on clinical outcomes in atrial fibrillation

8.5.1 Information from RCTs

In the pivotal RCTs comparing DOACs to warfarin in atrial fibrillation, subgroup analyses were performed to examine possible differences in treatment effect according to different levels of INR control. As a surrogate marker for INR control, the average center's time in the therapeutic range was estimated (cTTR). Additional analyses according to predicted individual TTR (iTTR) were sometimes performed.
A center mean TTR may not represent individual patients and may not represent the full effect of INR control on outcomes. This approach is also probably a marker of differences in overall care between centers.

8.5.1.1 Stroke/systemic embolism

In the individual trials, subgroup analyses found **no indication of a difference in treatment effect for stroke/systemic embolism according to different levels of cTTR (**Wallentin 2013(100), Wallentin 2010(101), Giugliano 2013(28)**,** Piccini 2014(102)). The stroke/systemic embolism results across the different subgroups were consistent with the overall trial results.

However, a meta-analysis (Carmo 2017(103)), pooling these trials, found a statistically significant interaction between cTTR and stroke/systemic embolism when comparing DOACs to warfarin, when a **threshold cTTR of 70%** was used: a benefit of DOACs over warfarin at cTTR<70% was seen, which was no longer apparent at cTTR>=70%.

8.5.1.2 Major bleeding

For major bleeding outcomes, the results vary:
For **apixaban** compared to warfarin, subgroup analyses found **no indication** of a difference in effect on major bleeding according to different levels of cTTR. The results for major bleeding across the different levels of cTTR were consistent with the overall trial results. Similar results were obtained when analyZing the results according to predicted individual TTR (iTTR). (Wallentin 2013(100))

When comparing **dabigatran 110** mg to warfarin, subgroup analyses found **no indication** of a difference in effect on major bleeding according to different levels of cTTR.
When comparing **dabigatran 150** mg to warfarin, subgroup analyses found a **lower rate of major bleeding with dabigatran in centers with poor INR control (cTTR<57.1%)** whilst the difference between dabigatran and warfarin was not statistically significant with higher cTTR. (Wallentin 2010(101))

For both doses of **edoxaban** compared to warfarin, subgroup analyses found **no indication** of a difference in effect on major bleeding according to different levels of cTTR. (Giugliano 2013(28))

When comparing **rivaroxaban** to warfarin, subgroup analyses found **a lower rate of major and clinically relevant non-major bleeding** with rivaroxaban in centers with **poor INR control**. In centers

with good INR control, the rate of major and clinically relevant nonmajor bleeding was higher with rivaroxaban compared to warfarin. (Piccini 2014(102))

A meta-analysis, pooling these trials, found no indication of a difference in treatment effect on major or clinically relevant non-major bleeding when comparing DOACs to warfarin according to cTTR, but reported high heterogeneity for these analyses (103).

8.5.1.3 Intracranial hemorrhage

The lower rate of intracranial hemorrhage with DOACs was preserved for all DOACs across all subgroups.

8.5.2 Information from observational studies

A **Swedish** retrospective cohort study included 40 449 patients newly treated with warfarin, followed them for a maximum of 5 years and analysed the rate of complications according to the patient's INR control (iTTR <70% vs >=70%) and INR variability (High vs low, compared to the mean variability). (104)

Patients with **good INR control (iTTR>=70%) had mortality rates that were more than 3x lower compared to patients with poor(er) INR control** (annual rate 1.29% pt/y (95%CI 1.18 to 1.39) versus 4.35 % pt/y (95%CI 4.03 to 4.66).

Rates of major bleeding and rates of thromboembolisms were also lower in patients with good INR control (respectively 1.61 (95%CI 1.49 to 1.73) vs 3.81 (95%CI 3.51 to 4.11) for major bleeding and 2.37 (95%CI 2.23 to 2.51) vs 4.41 (95%CI 4.09 to 4.73) for any thromboembolism).

For INR variability, the same pattern is observed: patients with low variability, rates of mortality, major bleeding and thromboembolism were lower than in patients with high INR variability.

Patients with good INR control were more likely to have had a previous stroke, but less likely to have other comorbidities such as hypertension, diabetes, heart failure, …

Please note that causality cannot be derived from an observational study.

8.6 Adherence and persistence in VTE: RCTs

In the trials comparing DOACs to VKA to prevent recurrent VTE, we find some information on adherence and peristence: for the DOACs, we have the results of pill counts. For warfarin, there is information on TTR. For both treatments, discontinuation rates are also reported.

DOAC in the trial	Adherence to DOAC (>=80% of pills taken)	mean TTR in warfarin arm (INR 2-3)
Apixaban AMPLIFY (61)	96%	61%
Dabigatran RE-COVER I (64)	98%	59.9%
Dabigatran RE-COVER II (65)	98%	56.9%
Edoxaban Hokusai VTE 2013 (67)	99%	63.5%
Rivaroxaban Einstein DVT (68)	NR	57.7%
Rivaroxaban Einstein PE (69)	94.2%	62.7%

DOAC in the trial	discontinuation		Duration of follow up
	DOAC	enoxaparin + warfarin	
Apixaban AMPLIFY (61)	14%	15%	6 months
Dabigatran RE-COVER I (64)	16%	14.5%	6 months
Dabigatran RE-COVER II (65)	14.7	14.1%	6 months
Edoxaban Hokusai VTE (67)	4.4%	4%	6 months
Rivaroxaban Einstein DVT (68)	11.3%	14.2%	3-6-12 months
Rivaroxaban Einstein PE (69)	10.7%	12.3%	3-6-12 months

A **meta-analysis** (Chatterjee 2014(91)) compared discontinuation rates between DOACs and warfarin in most of the VTE trials. **No difference in discontinuation rates** between DOACs and warfarin was found, although heterogeneity was high.

8.7 Adherence and persistence in VTE: observational studies

We included 1 systematic review(Vora 2016 (105)). From this, we selected 1 European retrospective cohort study of adequate size (Cohen 2013 (106)).
Detailed tables can be found in the full document (English).

A systematic review and meta-analysis of 12 observational studies with OAC reported persistence rates of 83% at 3 months, 62% at 6 months and 31% at 12 months (Vora 2016 (105)).
In this systematic review, 1 retrospective cohort study in the UK reported persistence rates with VKA of 77.4% at 3 months, 50.3% at 6 months and 11.4% at 12 months (Cohen 2013 (106)).

8.8 Impact of adherence and persistence on clinical outcomes in VTE: observational studies

2 retrospective cohort studies in the USA (Deitelzweig 2010(107); Chen 2013(108)) found a **higher risk of recurrent VTE** in patients who **discontinue** treatment compared to patients who do not.
1 of these studies (Chen 2013(108)) also reported a **higher risk of recurrent VTE in non-compliant** high-risk patients compared to compliant high-risk patients.
The risk of major bleeding was reported in 1 of these studies (Deitelzweig 2010(107)). Overall, discontinuation is associated with a slightly lower rate of major bleeding. However, Discontinuation within 3 months of treatment is associated with a higher rate of major bleeding compared to no discontinuation, probably reflecting the number of patients who stop due to bleeding complications.
Detailed tables can be found in the full document (English).

8.9 Low maintenance dose of DOACs

The KCE report (Van Brabandt 2017 (2)) discusses physician's adherence to appropriate dose prescription.

In Belgium, as in other countries, a reduced dose of a DOAC was used more often in real life than in the pivotal RCTs (see table below).

	Dabigatran 110	Rivaroxaban 15	Apixaban 2.5
% reduced dose in RCT	49.7	20.7	4.7
% reduced dose in Belgium	58.1	44.1	23.7

Table 12. From: KCE report (Van Brabandt 2017)

A reduced dose is required in impaired renal function, and for apixaban and edoxaban also according to age and weight. It is not clear from these data if patients are prescribed the correct dose.

In any case, because of the difference between doses in RCTs and current prescribing patterns, the efficacy and safety results observed in the RCTs may not be applicable in a real-world setting.

For information on the appropriateness of dose reduction, we advise you to consult the Summary of the Product Characteristics.

8.10 Interventions to improve adherence

We did not find any meta-analyses that specifically examined interventions to improve adherence to anticoagulants. We did find some meta-analyses about interventions to improve anticoagulation control with VKA use. Improved adherence may result from these interventions, although the primary aim is to improve clinical outcomes.

8.10.1 Educational and behavioural interventions

A meta-analysis comparing supplemental patient education to usual care in 545 VKA-anticoagulated patients found **no statistically significant difference in TTR** between both strategies. (Wong 2013(109))
GRADE very low-quality evidence

8.10.2 Point of care testing (POC) for VKA

Several meta-analyses have examined the benefit of point of care testing, in which a portable INR measuring device is used (based on capillary blood).
Possible strategies involve **self-monitoring** (patient checks INR and contacts physician for advice on dose-altering); **self-management** (patient checks INR and makes decisions about dose-altering); **POC testing by the physician** (patient has INR checked by the physician and receives immediate advice on dose-altering).

It is not entirely clear whether **self-monitoring or self-management** improves the percentage of INR measurement within the **target range**, or the % of time within the target range, compared to usual care. A systematic review found 18 studies that reported these outcomes, **but statistically significant improvements were only seen in less than half of the studies** (Heneghan 2016(110)).

Self-monitoring and self-management **reduce the risk of thromboembolic events** in anticoagulated patients, compared to usual care (Heneghan 2016(110); Sharma 2015(111); Gailly 2009 (112)).
GRADE: moderate quality of evidence
Self-management reduces **mortality rates** compared to usual care, self-monitoring does not result in a statistically significant reduced mortality rate (Heneghan 2016(110); Sharma 2015(111); Gailly 2009 (112)).
GRADE: moderate quality of evidence
Self-monitoring or self-management do not lead to a statistically significant reduction **in major bleeding**, compared to usual care (Heneghan 2016(110); Sharma 2015(111); Gailly 2009 (112)).
GRADE: moderate quality of evidence

8.10.3 Pharmacist – managed anticoagulation

A systematic review found 3 RCTs that compared pharmacist-managed anticoagulation services to routine medical care (Manzoor 2017(113)). Quality of anticoagulation control was better in the pharmacist-managed group in 2 of the RCTs. It is unclear how this would translate to the Belgian setting.

9 Adverse events

9.1 Low-molecular-weight heparins

- Bleeding[5]
- Thrombocytopenia, but lower risk than with non-fractionated heparins.[5]
- Hyperkalaemia[5]
- Rarely:
    - Allergic reactions [5]
    - Osteoporosis [5]
    - Alopecia with long-term use[5]

Contraindications

- Active bleeding and increased bleeding risk. [5]
- Thrombocytopenia and antecedents of thrombocytopenia caused by heparins. [5]
- Acute bacterial endocarditis. [5]
- Nadroparine: severe renal insufficiency. [5]

9.2 Vitamin K antagonists

- The vitamin K antagonists are a medication class with a narrow therapeutic-toxic margin. [5]
- Bleeding. [5] The annual incidence of severe bleeding in the AFFIRM study (4060 patients over 3.5 years) was 2% per annum. The connection between the intensity of the anticoagulant treatment and the risk of bleeding is very great. Randomised studies show that the cost-benefit relationship is best at an INR of between 2 and 3.[6]
- Rarely:
    - skin necrosis[5] (in 0.01 to 0.1% of patients. The morbidity of this complication is very high, however: in spite of adequate treatment, half of these patents must undergo an operation in which skin grafts may or may not be necessary. Prevention of coumarin-induced skin necrosis can occur by building the dose up carefully, in particular in the case of the elderly.)[6]
    - Allergic reactions [5]
- In pregnant women, vitamin K antagonists are contra-indicated: there is a teratogenic effect in the first trimester and an elevated risk of bleeding in the newborn, when administered at the end of pregnancy; low-molecular weight heparins are preferred. [5]
- Vitamin K antagonists have a vasodilator effect on coronary arteries, peripheral veins and capillary vessels, resulting in the Raynaud's phenomenon. Peripheral vasodilation can also be responsible for the cold feeling that some patients experience. [6]
- Only a few cases of liver damage have been reported. Usually it presents as a cholestatic clinical picture, approximately ten days after the beginning of the treatment with vitamin K antagonists. [6]

[5] Belgisch Centrum voor Farmacotherapeutische Information www.bcfi.be (consulted 31/08/2017)
[6] Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions (Fifteenth Edition), 2006.

Contraindications:

- Active bleeding and increased bleeding risk. [5]
- Acute bacterial endocarditis. [5]
- Pregnancy. [5]
- Hepatic insufficiency. [5]

9.3 Direct oral anticoagulants (DOAC)

Any possible long-term adverse events are not yet known.

- Bleeding: the risk increases in renal insufficiency[5].
- Gastro-intestinal disorders[5].
- Rarely: thrombopenia[5].
- Gastrointestinale bleeding: statististically significant increase in high dose DOACs (dabigatran etexilate 300 mg p.d., rivaroxaban 20 mg p.d., apixaban 10 mg p.d. and edoxaban 60 mg p.d.) versus warfarin (RR 1,25; 95 %-CI 1,01 to 1,55) [7].
- Dabigatran: suspicion of a slightly elevated risk of myocardial infarction. [5] (See chapter 'Dabigatran and Myocardial infarction).

Contraindications

- Active bleeding and increased bleeding risk. [5]
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. [5]
- Prosthetic heart valves (formal contra-indication for dabigatran, not recommended for the other DOACs). [5]
- Dabigatran: severe renal insufficiency (creatinine clearance <30mL/min). [5]

[7] *Folia Pharmacotherapeutica, May 2014*

9.3.1 AE from Summary of product characteristics: apixaban[8]

System Organ Class	Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp)	Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF)	Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)
Blood and lymphatic system disorders			
Anaemia	Common	-	-
Thrombocytopenia	Uncommon	-	-
Immune system disorders			
Hypersensitivity, allergic oedema and Anaphylaxis	Rare	Uncommon	
Pruritus	Uncommon	Uncommon	Uncommon
Nervous system disorders			
Brain haemorrhage	-	Uncommon	Rare
Eye disorders			
Eye haemorrhage (including conjunctival haemorrhage)	Rare	Common	Uncommon
Vascular disorders			
Haemorrhage, haematoma	Common	Common	Common
Hypotension (including procedural hypotension)	Uncommon	-	-
Intra-abdominal haemorrhage	-	Uncommon	-
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Uncommon	Common	Common
Hemoptysis	Rare	Uncommon	Uncommon
Respiratory tract haemorrhage	-	Rare	Rare
Gastrointestinal disorders			
Nausea	Common	-	-
Gastrointestinal haemorrhage	Uncommon	Common	Common
Haemorrhoidal haemorrhage, mouth haemorrhage	-	Uncommon	-
Haematochezia	Uncommon	Uncommon	Uncommon
Rectal haemorrhage, gingival bleeding	Rare	Common	Common
Retroperitoneal haemorrhage	-	Rare	-
Hepatobiliary disorders			
Transaminases increased, aspartate aminotransferase increased, gammaglutamyltransferase increased, liver function test abnormal, blood alkaline	Uncommon	-	-

[8] ema.europa.eu. (2017). Eliquis – *Summary of product characteristics (SPC)* [online] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf [accessed 31 Aug. 2017]

phosphatase increased, blood bilirubin increased			
Skin and subcutaneous tissue disorders			
Skin rash	-	Uncommon	-
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage	Rare	-	
Renal and urinary disorders			
Haematuria	Uncommon	Common	Common
Reproductive system and breast disorders			
Abnormal vaginal haemorrhage, urogenital haemorrhage	-	Uncommon	Uncommon
General disorders and administration site conditions			
Application site bleeding	-	Uncommon	-
Investigations			
Occult blood positive	-	Uncommon	Uncommon
Injury, poisoning and procedural complications			
Contusion	Common	Common	Common
Post procedural haemorrhage (including post procedural haematoma, wound haemorrhage, vessel puncture site haematoma and catheter site haemorrhage), wound secretion, incision site haemorrhage (including incision site haematoma), operative haemorrhage	Uncommon	-	-
Traumatic haemorrhage, post procedural haemorrhage, incision site haemorrhage	-	Uncommon	Uncommon

Table 13: Adverse reactions ranked under headings of system organ class and frequency using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data) for VTEp, NVAF, and VTEt respectively.

9.3.2 AE from Summary of product characteristics: dabigatran[9]

System Organ Class	Frequency
Blood and lymphatic system disorders	
Haemoglobin decreased	Common
Anaemia	Uncommon
Haematocrit decreased	Uncommon
Thrombocytopenia	Rare
Immune system disorder	
Drug hypersensitivity	Uncommon
Anaphylactic reaction	Rare
Angioedema	Rare
Urticaria	Rare
Rash	Rare
Pruritus	Rare
Bronchospasm	Not known
Nervous system disorders	
Intracranial haemorrhage	Rare
Vascular disorders	
Haematoma	Uncommon
Wound haemorrhage	Uncommon
Haemorrhage	Rare
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Uncommon
Haemoptysis	Rare
Gastrointestinal disorders	
Gastrointestinal haemorrhage	Uncommon
Rectal haemorrhage	Uncommon
Haemorrhoidal haemorrhage	Uncommon
Diarrhoea	Uncommon
Nausea	Uncommon
Vomiting	Uncommon
Gastrointestinal ulcer, including oesophageal ulcer	Rare
Gastroesophagitis	Rare
Gastroesophageal reflux disease	Rare
Abdominal pain	Rare
Dyspepsia	Rare
Dysphagia	Rare
Hepatobiliary disorders	
Hepatic function abnormal/ Liver function test abnormal	Common
Alanine aminotransferase increased	Uncommon
Aspartate aminotransferase increased	Uncommon
Hepatic enzyme increased	Uncommon
Hyperbilirubinaemia	Uncommon

[9] ema.europa.eu. (2017). *Pradaxa – Summary of product characteristics (SPC)* [online] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf [accessed 31 Aug. 2017]

Skin and subcutaneous tissue disorder	
Skin haemorrhage	Uncommon
Musculoskeletal and connective tissue disorders	
Haemarthrosis	Uncommon
Renal and urinary disorders	
Genitourological haemorrhage, including haematuria	Uncommon
General disorders and administration site conditions	
Injection site haemorrhage	Rare
Catheter site haemorrhage	Rare
Bloody discharge	Rare
Injury, poisoning and procedural complications	
Traumatic haemorrhage	Uncommon
Post procedural haematoma	Uncommon
Post procedural haemorrhage	Uncommon
Post procedural discharge	Uncommon
Wound secretion	Uncommon
Incision site haemorrhage	Rare
Anaemia postoperative	Rare
Surgical and medical procedures	
Wound drainage	Rare
Post procedural drainage	Rare

Table 14: Adverse reactions ranked under headings of System Organ Classes (SOC) and frequency using the following convention: very common (≥ 1/10), common (≥ 1 /100 to <1 /10), uncommon (≥ 1/1,000 to <1 /100), rare (≥ 1 /10,000 to <1 /1,000), very rare (<1 /10,000), not known (cannot be estimated from the available data).

9.3.3 AE from Summary of product characteristics: edoxaban[10]

System Organ Class	Frequency
Blood and lymphatic system disorders	
Anaemia	Common
Immune system disorders	
Hypersensitivity	Uncommon
Anaphylactic reaction	Rare
Allergic oedema	Rare
Nervous system disorders	
Dizziness	Common
Headache	Common
Intracranial haemorrhage (ICH)	Uncommon
Subarachnoid haemorrhage	Rare
Eye disorders	
Conjunctival/Scleral haemorrhage	Uncommon
Intraocular haemorrhage	Uncommon
Cardiac disorders	
Pericardial haemorrhage	Rare
Vascular disorders	
Other haemorrhage	Uncommon
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Common
Haemoptysis	Uncommon
Gastrointestinal disorders	
Abdominal pain	Common
Lower GI haemorrhage	Common
Upper GI haemorrhage	Common
Oral/Pharyngeal haemorrhage	Common
Nausea	Common
Retroperitoneal haemorrhage	Rare
Hepatobiliary disorders	
Blood bilirubin increased	Common
Gammaglutamyltransferase increased	Common
Blood alkaline phosphatase increased	Uncommon
Transaminases increased	Uncommon
Aspartate aminotransferase increased	Uncommon
Skin and subcutaneous tissue disorders	
Cutaneous soft tissue haemorrhage	Common
Rash	Common
Pruritus	Common
Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	
Intramuscular haemorrhage (no compartment syndrome)	Rare
Intra-articular haemorrhage	Rare

[10] ema.europa.eu. (2017). *Pradaxa – Summary of product characteristics (SPC)* [online] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf [accessed 31 Aug. 2017]

Renal and urinary disorders	
Macroscopic haematuria/urethral haemorrhage	Common
Reproductive system and breast disorders	
Vaginal haemorrhage	Common
General disorders and administration site conditions	
Puncture site haemorrhage	Common
Investigations	
Liver function test abnormal	Common
Injury, poisoning and procedural complications	
Surgical site haemorrhage	Uncommon
Subdural haemorrhage	Rare
Procedural haemorrhage	Rare

Table 15: Adverse reactions ranked under headings of System Organ Classes (SOC) and frequency using the following convention: very common (≥ 1/10), common (≥ 1 /100 to <1 /10), uncommon (≥ 1/1,000 to <1 /100), rare (≥ 1 /10,000 to <1 /1,000), very rare (<1 /10,000), not known (cannot be estimated from the available data).

9.3.4 AE from Summary of product characteristics: rivaroxaban[11]

System Organ Class	Frequency
Blood and lymphatic system disorders	
Anaemia	Common
Thrombocythemia	Uncommon
Immune system disorders	
Allergic reaction	Uncommon
Allergic dermatitis	Uncommon
Nervous system disorders	
Dizziness	Common
Headache	Common
Cerebral and intracranial haemorrhage	Uncommon
Syncope	Uncommon
Eye disorders	
Eye haemorrhage	Common
Cardiac disorders	
Tachycardia	Uncommon
Vascular disorders	
Hypotension	Common
Haematoma	Common
Respiratory, thoracic and mediastinal disorders	
Epistaxis	Common
Haemoptysis	Common
Gastrointestinal disorders	
Gingival bleeding,	Common
Gastrointestinal tract haemorrhage	Common
Gastrointestinal and abdominal pains	Common
Dyspepsia	Common
Nausea	Common
Obstipation	Common
Diarrhoea	Common
Vomiting	Common
Dry mouth	Uncommon
Hepatobiliary disorders	
Hepatic function abnormal	Uncommon
Jaundice	Rare
Skin and subcutaneous tissue disorders	
Pruritus	Common
Rash	Common
Ecchymosis	Common
Cutaneous and subcutaneous hemorrage	Common
Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	
Pain in extremity	Common
Haemarthrosis	Uncommon

[11] ema.europa.eu. (2017). *Xarelto – Summary of product characteristics (SPC)* [online] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf [accessed 31 Aug. 2017]

Muscle haemorrhage	Rare
Compartment syndrome secondary to a bleeding	Not known
Renal and urinary disorders	
Urogenital tract haemorrhage	Common
Renal impairment	Common
Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion	Not known
General disorders and administration site conditions	
Fever	Common
Peripheral oedema	Common
Decreased general strength and energy	Common
Feeling unwell	Uncommon
Localised oedema	Rare
Investigations	
Increase in transaminases	Common
Increased bilirubin	Uncommon
Increased blood alkaline phosphatase	Uncommon
Increased LDH	Uncommon
Increased lipase	Uncommon
Increased amylase	Uncommon
Increased GGT	Uncommon
Bilirubin conjugated increased	Rare
Injury, poisoning and procedural complications	
Postprocedural haemorrhage	Common
Vascular pseudoaneurysm	Rare

Table 16: Adverse reactions ranked under headings of System Organ Classes (SOC) and frequency using the following convention: very common (≥ 1/10), common (≥ 1 /100 to <1 /10), uncommon (≥ 1/1,000 to <1 /100), rare (≥ 1 /10,000 to <1 /1,000), very rare (<1 /10,000), not known (cannot be estimated from the available data).

Appendices

10 Guidelines - details

10.1 General information on the selected guidelines

10.1.1 Selected

10.1.1.1 For atrial fibrillation

Abbreviation	Guideline
AHA/ACC/HRS 2014	American Heart Association / American College of Cardiology / Heart Rhythm Society Guideline for the management of patients with atrial fibrillation
CCS 2016/2014/2012	Canadian Cardiovascular Society - Focused 2012 update of the CCS atrial fibrillation guidelines : recommendations for stroke prevention and rate/rhythm control - 2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation - 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation
ESC 2016 AF	European Society of cardiology / Guidelines for the management of atrial fibrillation developed in collaboration with EACTS
NICE 2014	National Institute for health and Care Excellence / Atrial Fibrillation

Table 17: selected guidelines for atrial fibrillation and their abbreviations as used in this report

The recent KCE report on anticoagulants in non-valvular atrial fibrillation (Van Brabandt, 2017(2) will be reported alongside these guidelines.

10.1.1.2 For venous thromboembolism

Abbreviation	Guideline
ACCP 2016	American College of Chest Physicians / Antithrombotic therapy for VTE disease: CHEST Guideline and Expert 2016
ESC 2014	European Society of Cardiology / Acute pulmonary embolism (diagnosis and management) 2014

Table18: selected guidelines for venous thromboembolism and their abbreviations as used in this report

10.1.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in the tables below.

10.1.2.1 AHA/ACC/HRS 2014

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.
*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes mellitus, history of prior myocardial infarction, history of heart failure, and prior aspirin use.
†For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

(*cited from AHA/ACC/HRS 2014 AF)*

10.1.2.2 CCS 2016/2014/2012

CCS 2016/2014/2012	
Recommendations	• "We recommend": strength and quality are strong • "We suggest": strength and quality of evidence is not strong
Quality of evidence	High
	Moderate
	Low
	Very low
Strength of recommendation	Strong
	Weak

Table19: Grades of recommendation and quality of evidence in the CCS 2016/2014/2012 AF guideline

10.1.2.3 ESC 2016 AF

Table 1: Classes of Recommendations		
Classes of Recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2 - Levels of Evidence

Table 2: Level of Evidence	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

(cited from the ESC 2016 atrial fibrillation guidelines)

10.1.2.4 NICE 2014

NICE 2014		
The quality of evidence is assessed by using the GRADE approach, but where GRADE allocates labels or symbols to represent the strength of a recommendation, NICE does not do this. Instead, the concept of strength is reflected in the wording of the recommendation (see section 9.3.3 in the NICE guidelines manual 2012).		
Recommendations that must be used	There is a legal duty to apply the recommendation / intervention	Use "must" or "must not" Use the passive voice: "intervention x must be used"
Recommendations that should be used	The intervention will do more good than harm and will be cost-effective	Use direct instructions Prefer " (do not) offer, refer, advise, discuss" to "should"
Recommendations that could be used	The intervention will do more good than harm for most patients and will be cost-effective Other options may be similarly cost-effective Some patients may opt for a less effective but cheaper intervention Results of the intervention are more likely to vary	Use direct instructions Prefer "(do not) consider" to "could" Other options depending on phrasing: "think about, assess".

Table20: Levels of evidence and strength of recommendations of the NICE 2014 guideline

10.1.2.5 ACCP 2016

Table 4—*Strength of the Recommendations Grading System*

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burdens or vice versa.	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low- or very-low-quality evidence (1C)	Benefits clearly outweigh risk and burdens or vice versa.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balanced with risks and burden.	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balanced with risks and burden.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.	Best action may differ depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, low- or very-low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.

(*cited from the methodology supplement to the ACCP 2016 VTE guideline)*

10.1.2.6 ESC 2014

The classes of recommendations and levels of evidence are identical to the ESC 2016 Atrial Fibrillation guideline (see above).

10.1.3 Agree II score

Information about the Agree II score can be found in the section "Methodology".
A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in the table below. The total domain score is also reported in this table.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
AHA/ACC/HRS 2014	6	2	5	6	6	7	6	7	**45**	**80.00%**
CCS 2016/2014/2012	2	3	3	4	7	6	6	7	**38**	**68.00%**
ESC 2016 AF	2	2	2	4	7	7	5	5	**34**	**61.00%**
NICE 2014	6	7	7	7	7	7	7	5	**53**	**94.00%**
ACCP 2016	5	4	7	6	6	7	6	7	**48**	**86.00%**
ESC 2014	2	2	2	4	7	7	5	5	**34**	**61.00%**

Table21: AGREE score of selected guidelines on item "Rigour of development"

10.1.4 Included populations – interventions – main outcomes

AHA/ACC/HRS 2014	
Population	Patients with atrial fibrillation
Intervention	Screening tools, diagnosis, risk evaluation, prevention of thromboembolism, anticoagulant treatment, rate and rhythm control, surgical treatment, bridging
Outcomes	Not clearly specified. From observation: stroke / embolism, major bleedings, TTR

Table22: included populations, interventions and main outcomes of the AHA/ACC/HRS 2014 guideline

CCS 2016/2014/2012	
Population	Patients with atrial fibrillation
Intervention	Diagnosis, risk stratification, anticoagulation therapy, rate control, rhythm control
Outcomes	Not clearly specified. From observation: (ischemic) stroke, bleeding, mortality

Table23: included populations, interventions and main outcomes of the CCS 2016/2014/2012 guideline

ESC 2016 AF	
Population	Patients with atrial fibrillation
Intervention	Diagnosis, classification, anticoagulation, rate control, rhythm control, minimizing of bleeding risk, management of bleeding, catheter ablation,
Outcomes	Stroke / systemic embolism, Ischemic stroke, haemorrhagic stroke, major bleeding, intracranial bleeding, gastro-intestinal major bleeding, myocardial infarction, death from any cause

Table24: included populations, interventions and main outcomes of the ESC 2016 AF guideline

NICE 2014	
Population	Patients with atrial fibrillation
Intervention	Antiplatelets, Dual antiplatelets, Anticoagulants, Anticoagulants and antiplatelets, Anticoagulants and dual antiplatelets
Outcomes	Mortality Ischaemic stroke Haemorrhagic stroke Major bleeding Hospitalisation Health related quality of life Thromboembolic complications

Table25: included populations, interventions and main outcomes of the NICE 2014 guideline

ACCP 2016	
Population	Patients with both DVT and PE
Intervention	Anticoagulant therapy, thrombolytic therapy, surgical treatments, management of recurrent VTE
Outcomes	All-cause mortality, recurrent VTE, major bleeding

Table26: included populations, interventions and main outcomes of the ACCP 2016 guideline

ESC 2014	
Population	Patients with PE
Intervention	Diagnosis, acute phase treatments, anticoagulation, surgical treatments, extended anticoagulation, discharging and home treatment
Outcomes	Not mentioned outright. Includes (but not limited to): recurrence of PE or DVT, major bleedings, mortality

Table27: included populations, interventions and main outcomes of the ESC 2014 guideline

10.1.5 Members of the development group / target audience

AHA/ACC/HRS 2014	
Development group	Cardiologists, cardiac surgeons, neurologists
Target audience	Cardiologists, cardiac surgeons, general practitioners

Table28: Members of the development group and target audience of the AHA/ACC/HRS 2014 guideline

CCS 2016/2014/2012	
Development group	Cardiologists, pharmacologists (note: complete list could not be retrieved from website)
Target audience	Cardiologists, general practitioners

Table29: Members of the development group and target audience of the CCS 2016/2014/2012 guideline

ESC 2016 AF	
Development group	Not specified
Target audience	Cardiologists, general practitioners

Table30: Members of the development group and target audience of the ESC 2016 AF guideline

NICE 2014	
Development group	Health professionals, researchers, lay members
Target audience	Cardiologists, general practitioners

Table 31: Members of the development group and target audience of the NICE 2014 guideline

ACCP 2016	
Development group	General internists, thrombosis specialists, pulmonologists, hematologists and methodologists
Target audience	not specified

Table32: Members of the development group and target audience of the ACCP 2016 guideline

ESC 2014	
Development group	Not specified
Target audience	Not specified Note: seeing as diagnosis and treatment of emergency presentations of PE are part of the guideline it is probably aimed at emergency physicians, surgeons, specialists and general practitioners

Table33: Members of the development group and target audience of the ESC 2014 guideline

10.1.6 Method of reporting on the recommendations and notes

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Even though the NICE 2015 guideline did not grade its recommendations, it does appraise and determine a level of evidence for the studies leading to the recommendations. For that reason, the recommendations of the NICE 2015 guideline are also written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

10.2 Atrial Fibrillation

10.2.1 Adherence

10.2.1.1 AHA/ACC/HRS 2014

Adherence to therapy is not outright mentioned in this guideline.

10.2.1.2 CCS 2016/2014/2012

Physician-patient discussions are necessary to ensure the patient understands the importance of long-term adherence to OAC therapy (not part of a recommendation but of the introduction).

10.2.1.3 ESC 2016

- Adherence appears in the text of the guideline as a component of "integrated atrial fibrillation care".
Recommendation: **Placing patients in a central role in decision-making should be considered in order to tailor management to patient preferences and improve adherence to long-term therapy. (IIa, C)**
Patients should have a central role in the care process. As treatment of AF requires patients to change their lifestyles and adhere to chronic therapy, at times without an immediately tangible benefit, they need to understand their responsibilities in the care process. Physicians and healthcare professionals are responsible for providing access to evidence-based therapy, but adherence to therapy is ultimately the responsibility of informed and autonomous patients, best described as 'shared accountability'. Hence, information and the education of patients, and often of their partners and relatives, is indispensable to encourage a self-management role and to empower patients to participate in shared decision-making, and to support understanding of the disease and the suggested treatments.
Shared decision-making an patient-centered organization of care can help to ensure adherence to management.

- Adherence to therapy is later also mentioned as a performance indicator of patient education and self-care capacities.
Recommendation: **Tailored patient education is recommended in all phases of AF management to support patients' perception of AF and to improve management (I,C).**
Recommendation: **Patient involvement in the care process should be considered to encourage self-management and responsibility for lifestyle changes (IIa, C).**
Recommendation**: Shared decision making should be considered to ensure that care is based on the best available evidence preferences of the patient (IIa, C).**
Knowledge (about disease, about treatment, about management goals) and capabilities (what to do if…) are considered to be an integral part of follow-up with the aim to improve adherence.

- The follow-up of adherence is also mentioned in the context of prognostic factors: risk of stroke, bleeding an mortality will be influenced by adherence.
We find one more recommendation in this context:

Recommendation: **In patients who suffer a TIA or stroke while on anticoagulation, adherence to therapy should be assessed and optimized (IIa, C).**

10.2.1.4 NICE 2014

Reassess anticoagulation for a person with poor anticoagulation control shown by any of the following:

- **2 INR values higher than 5 or 1 INR value higher than 8 within the past 6 months**
- **2 INR values less than 1.5 within the past 6 months**
- **TTR less than 65%. [new 2014]**

When reassessing anticoagulation, take into account and if possible address the following factors that may contribute to poor anticoagulation control:

- **cognitive function**
- **adherence to prescribed therapy**
- **illness**
- **interacting drug therapy**
- **lifestyle factors including diet and alcohol consumption.**

(Recommendation that should be used)

10.2.1.5 KCE 2017

The relative risk for discontinuation of the study drug in the VKA vs the DOAC arms were comparable in the blinded RCTs, but the discontinuation rates were high in both arms (around 25% in each arm).

The RE-LY trial (dabigatran vs VKA) was the only one of the RCTs in which patients in the VKA arm were not blinded. Although a higher discontinuation rate might have been expected due to the inconvenience of regular blood testing needed for anticoagulation monitoring in the VKA group, this was not the case. Significantly more patients in the DOAC arm discontinued the drug. (RR 1.26; 95%CI: 1.18-1.35).

Real world data from Germany indicate that persistence on oral anticoagulants at 1 year was better for DOACs than for VKAs with proportions of 63.6% and 79.2% respectively.98 In a Swedish study, the overall persistence with any oral anticoagulant was high with 88.2 % at 1 year and 82.9% at 2 years. Multivariate analysis confirmed significantly higher persistence with warfarin and apixaban than with dabigatran or rivaroxaban.

Non-adherence might be less well tolerated for DOACs than for VKAs, because of their shorter half-life. In the 2016 version of the US Clinical Performance and Quality Measures, it is stressed that missing even one dose of a DOAC can result in a period without protection from thromboembolism.

10.2.2 First treatment choice: starting with VKA or DOAC?

Note from the literature group: comparisons of VKA or DOACs with ASA / antiplatelet and combinations thereof are done by some guidelines but aren't within the scope of this review.

The following table summarizes recommendations once it has been established that anticoagulation was necessary. How this need is established depends on guidelines, scales (CHA_2DS_2-VAsc for example) and thresholds used by the guideline. How to make the decision to start anticoagulation falls outside of the scope of this literature review.
The first three guidelines in this table agree that in the case of nonvalvular atrial fibrillation, a DOAC is preferable as a first treatment.
AHA/ACC/HRS 2014 gives a higher QoE for their recommendation of using warfarin after a stroke or previous TIA in NVAF, compared to a lower QoE for DOACS. Warfarin is also recommended for patients with end-stage CKD. Dabigatran and rivaroxaban are not recommended and dabigatran is even recommended against in CKD patients.
NICE 2014 mentions that choice of OAC therapy must be discussed with the patient, but that with NVAF and in the presence of certain risk factors, a DOAC is recommended.

	Warfarin	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
AHA/ACC/HRS 2014 (LoE)	For AF patients with mechanical heart valves (I,B) NVAF with prior stroke, TIA or CHA2DS2VASc ≥2 (I, A) NVAF and CHA2DS2VASc ≥2 and end-stage CKD (IIb, B)	NVAF with prior stroke, TIA or CHA2DS2VASc ≥2 (I, B)	NVAF with prior stroke, TIA or CHA2DS2VASc ≥2 (I, B) Should NOT be used in patient with a mechanical heart valve (III harm, B) Not recommended for patients with end-stage CKD (III no benefit, C)		NVAF with prior stroke, TIA or CHA2DS2VASc ≥2 (I, B) Not recommended for patients with end-stage CKD (III no benefit, C)
CCS 2016/2014/2012	AF and mechanical heart valves, rheumatic mitral stenosis, or moderate and severe nonrheumatic mitral stenosis (strong, mod quality)	A DOAC is preferred for NVAF (strong, high QoE) also in the case of CAD + risk factors (stroke, TIA, DM, hypertension, heart failure) a DOAC is preferred (conditional recommendation, low QoE)			
ESC 2016	for AF patients with moderate to severe mitral stenosis (QoE: C) or mechanical heart valves (QoE: B)	A DOAC is preferred to VKA in patient eligible for DOACS (IA)			
NICE 2014		Recommended in NVAF and risk factor(s): -prior stroke or TIA -≥75y -hypertension -diabetes mellitus -symptomatic heart failure	Recommended in patients with NVAF and risk factor(s): -previous stroke, TIA or systemic embolism -LV ejection fraction <40% -symptomatic HF (NYHA ≥2) -≥75 y -≥65y and CAD, DM or hypertension		Recommended in patients with NVAF and risk factor(s): -prior stroke or TIA -congestive heart failure -hypertension -≥75 y -diabetes mellitus

Table34: choice of OAC medication

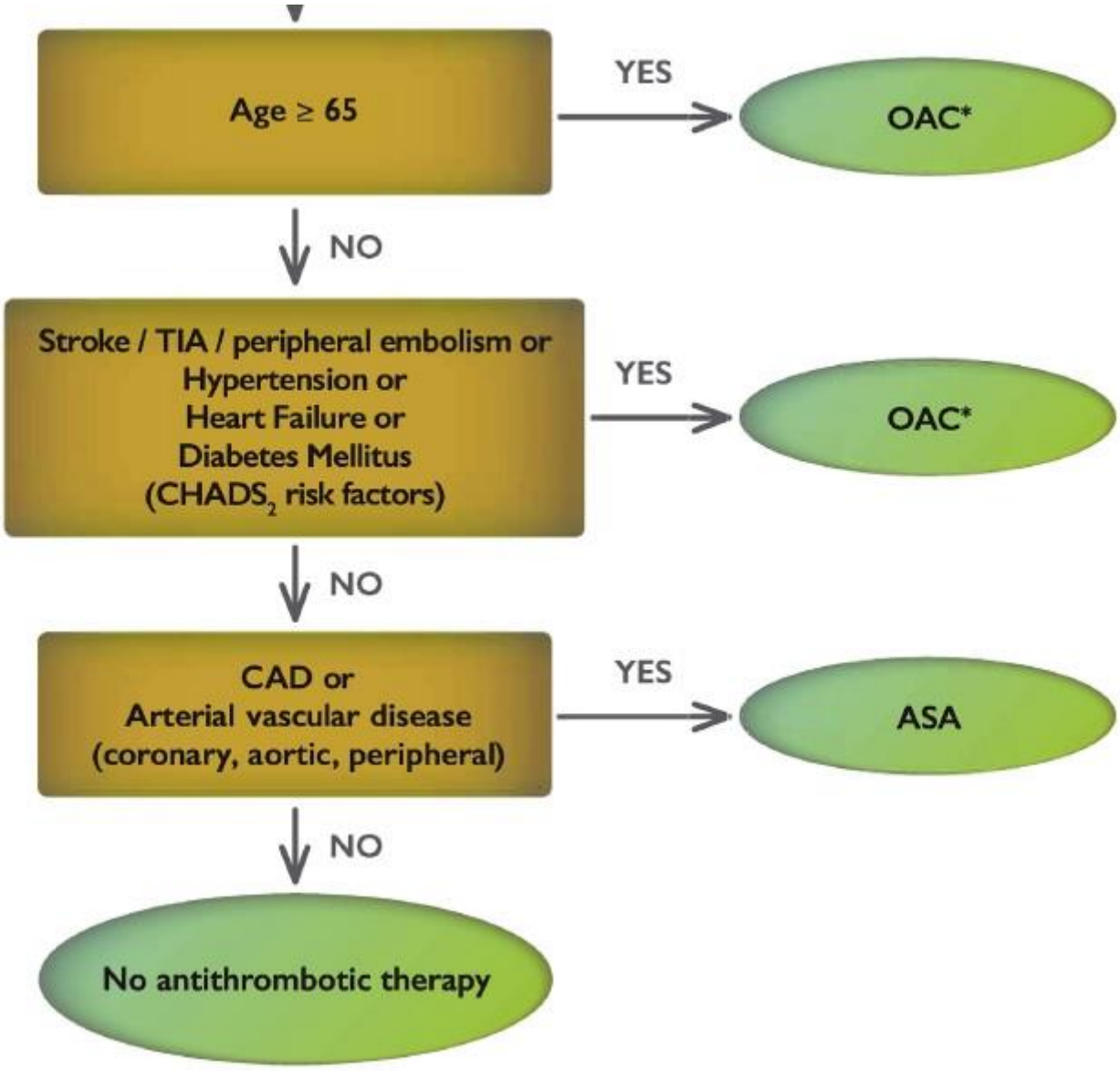
10.2.2.1 AHA/ACC/HRS 2014

For patients with AF who have mechanical heart valves, warfarin is recommended and the target international normalized ratio (INR) intensity (2.0 to 3.0 or 2.5 to 3.5) should be based on the type and location of the prosthesis (174-176). (Class I, Level of Evidence: B)

For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA2DS2-VASc score of 2 or greater, oral anticoagulants are recommended. Options include: warfarin (INR 2.0 to 3.0) (Level of Evidence: A), dabigatran (Level of Evidence: B), rivaroxaban (Level of Evidence: B), or apixaban. (Class I Level of Evidence: B)
For patients with nonvalvular AF with a CHA2DS2-VASc score of 2 or greater and who have end-stage CKD (creatinine clearance [CrCl] <15 mL/min) or are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation (185). (Class IIa, Level of Evidence: B)
The direct thrombin inhibitor, dabigatran, and the factor Xa inhibitor, rivaroxaban, are not recommended in patients with AF and end-stage CKD or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits (177-179, 187-189). (Class III no benefit, Level of Evidence: C)
The direct thrombin inhibitor, dabigatran, should not be used in patients with AF and a mechanical heart valve (190). (Class III harm, Level of Evidence: B)

10.2.2.2 CCS 2016/2014/2012

We recommend that when OAC therapy is indicated for patients with nonvalvular AF, most patients should receive dabigatran, rivaroxaban, apixaban, or edoxaban (*) **(when approved) in preference to warfarin (Strong Recommendation, High-Quality Evidence)**.(CCS 2014 and 2012)
When OAC is indicated in the presence of CAD, we suggest a DOAC in preference to warfarin for NVAF (Conditional Recommendation, Low-Quality Evidence).(CCS 2016)



Figuur 1: CSS algorithm ("CHADS65") for OAC therapy in AF from CSS guideline 2016

Values and preferences. This recommendation places a relatively high value on comparisons with warfarin showing that dabigatran and apixaban have greater efficacy and rivaroxaban has similar efficacy for stroke prevention; dabigatran and rivaroxaban have no more major bleeding and apixaban has less; all 3 new OACs(*) **have less intracranial hemorrhage and are much simpler to use. The recommendation places less value on the following features of warfarin: long experience with clinical use, availability of a specific antidote, and a simple and standardized test for intensity of anticoagulant effect. The preference for 1 of the new OACs over warfarin is less marked among patients already receiving warfarin with stable INRs and no bleeding complications**.(CSS 2012)

(*) The recommendation from 2012 is the same as the one in 2014 safe for the newer OAC edoxaban.

It is also recommended that patients who refuse warranted OAC therapy should receive the combination of ASA and clopidogrel. (CCS 2014)

10.2.2.3 ESC 2016

Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves. (IB)
When oral anticoagulation is initiated in a patient with AF who is eligible for a DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a DOAC is recommended in preference to a vitamin K antagonist. (IA)
Both VKAs and DOACs are effective for the prevention of stroke in AF. A meta-analysis based on the high-dose treatment groups of the pivotal studies of warfarin vs. DOACs included 42 411 patients receiving a DOAC and 29 272 receiving warfarin. DOACs in these dosages significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0.81; 95% CI 0.73– 0.91; P<0.0001), mainly driven by a reduction in haemorrhagic stroke (RR 0.49; 95% CI 0.38–0.64; P < 0.0001). Mortality was 10% lower in patients randomized to DOAC therapy (RR 0.90; 95% CI 0.85–0.95; P =0.0003) and intracranial haemorrhage was halved (RR 0.48; 95% CI 0.39–0.59; P<0.0001), while gastrointestinal bleeding events were more frequent (RR 1.25; 95% CI 1.01–1.55; P=0.04). The stroke reduction with DOACs was consistent in all evaluated subgroups, while there was a suggestion of greater relative reduction in bleeding with DOACs at centres with poor INR control (interaction P =0.022). Notably, the substantial reduction in intracranial haemorrhage by DOACs compared with warfarin seems unrelated to the quality of INR control.

10.2.2.4 NICE 2014

Discuss the options for anticoagulation with the person and base the choice on their clinical features and preferences. [new 2014]

Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorisation, that is, in people with non-valvular atrial fibrillation with 1 or more risk factors such as:

- **prior stroke or transient ischaemic attack**
- **age 75 years or older**
- **hypertension**
- **diabetes mellitus**
- **symptomatic heart failure.**

The decision about whether to start treatment with apixaban should be made after an informed discussion between the clinician and the person about the risks and benefits of apixaban compared with warfarin, dabigatran etexilate and rivaroxaban. For people who are taking warfarin, the potential risks and benefits of switching to apixaban should be considered in light of their level of international normalised ratio (INR) control.

[from Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation (NICE technology appraisal guidance).]

Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with non-valvular atrial fibrillation with one or more of the following risk factors:

- **previous stroke, transient ischaemic attack or systemic embolism**
- **left ventricular ejection fraction below 40%**
- **symptomatic heart failure of New York Heart Association (NYHA) class 2 or above**
- **age 75 years or older**
- **age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.**

The decision about whether to start treatment with dabigatran etexilate should be made after an informed discussion between the clinician and the person about the risks and benefits of dabigatran etexilate compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to dabigatran etexilate should be considered in light of their level of international normalised ratio (INR) control. [This recommendation is from Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (NICE technology appraisal guidance 249).]

Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with non-valvular atrial fibrillation with one or more risk factors such as:

- **prior stroke or transient ischaemic attack.**
- **congestive heart failure**
- **hypertension**
- **age 75 years or older**
- **diabetes mellitus**

The decision about whether to start treatment with rivaroxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of rivaroxaban compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to rivaroxaban should be considered in light of their level of international normalised ratio (INR) control.
[This recommendation is from Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation (NICE technology appraisal guidance 256).

10.2.2.5 KCE 2017

KCE 2017 doesn't give recommendations but states the following:

ESC favours DOACs above VKA in its 2016 version.

The AHA/ACC does not clearly formulate a preference on what type of anticoagulant to prescribe, although it stipulates that the level of evidence for VKAs […] is higher than for DOACs (level B, referring to the fact that for each DOAC only one RCT has been published).

10.2.3 Switch from VKA to DOAC or reversed

10.2.3.1 AHA/ACC/HRS 2014

For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor (dabigatran, rivaroxaban, or apixaban) is recommended. (Level of Evidence: C)
Re-evaluation of the need for and choice of antithrombotic therapy at periodic intervals is recommended to reassess stroke and bleeding risks. (Level of Evidence: C)

10.2.3.2 CCS 2016/2014/2012

There is no information on when to switch to a DOAC.

10.2.3.3 ESC 2016

AF patients already on treatment with a vitamin K antagonist may be considered for DOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to DOAC (e.g. prosthetic valve). (IIb, A)

10.2.3.4 NICE 2014

Reassess anticoagulation for a person with poor anticoagulation control shown by any of the following:

- **2 INR values higher than 5 or 1 INR value higher than 8 within the past 6 months**
- **2 INR values less than 1.5 within the past 6 months**
- **TTR less than 65%. [new 2014]**

If poor anticoagulation control cannot be improved, evaluate the risks and benefits of alternative stroke prevention strategies and discuss these with the person.
The decision about whether to start treatment with apixaban should be made after an informed discussion between the clinician and the person about the risks and benefits of apixaban compared with warfarin, dabigatran etexilate and rivaroxaban. For people who are taking warfarin, the potential risks and benefits of switching to apixaban should be considered in light of their level of international normalised ratio (INR) control. [This recommendation is from Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (NICE technology appraisal guidance 249).]

The decision about whether to start treatment with dabigatran etexilate should be made after an informed discussion between the clinician and the person about the risks and benefits of dabigatran etexilate compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to dabigatran etexilate should be considered in light of their level of international normalised ratio (INR) control. [This recommendation is from Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation (NICE technology appraisal guidance 249).]

The decision about whether to start treatment with rivaroxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of rivaroxaban compared with warfarin. For people who are taking warfarin, the potential risks and benefits of

switching to rivaroxaban should be considered in light of their level of international normalised ratio (INR) control.
[This recommendation is from Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation (NICE technology appraisal guidance 256).

10.2.3.5 KCE 2017

No mention of those recommendations.

10.2.4 Choice between DOACS

10.2.4.1 AHA/ACC/HRS 2014

The direct thrombin inhibitor, dabigatran, and the factor Xa inhibitor, rivaroxaban, are not recommended in patients with AF and end-stage CKD or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits (177-179, 187-189). (Class III no benefit, Level of Evidence: C)

The direct thrombin inhibitor, dabigatran, should not be used in patients with AF and a mechanical heart valve (190). (Class III harm, Level of Evidence: B)

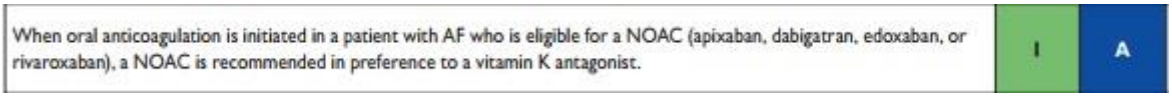
10.2.4.2 CCS 2016/2014/2012

While not a formal recommendation, the guideline mentions the studies done on dabigatran and dose adjustment (110 mg rather than 150mg) for dabigatran in elderly patients (≥75y).

10.2.4.3 ESC 2016

No differences are made between DOACS by the guideline. When a DOAC is recommended all are mentioned in one sequence.

For example:



Figuur 2: Screen capture from the ESC 2016 guideline, illustrating that no DOAC is preferred to another in this recommendation.

10.2.4.4 NICE 2014

Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorisation, that is, in people with non-valvular atrial fibrillation with 1 or more risk factors such as:

- **prior stroke or transient ischaemic attack**
- **age 75 years or older**
- **hypertension**
- **diabetes mellitus**
- **symptomatic heart failure.**

Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with non-valvular atrial fibrillation with one or more of the following risk factors:

- **previous stroke, transient ischaemic attack or systemic embolism**
- **left ventricular ejection fraction below 40%**
- **symptomatic heart failure of New York Heart Association (NYHA) class 2 or above**
- **age 75 years or older**

- **age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.**

Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with non-valvular atrial fibrillation with one or more risk factors such as:

- **prior stroke or transient ischaemic attack.**
- **congestive heart failure**
- **hypertension**
- **age 75 years or older**
- **diabetes mellitus**

See also Table9: choice of OAC medication

10.2.4.5 KCE 2017

KCE 2017 doesn't give recommendations but states the following:

Within the group of DOACs, none of the guidelines recommend one DOAC over another.

10.3 Deep vein thrombosis and pulmonary embolism

10.3.1 Adherence

10.3.1.1 ACCP 2016

The guideline does not make a recommendation about adherence.
However, it mentions that VKA can be a choice in case of poor compliance because INR monitoring can help detect problems. It also states that patients may be more compliant with a DOAC because it is less complex.

10.3.1.2 ESC 2014

No mention of adherence.

10.3.2 First treatment choice: DOACs or VKA?

10.3.2.1 ACCP 2016

The guideline doesn't make a difference in its recommendations between DVT and PE

For the first three months:
In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).
For patients with DVT of the leg or PE and no cancer who are not treated with dabigatran, rivaroxaban, apixaban, or edoxaban, we suggest VKA therapy over LMWH (Grade 2C).
Remarks: Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy.

Based on less bleeding with DOACs and greater convenience for patients and healthcare providers, we now suggest that a DOAC is used in preference to VKA for the initial and long-term treatment of VTE in patients without cancer.

In patients with VTE and cancer ("cancer-associated thrombosis"), as noted earlier in this section, we still suggest LMWH over VKA. In patients with VTE and cancer who are not treated with LMWH, we do not have a preference for either an DOAC or VKA.
In the absence of direct comparisons between DOACs, and no convincing indirect evidence that one DOAC is superior to another, we do not have a preference for one DOAC over another DOAC

This decision is also expected to be sensitive to patient preferences.

TABLE 6] Factors That May Influence Which Anticoagulant Is Chosen for Initial and Long-Term Treatment of VTE

Factor	Preferred Anticoagulant	Qualifying Remarks
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran, and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR raised because of liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance <30 mL/min	VKA	NOACs and LMWH contraindicated with severe renal impairment. Dosing of NOACs with levels of renal impairment differ with the NOAC and among jurisdictions.
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other NOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of GI bleeding	VKA, apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban, and edoxaban may be associated with more GI bleeding than VKA.
Poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a NOAC because it is less complex.
Thrombolytic therapy use	UFH infusion	Greater experience with its use in patients treated with thrombolytic therapy
Reversal agent needed	VKA, UFH	
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta
Cost, coverage, licensing	Varies among regions and with individual circumstances	

INR = International Normalized Ratio; NOAC = non-vitamin K oral coagulant. See Table 1 legend for expansion of other abbreviations.

10.3.2.2 ESC 2014

In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0 – 3.0). Class I, level B

As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily) is recommended. Class I, level B.

As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily) is recommended. Class I, level B.

As an alternative to VKA treatment, administration of dabigatran (150 mg twice daily or 110 mg twice daily for patients ≥80 years of age or those under concommitzant verapamil treatment) is recommended following acute phase anticoagulation. Class I, level B.

As an alternative to VKA treatment, administration of edoxaban is recommended following acute-phase parenteral coagulation. Class I, level B.

New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment. Class III, category A.

Explanation for the choice between DOACs and VKA's:

In summary, the results of the trials using DOACs in the treatment of VTE indicate that these agents are non-inferior (in terms of efficacy) and possibly safer (particularly in terms of major bleeding) than the standard heparin/VKA regimen.299 High TTR values were achieved under VKA treatment in all trials; on the other hand, the study populations included relatively young patients, very few of whom had cancer. At present, DOACs can be viewed as an alternative to standard treatment. At the moment of publication of these guidelines, rivaroxaban, dabigatran and apixaban are approved for treatment of VTE in the European Union; edoxaban is currently under regulatory review. Experience with DOACs is still limited but continues to accumulate. Practical recommendations for the handling of DOACs in different clinical scenarios and the management of their bleeding complications have recently been published by the European Heart Rhythm Association.

For patients with PE and cancer, weight adjusted LMWH should be considered for the first 3 – 6 months. Class Iia, level C.

10.3.3 Duration of treatment

10.3.3.1 ACCP 2016

In patients with a proximal DVT of the leg or PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer, time-limited period (eg, 6, 12, or 24 months) (Grade 1B), or (iii) extended therapy (no scheduled stop date) (Grade 1B).

In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B) and (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B), and recommend treatment for 3 months over extended therapy if there is a high risk of bleeding (Grade 1B).
Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually)

In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor, we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C); we recommend treatment with anticoagulation for 3 months over treatment of a longer, time-limited period (eg, 6, 12, or 24 months) (Grade 1B); and we recommend treatment with anticoagulation for 3 months over extended therapy (no scheduled stop date) (Grade 1B).

Remarks: Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however, it is anticipated that not all patients who are diagnosed with isolated distal DVT will be prescribed anticoagulants

In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B), and we recommend treatment with anticoagulation for 3 months over treatment of a longer, time-limited period (eg, 6, 12, or 24 months) (Grade 1B)
Remarks: After 3 months of treatment, patients with unprovoked DVT of the leg or PE should be evaluated for the risk-benefit ratio of extended therapy. Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however, it is anticipated that not all patients who are diagnosed with isolated distal DVT will be prescribed anticoagulants.

In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and a (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B)
Remarks: Patient sex and D-dimer level measured a month after stopping anticoagulant therapy may influence the decision to stop or extend anticoagulant therapy (see text). In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

In patients with a second unprovoked VTE and who have a (i) low bleeding risk (see text), we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months (Grade 1B); (ii) moderate bleeding risk (see text), we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B); or (iii) high bleeding risk (see text), we suggest 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 2B)
Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

In patients with DVT of the leg or PE and active cancer ("cancer-associated thrombosis") and who (i) do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B), and (ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B).
Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually)

10.3.3.2 ESC 2014

For patients with PE secondary to a transient risk factor oral anticoagulation is recommended for 3 months. Class I, level B

For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months. Class I, level A

Extended anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk. Class IIa, level B.

Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE. Class I, level B.

Rivaroxaban (20 mg once daily), dabigatran (150 mg twice daily or 110 mg twice daily for patients ≥80 of age or those under concomitant verapamil treatment) or apixaban (2.5 mg twice daily) should be considered as an alternative to VKA (except for patients with severe renal impairment) if extended anticoagulation treatment is necessary. Class IIa, level B.

In patients who receive extended anticoagulation, the risk-benefit ratio of continuing such treatment should be reassessed at regular intervals. Class I, level C.

For patients with PE and cancer, weight adjusted LMWH should be considered for the first 3 – 6 months. Class IIa, level C.

In patients with PE and cancer, extended anticoagulation (beyond de first 3 – 6 months) should be considered for an indefinite period or until the cancer is cured. Class IIa, level C.

10.3.4 Switch from VKA to DOAC or reversed

10.3.4.1 ACCP

Only switching from either or the VKA's or DOACs to LMWH is mentioned (in the case of a recurrent VTE while on OAC therapy).

10.3.4.2 ESC 2014

There is no formal recommendation about when to switch from one to the other. However, the recommendations for anticoagulant treatment of choice during the acute phase of treatment mention VKA as being on par with DOACs, wheres recommendations for longer treatment recommend to consider DOACS as an alternative to VKA (see above). Following this implies a possible switch from VKA to DOAC when therapy is extended.

10.4 Bridging

10.4.1 AHA/ACC/HRS 2014

Bridging therapy with unfractionated heparin or low-molecular weight heparin (LMWH) is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions on bridging therapy should balance the risks of stroke and bleeding. (Class of recommendation: I, Level of Evidence: C)

For patients with AF without mechanical heart valves who require interruption of warfarin or new anticoagulants for procedures, decisions about bridging therapy (LMWH or unfractionated heparin) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated. (Class of recommendation: I, Level of Evidence: C)

Interruption of anticoagulation is often considered for patients with AF who have episodes of bleeding or require surgical or interventional procedures associated with a bleeding risk. There is sparse evidence on which to base specific recommendations on the use of bridging of oral anticoagulants among patients with nonvalvular AF with adjusted-dose heparin or LMWH, however, additional studies (e.g., BRIDGE [Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery]) are on-going. The duration of interruption and timing of resumption of anticoagulation after the procedure is guided by individualized consideration of the risk of thrombotic events and the severity of the operative and perioperative bleeding risk. For patients who are treated with warfarin and who are at low risk of thromboemboli, or are back in normal sinus rhythm and are undergoing surgical or diagnostic procedures that carry a risk of bleeding, stopping warfarin for up to 1 week and allowing the INR to normalize without substituting UFH is a recognized approach. Warfarin is then resumed after adequate hemostasis has been achieved. For patients at higher risk of thromboembolism (mechanical valves, prior stroke, CHA2DS2-VASc score $\geqslant$2), bridging with UFH or LMWH is a common practice, although data for LMWH are limited.

An increasingly common approach, especially for pacemaker or implantable cardioverter-defibrillator implantation, catheter ablation, coronary angiography, and other vascular interventions, is to perform the procedure without interrupting warfarin.

Radiofrequency catheter ablation of AF performed with a therapeutic INR does not increase bleeding risk and reduces the risk of emboli. Pacemaker or defibrillator implantation with a therapeutic INR has a lower risk of postoperative bleeding than discontinuing warfarin and initiating bridging anticoagulation with UFH or LMWH, and may be considered in those patients requiring device implantation who also have a moderate-to-high thromboembolic risk.

For oral factor Xa inhibitors and direct thrombin inhibitors, there is limited experience with drug withdrawal prior to surgical procedures. In the ROCKET AF trial, rivaroxaban was held for 2 days prior to elective surgery or invasive procedure and for 24 hours prior to semiurgent procedures. The increased risk of bleeding should be weighed carefully against the urgency of surgery or an invasive procedure. Interruption of anticoagulation should be guided by the pharmacologic properties of the drug. The timing of resumption should take into account the fact that anticoagulation, in contrast to

warfarin, is achieved promptly, and that reversal agents are not yet available for these agents, which complicates management if bleeding occurs. For elective surgery, holding these agents for 1 day (2 doses for dabigatran and apixaban; 1 dose for rivaroxaban) prior to the procedure is generally sufficient for patients with normal renal function. The need for complete hemostasis (e.g., for spinal puncture, spinal/epidural catheter, or major surgery) will demand a longer period of discontinuation of ⩾48 hours for patients with normal renal function. An activated partial thromboplastin time for dabigatran and prothrombin time for apixaban and rivaroxaban may provide useful information; a level close to control suggests a low serum concentration of these agents. For patients undergoing catheter ablation, or any procedure in which perforation of the heart chamber is possible, these new agents need to be used with caution because of the lack of approved antidotes in the event of cardiac tamponade. In some cases, activated prothrombin complex concentrate and recombinant factor VIIa have been used to reverse the anticoagulant effects of these new agents. Specific reversing agents are not currently available but are under development.

10.4.2 CCS 2016/2014/2012

We suggest that interruption of anticoagulant therapy, particularly for VKAs, in a patient with AF/AFL is not necessary for most procedures with a low risk of bleeding, such as cardiac device implantation (pace- maker or implantable defibrillator), and most dental procedures (Table 1) (Conditional Recommendation, Moderate-Quality Evidence).

When a decision to interrupt warfarin therapy for an invasive procedure has been made for a patient with AF/AFL (atrial flutter), we suggest that bridging therapy with LMWH or UFH be instituted when the INR is below therapeutic level only in patients at high risk of thromboembolic events (CHADS2, score >= 4, mechanical heart valve, stroke/transient ischemic attack within 3 months, rheumatic heart disease) (Conditional Recommendation, Low-Quality Evidence).

We recommend no bridging (LMWH or UFH) for NVAF patients receiving DOACs who undergo elective surgery or invasive procedures requiring interruption of anticoagulation (Strong Recommendation, Moderate-Quality Evidence).

When patients receiving OACs or APT agents need surgery or invasive diagnostic procedures, the risk of SSE while the antithrombotic agent is reduced or stopped must be weighed against the risk of bleeding during or after the procedure.

Risks of major bleeding for various procedures have been categorized as very low, low, intermediate, and high by Thrombosis Canada (Table 1)

The current AF guidelines no longer differentiate low risk from very low risk. These procedures can generally be safely performed without interrupting antithrombotic therapy, provided the INR is not supratherapeutic in the case of warfarin. In the case of cardiac device implantation, superiority of uninterrupted warfarin has been shown, and an RCT is currently under way to determine the safety of uninterrupted DOACs for such procedures. Interruption of anticoagulation remains recommended for procedures with an intermediate or high risk of major bleeding.

When a decision to interrupt warfarin therapy has been made for an invasive procedure with an intermediate or high risk of major bleeding, bridging with LMWH or UFH when the INR has decreased below therapeutic levels should be considered for patients with high stroke risk. A meta-analysis of 33 observational studies and 1 RCT involving 7118 patients (< 50% with AF) reported that warfarin discontinuation with bridging therapy, compared with warfarin discontinuation without bridging therapy, was associated with increased overall bleeding (13.1% vs 3.4%; P < 0.0001) and major bleeding (4.2% vs 0.9%; P ¼ 0.004), but with no reduction in thromboembolic events (0.9% vs 0.6%; P ¼ 0.50). More recently, in the randomized double-blinded placebo-controlled Bridging Anticoagulation in Patients Who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial the value of bridging in 1884 AF patients needing to interrupt warfarin for an elective surgery/invasive procedure was assessed. Patients were randomized to placebo injections or LMWH from 3 days to 1 day before the procedure, and for 5-10 days after the procedure. The study showed that no bridging was non-inferior to bridging for arterial thromboembolism, but was associated with significantly fewer major and minor bleeds. There were

no significant differences for any other outcomes. We have therefore increased the threshold for bridging to patients with CHADS2 score >= 4, instead of CHADS2 score >= 3. Mechanical heart valves and recent transient ischemic attack or stroke are considered very high-risk factors for thromboembolism, and such patients were excluded from the BRIDGE trial. Heparin bridging continues to be recommended for patients with these risk factors as well as for those with rheumatic heart disease.

Bridging is not generally necessary for DOACs because their half-lives are similar to those of LMWH. Bleeding and thromboembolic outcomes in the periprocedural period using DOACs vs warfarin have been investigated in the RE-LY, ROCKET AF, and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trials.73-75 In these studies, DOACs and warfarin were generally interrupted. There were no statistically significant differences between the dabigatran, rivaroxaban, or the apixaban groups and their respective warfarin groups with respect to bleeding or thromboembolic complications. Data are also available from observational studies of DOAC interruption. The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) is a prospective, observational registry study of US patients with AF.76 Of 7372 patients treated with OAC, 2803 interruption events occurred in 2200 patients (30%). Median follow-up was 2 years. OAC interruptions were common for major and minor procedures, with bridging used in one-quarter of the cases. The findings suggested that bridging anticoagulation was associated with increased risk of bleeding and adverse events. In the Perioperative Dabigatran Study,77 a Canadian multicenter prospective study of perioperative management, 541 adult patients receiving dabigatran for any indication (97% AF) underwent an invasive procedure requiring DOAC interruption. The outcomes of the study included major and minor bleeding, thromboembolism, and death, and suggested that interruption of dabigatran without bridging is safe. Observational analyses from the Dresden DOAC Registry (76% rivaroxaban, 24% dabigatran) suggested no difference in bleeding or thromboembolic complications in the periprocedural period between rivaroxaban and dabigatran. Heparin bridging did not reduce cardiovascular events but led to significantly higher rates of major bleeding.

Table 1. Bleeding risks for various invasive/surgical procedures

High risk
Neurosurgery (intracranial or spinal surgery)
Cardiac surgery (coronary artery bypass or heart valve replacement)
Major vascular surgery (abdominal aortic aneurysm repair, aortofemoral bypass)
Major urologic surgery (prostatectomy, bladder tumour resection)
Major lower limb orthopaedic surgery (hip/knee joint replacement surgery)
Lung resection surgery
Intestinal anastomosis surgery
Selected invasive procedures (kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy or biopsies)
Intermediate risk
Other intra-abdominal surgery
Other intrathoracic surgery
Other orthopaedic surgery
Other vascular surgery
Low risk
Laparoscopic cholecystectomy
Laparoscopic inguinal hernia repair
Dental procedures
Dermatologic procedures
Ophthalmologic procedures*
Coronary angiography
Gastroscopy or colonoscopy
Selected invasive procedures (bone marrow aspirate and biopsy, lymph node biopsy, thoracentesis, paracentesis, arthrocentesis)
Cardiac implantable device surgery (pacemaker or implantable defibrillator)†
Very low risk
Dental extractions (1 or 2 teeth) or teeth cleaning
Skin biopsy or skin cancer removal
Cataract removal

* Selected ophthalmic procedures might be high risk such as those with retrobulbar block.

† Based on results from the **Bri**dge or Contin**ue** Coumad**in** for Device **S**urg**e**ry Randomized **Control**led Trial (BRUISECONTROL) trial.

10.4.3 ESC 2016

Most cardiovascular interventions (e.g. percutaneous coronary intervention or pacemaker implantation) can be performed safely on continued OAC. When interruption of OAC is required, bridging does not seem to be beneficial, except in patients with mechanical heart valves: In a randomized trial of 1884 patients with AF, interruption of anticoagulation was non-inferior to heparin bridging for the outcome of arterial thrombo-embolism (incidence of 0.4% and 0.3%, respectively) and resulted in a lower risk of major bleeding (1.3% and 3.2%, respectively). OAC interruptions should be minimized to prevent stroke.*

This trial is the “BRIDGE” trial, by Douketis et al 2015.

11 Evidence tables. DOACs vs warfarin in atrial fibrillation

11.1 Apixaban 5mg 2x/d vs warfarin in atrial fibrillation

11.1.1 Clinical evidence profile

Ref	n / Population	Comparison	Outcomes		Methodological
Granger 2011(23) ARISTOTLE Design: RCT, P non- inferiority Duration of follow-up: median 1.8y	n= 18.201 -mean age 70 y -19% prior stroke, TIA or systemic embolism mean $CHADS_2$ 2.1 +/- 1.1 34% $CHADS_2$=1 35.8% $CHADS_2$=2 30.2% $CHADS_2$ ≥3 Priorstroke/TIA:19.5% Type 2 diabetes: 25.0% Congestive heart failure: 35.5% Hypertension requiring treatment: 87.5% CrCL ≤50ml/min: 16.6% previous use of VKA:	apixaban 2x5mg/d vs warfarin (INR 2.0-3.0) <u>Remarks</u> dose reduction of apixaban: (2x2.5mg for >80y or creat >1.5mg/dl or <60kg (≥ 2 factors) (4.7% received reduced dose) Randomization was stratified according to	**Adherence**		RANDO: method not described ALLOCATION CONC: not described BLINDING : Participants: yes Personnel: yes Assessors: probably FOLLOW-UP: Lost to follow-up: 0.4% No data on vital status at end of trial: 2.1% Permanent discontinuation of study drug: 25.3% apixaban, (3.6% due to death; 7.4% due to AE) 27.5% warfarin (3.8% due to death; 8.1% due to AE) (P = 0.001). Drop-outs and Exclusions: • Described: yes • Balanced across groups: mostly; Fewer patients in
			TTR in warfarin group	mean 62.2%	
			Efficacy		
			Stroke (ischemic or hemorrhagic) or systemic embolism (PO)	Apixaban 1.27%/y vs 1.60%/y warfarin **HR= 0.79 (95%CI 0.66-0.95)** **p<0.001 for non-inferiority** **p = 0.01 for superiority** *estimated NNT/2y=152 (92 to 625)*	
			Ischemic stroke	Apixaban 1.19%/y vs 1.51%/y warfarin **HR 0.79 (95%CI 0.65-0.95), p = 0.01**	
			Hemorrhagic stroke	Apixaban 0.24%/y vs 0.47%/y warfarin **HR 0.51 (95%CI 0.35-0.75), p<0.001**	
			Mortality	Apixaban 3.52%/y vs 3.94%/y warfarin **HR 0.89 (95%CI 0.80-0.998), p=0.047** *estimated NNT/2y=119(64 to 6345)*	
			Myocardial infarction	Apixaban 0.53%/y vs 0.61%/y warfarin NS: HR 0.37 (95%CI 0.66-1.17), p=0.37	
			Harms		
			Bleeding outcomes		

	57% <u>Inclusion</u> - atrial fibrillation or flutter - increased risk of stroke = at least 1 additional risk factor: ≥75y, previous stroke or TIA, heart failure, diabetes, hypertension <u>Exclusion</u> - Mitral stenosis - Prosthetic heart valve - Stroke < 7d - Creat clearance <25ml/min - a need for aspirin >165 mg/d or for both aspirin and clopidogrel all study centers were encouraged to enroll a sizable proportion of patients (≥40%) who had not previously received warfarin	whether patients had received warfarin previously and according to clinical site	Intracranial	Apixaban 0.33%/y vs 0.80%/y warfarin **SS less intracranial bleedings with apixaban: HR 0.42 (95%CI 0.30-0.58), p<0.001** *estimated NNT/2y=107(83 to 149)*	the apixaban group than in the warfarin group discontinued a study drug before the end of the study ITT: yes safety population: all patients who received at least one dose of a study drug and included all events from the time the first dose of a study drug was received until 2 days after the last dose was received. SELECTIVE REPORTING: - no reporting of per protocol analysis OR 'evaluable subjects dataset' for non-inferiority. - Other important methodological remarks -The primary non-inferiority hypothesis required that apixaban preserve at least 50% of the relative reduction in the risk of stroke or systemic embolism associated with warfarin (62%) in six previous, major randomized, controlled trials - upper boundary of the 95% confidence interval for the relative risk would be < 1.38
			Any bleeding	Apixaban 18.1%/y vs warfarin 25.8%/y **SS less any bleedings with apixaban, p<0.001**	
			ISTH major bleeding (PO)	Apixaban 2.13%/y vs warfarin 3.09%/y **HR 0.69 (95%CI 0.60–0.80)** **SS less ISTH major bleedings with apixaban, p <0.001**	
			Major or clinically relevant non-major bleeding	**4.07%/y vs 6.01%/y** **HR 0.68 (0.61–0.75)** **p<0.001**	
			Fatal bleeding	Not reported	
			GI-bleeding	Apixaban 0.76%/y vs warfarin 0.86%/y HR 0.89 (0.70–1.15) NS, p = 0.37	
			AE's		
			No statistical analysis		

				- non-inferiority design combined with superiority design, with intention to treat analysis (no per protocol analysis) -34% $CHADS_2$=1 - heterogeneous population - To control the overall type I error, prespecified hierarchical sequential testing was performed - Sponsor: Bristol-Myers Squibb and Pfizer

*ISTH bleeding definition:
Major bleeding: fall in hemoglobin of ≥2 g/dl or with transfusion of ≥2 units of PRBC or whole blood or that occurs in a critical location i.e. intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial or that causes death.
Minor bleeding: does not meet criteria for major bleeding and requires medical or surgical intervention to treat the bleeding

11.1.2 Subgroup analysis according to age. Apixaban 5mg 2x/d vs warfarin.

Reference	n	subgroup	Outcome	Results Apixaban vs warfarin event rate (%/y) HR (95%CI)	Remarks
Granger 2011(23) ARISTOTLE and Halvorsen 2014(42)	5471	<65y	**stroke**	1.0%/y vs 0.9%/y HR 1.16 (0.77-1.73)	Prespecified analysis: YES stratified at randomization: NO Baseline characteristics of different subgroups: Patients 75 years or older of age were more likely to be female, have prior stroke, prior bleeding, or impaired renal function, but less likely to have a history of congestive heart failure or diabetes. CHADS2 score was ≥3 in 20.1% of patients aged ,65 years vs. 48.5% of patients ≥75 years. A HAS-BLED score of ≥3 was found in only 5.3% of patients ,65 years of age, compared with 27.9% of patients 65–74 years and 33.7% of patients ≥75 of age
	7052	65 to <75y	**stroke**	1.3%/y vs 1.7%/y **HR 0.72(0.54-0.96)**	
	5678	≥75y	**stroke**	1.6%/y vs 2.2%/y **HR 0.71(0.53-0.95)**	
				P for interaction 0.12 NS	
	5455	<65y	**major bleeding**	1.2%/y vs 1.5%/y HR 0.78(0.55-1.11)	
	7030	65 to <75y	**major bleeding**	2.0%/y vs 2.8%/y **HR 0.71(0.56-0.89)**	
	5655	≥75y	**major bleeding**	3.3%/y vs 5.2%/y **HR 0.64 (0.52-0.79)**	
				P for interaction 0.64 NS	

*Author's summary (Halvorsen 2014) :" The rates of stroke, all-cause death, and major bleeding were higher in the older age groups (P , 0.001 for all). Apixaban was more effective** than warfarin in preventing stroke and reducing mortality across all age groups, and associated with less major bleeding, less total bleeding, and less intracranial haemorrhage regardless of age (P interaction .0.11 for all). Results were also consistent for the 13% of patients ≥80 years. No significant interaction with apixaban dose was found with respect to treatment effect on major outcomes."*

**Reviewers comment: not SS lower for all subgroups

Note: Similar results in Alexander 2016(114)

11.1.3 Subgroup analysis according to renal function: eGFR (Cockroft – Gault). Apixaban 5mg 2x/d vs warfarin.

Reference	n	subgroup eGFR	Outcome	Results Apixaban vs warfarin HR (95%CI)	Remarks
Granger 2011(23) ARISTOTLE and Hohnloser 2012(49) and Alexander 2016(114)	7518	>80 mL/min	stroke/ SE	HR 0.88 (6.64 to 1.22)	Prespecified analysis: YES Stratified at randomization: NO Baseline characteristics of different subgroups: p<0.001 for all major baseline characteristics **Similar results when eGFR calculated with Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)** **All interactions NS when eGFR calculated with serum Cystatin C.** ***the more pronounced benefit of apixaban at lower eGFR was also reported by Alexander 2016(114)**
	7587	>50–80 mL/min	stroke/SE	**HR 0.74 (0.56 to 0.97)**	
	3017	≤50 mL/min	stroke/SE	HR 0.79 (0.55 to 1.14)	
				P for interaction 0.705 NS	
	7496	>80 mL/min	major bleeding	HR 0.80 (0.61 to 1.04)	
	7567	>50–80 mL/min	major bleeding	**HR 0.77 (0.62 to 0.94)**	
	3005	≤50 mL/min	major bleeding	**HR 0.50 (0.38 to 0.66)**	
				P for interaction 0.030* **SS**	

Author's abstract

"Apixaban was more effective than warfarin in preventing stroke or systemic embolism and reducing mortality irrespective of renal function. These results were consistent, regardless of methods for GFR estimation. Apixaban was associated with less major bleeding events across all ranges of eGFRs.
The relative risk reduction in major bleeding was greater in patients with an eGFR of ≤50 mL/min using Cockcroft– Gault (hazard ratio (HR) 0.50 [95% confidence interval (CI) 0.38–0.66], interaction P < 0.005) or CKD-EPI equations [HR 0.48 (95% CI 0.37–0.64), interaction P <0.003]"

11.1.4 Post hoc analysis according to worsening renal function over time. Apixaban 5mg 2x/d vs warfarin.

Reference	n	subgroup Renal function	Outcome	Results apixaban vs vs warfarin	Remarks
Bohm 2014(53)	2294	decrease 20% yes	Stroke/SE	0.83 (0.52 – 1.32)	Prespecified analysis: NO stratified at randomization: NO Baseline characteristics of different subgroups: see below
	14575	decrease 20% no	Stroke/SE	0.75(0.59 – 0.94)	
				P for interaction 0.70 NS	
	2294	decrease 20% yes	Major bleeding	0.78(0.54 – 1.11)	
	14575	decrease 20% no	Major bleeding	0.70(0.59 – 0.84)	
				P for interaction NS	

Author's summary: "*Worsening in estimated glomerular filtration more than 20% was observed in 2294 patients (13.6%) and was associated with older age and more cardiovascular comorbidities. The risks of stroke or systemic embolism, major bleeding, and mortality were higher in patients with worsening renal function (HR, 1.53; 95%CI, 1.17-2.01 for stroke or systemic embolism; HR, 1.56; 95%CI, 1.27-1.93 for major bleeding; and HR, 2.31; 95%CI, 1.98-2.68 for mortality). The beneficial effects of apixaban vs warfarin on rates of stroke or systemic embolism and major bleeding were consistent in patients with normal or poor renal function over time and also in those with worsening renal function.*"

"In most of the 16869 patients with repeated measurements in the ARISTOTLE trial (86.5%), overall renal function declined very slowly over time. However, in the selected group of patients with AF with older age, low hematocrit level, presence of heart failure, vascular disease, or diabetes, there was a risk for a more rapid decline in renal function over time.

"Exploratory post hoc analyses concerning the effect of apixaban or warfarin study treatment on renal function during the trial only showed small differences, possibly affected by confounding factors."

11.1.5 Subgroup analysis according to predicted center INR control. Apixaban 5mg 2x/d vs warfarin.

Reference	n	subgroup mean cTTR(%)	Outcome	Results apixaban vs warfarin	Remarks
Wallentin 2013(100)	2243	24.3 - 60.5	Stroke/SE	0.73 (0.53-1.00)	Prespecified analysis: cTTR YES stratified at randomization: only per centre Baseline characteristics of different subgroups:
	2287	60.6 - 66.3	Stroke/SE	0.94 (0.67-1.31)	
	2301	66.4 - 71.1	Stroke/SE	0.64 (0.42-0.97)	
	2289	71.2 - 83.2	Stroke/SE	0.88 (0.57-1.35)	
				P for interaction 0.078 NS	
	2232	24.3 - 60.5	Major bleeding	0.50 (0.36-0.70)	
	2284	60.6 - 66.3	Major bleeding	0.64 (0.48-0.86)	
	2290	66.4 - 71.1	Major bleeding	0.85 (0.65-1.11)	
	2282	71.2 - 83.2	Major bleeding	0.75 (0.58-0.97)	
				P for interaction 0.095 NS	

11.1.6 Subgroup analysis according to predicted individual TTR. Apixaban 5mg 2x/d vs warfarin.

Reference	n	subgroup predicted iTTR(%)	Outcome	Results apixaban vs warfarin	Remarks
Wallentin 2013(100)	2279	15.1 - 59.9	Stroke/SE	0.70 (0.52-0.94)	Prespecified analysis: iTTR NO stratified at randomization: NO Baseline characteristics of different subgroups: statistically significant differences for almost all baseline characteristics.
	2234	60.0 - 65.9	Stroke/SE	0.92 (0.65-1.30)	
	2294	66.0 - 71.2	Stroke/SE	0.74 (0.49-1.13)	
	2313	71.3 - 85.3	Stroke/SE	0.87 (0.57-1.33)	
				P for interaction 0.060 NS	
	2268	15.1 - 59.9	Major bleeding	0.48 (0.35-0.67)	
	2228	60.0 - 65.9	Major bleeding	0.68 (0.51-0.91)	

	2283	66.0 - 71.2	Major bleeding	0.87 (0.67-1.14)	
	2309	71.3 - 85.3	Major bleeding	0.73 (0.55-0.94)	
				P for interaction 0.078 NS	

For each patient, a **center average TTR** was estimated with the use of a linear mixed model on the basis of the real TTRs in its warfarin-treated patients, with a fixed effect for country and random effect for center.
For each patient, an **individual TTR** was also predicted with the use of a linear mixed effects model including patient characteristics as well.
The center's average TTR (cTTR) were assigned to all patients representing the center's predicted quality of INR control during the trial.
The indivual patient's TTR (iTTR) was applied as an estimate of the individual quality of INR control that could be expected given a patient's center and baseline characteristics.
The results of these calculations may thus be a model to guide treatment choice between a DOAC and a VKA, before the start of the treatment, to possibly identify patients who will do worse or better on warfarin.

Author's conclusions: "The benefits of apixaban compared with warfarin for stroke or systemic embolism, bleeding, and mortality appear similar across the range of centers' and patients' predicted quality of international normalized ratio control."

11.2 Dabigatran 110 mg or 150 mg 2x/d vs warfarin in atrial fibrillation

11.2.1 Clinical evidence profile. Dabigatran 110mg 2x/d vs warfarin

Ref	n / Population	Comparison	Outcomes		Methodological
Connolly 2009 RE-LY(24) ***Revised:*** *- Connolly 2010(25) and and Hohnloser 2012(26) *** *- Connolly 2014 (27)** Design: RCT P non-inferiority Duration median follow-up 2y	n= 18.113 -mean age 71y -mean $CHADS_2$ 2.1 -$CHADS_2$ 0-1=32% $CHADS_2$ 2= 35.5% $CHADS_2$ 3-6= 32.5% -20% previous stroke/TIA Prior stroke/TIA:20% Type 2 diabetes: 23% Congestive heart failure: 32% Hypertension requiring treatment: 79% CrCL ≤50ml/min:NR previous use of VKA: 50% <u>Inclusion</u> - atrial fibrillation - increased risk of stroke: previous stroke/TIA, heart	Dabigatran 2x110mg/d vs warfarin INR 2.0-3.0	TTR in warfarin group	64% of study period	- Jadad score RANDO: 2/2 central automated telephone system ALLOCATION CONCEALMENT: low risk of bias BLINDING:no - ITT: yes (not defined) lost to follow-up 0.1% discontinuation at 1 y dabi 110 14.5% dabi 150 15.5% warfarin 10.2% discontinuation at 2y dabi 110 20.7% dabi 150 21.2% warfarin 16.6% - Other important methodological remarks? - issues with reporting of endpoints(2
			INR 1.8 – 3.2	not reported	
			No drug interruption (>3d)	not reported	
			Other adherence parameter	not reported	
			Efficacy		
			Stroke (ischemic or hemorrhagic) or systemic embolism (PO)*	Dabigatran 110mg: 1.54%/y Warfarine: 1.72%/y **RR 0.89 (0.73–1.09), p<0.001 for non-inferiority** Not superior (p=0.27)	
			Ischemic or unspecified stroke*	Dabigatran 110mg: 1.34%/y Warfarine: 1.22%/y NS: RR 1.10 (0.88–1.37) (p=0.42)	
			Hemorrhagic stroke	Dabigatran 110mg: 0.12%/y Warfarine: 0.38%/y **Superior: RR 0.31 (95%CI 0.17-0.56), p<0.001** *estimated NNT/2y : 193 (159-299)*	
			Disabling or fatal stroke	Dabigatran 110mg: 0.94%/y Warfarine: 0.1.0%/y NS	
			Mortality	Dabigatran 110mg: 3.75%/y	

	failure, ≥75y, or 65-74Y+diabetes, hypertension or coronary artery disease <u>Exclusion</u> - stroke <14d or severe stroke <6m - severe heart valve disorder -Increased risk of hemorrhage - creatinine clearance < 30ml/min - liver failure			Warfarine: 4.13%/y NS: RR 0.91 (95%CI 0.80-1.03) (p=0.13)	revisions of data) - adjudicator was not always blinded(115) - warfarin therapy not blinded (open label) - non-inferiority design combined with superiority design, with intention to treat analysis (no per protocol analysis) To satisfy the non-inferiority hypothesis, the upper bound of the onesided 97.5% confidence interval for the relative risk of an outcome with dabigatran as compared with warfarin needed to fall below 1.46. The margin of 1.46 represents half the 95% confidence interval of the estimated effect of control therapy over warfarin
			Myocardial infarction**	Dabigatran 110mg: 0.82%/y Warfarine: 0.64%/y NS: 1.29 (0.96–1.75) (p=0.09)	
			Harms		
			Bleeding outcomes		
			Major bleeding (PO)*	Dabigatran 110mg 2.92%/y vs warfarin 3.61%/y **SS less major bleeding with dabigatran 110 mg RR 0.80 (0.70–0.93),P = 0.003** *estimated NNT/2y : 73(47-198)*	
			Intracranial	Dabigatran 110mg 0.23%/y vs warfarine 0.74%/y **SS less intracranial bleedings with dabigatran 110mg: RR 0.31 (95%CI 0.20-0.47), p<0.001** *estimated NNT/2y : 98(85-128)*	
			Major life threatening bleeding*	1.27%/y vs 1.87%/y **SS less major life threatening bleedings with dabigatran 110mg: 0.67 (0.55–0.83), p<0.001** *estimated NNT/2y: 84(60-158)*	
			Major or minor bleeding	14.62%/y vs 18.15%/y **SS less major or minor bleedings with dabigatran 110mg: RR = 0.78 (95%CI 0.74-0.83) P<0.001** *estimated NNT/2y :15(11-17)*	
			Minor bleeding	13.16%/y vs 16.37%/y **SS less minor bleedings with dabigatran 110mg RR = 0.79 (95%CI 0.74-0.84), p<0.001** *estimated NNT : 16(12-19)*	
			Major non life	1.66%/y vs 1.76%/y	

			threatening bleeding	NS: RR 0.94 (95%CI 0.78-1.15), p=0.56	- Sponsor: Boehringer Ingelheim
			GI-bleeding	1.12%/y vs 1.02/y NS: RR1.10 (95%CI 0.86-1.41), p=0.43	
			AE's		
			SS more dyspepsia with dabigatran11.8% vs 5.8% (p<0.001)		

11.2.2

11.2.3 Clinical evidence profile. Dabigatran 150mg 2x/d vs warfarin

Ref	n / Population	Comparison	Outcomes		Methodological
Connolly 2009 RE-LY(24) ***Revised:*** *- Connolly 2010(25) and and Hohnloser 2012(26) *** *- Connolly 2014 (27)** Design: RCT P non-inferiority Duration median follow-up 2y		Dabigatran 2x150mg/d vs warfarin INR 2.0-3.0	**Efficacy**		
			Stroke (ischemic or hemorrhagic) or systemisch embolism (PO) *(27)*	Dabigatran 150mg: 1.12%/y Warfarin: 1.72%/y **RR 0.66 (95%CI 0.52-0.81),** **p<0.001 for non-inferiority** **p<0.001 for superiority** *estimated NNT/2y: 84(61-153)*	
			Ischemic or unspecified stroke*(27)*	Dabigatran 150mg: 0.93%/y Warfarin: 1.22%/y **RR 0.76 (0.59–0.97) p=0.03** **SS less with dabigatran 150** *estimated NNT/2y: 173(100-1367)*	
			Hemorrhagic stroke	Dabigatran 150mg: 0.10%/y Warfarin: 0.38%/y **RR 0.26 (95%CI 0.14-0.49), p<0.001** **SS less with dabigatran 150** *estimated NNT/2y : 179(153-258)*	
			disabling or fatal stroke	Dabigatran 150mg: 0.66%/y Warfarine: 0.1.0%/y SS less with dabi	
			Mortality	Dabigatran 150mg: 3.64%/y Warfarin: 4.13%/y NS: RR 0.88 (95%CI 0.77-1.00) (p=0.051)	
			Myocardial infarction	**<u>Original article</u>** Dabigatran 150mg: n = 89 ; 0.74%/y Warfarin: n = 63 ; 0.53%/y **SS more MI in dabigatran group:** **RR 1.38 (95%CI 1.00-1.91) p = 0.048** ***estimated NNH/2y: 239(∞ -104)***	

				<u>after revision</u> *(26)* **<u>(4 cases of acute MI and 28 cases of silent MI were discovered)</u>** Dabigatran 150mg: 0.81%/y Warfarin: 0.64%/y RR 1.27 (0.94–1.71) NS p = 0.12	
			Harms		
			Bleeding outcomes		
			Major bleeding (PO) *(27)*	Dabigatran 150mg 3.4%/y vs warfarine 3.61%/y RR 0.94 (0.82–1.08) P = 0.41 NS	
			Intracranial	Dabigatran 150mg 0.30%/y vs warfarin 0.74%/y **SS less intracranial bleedings with dabigatran: RR 0.40 (95%CI 0.27-0.60), p<0.001** **estimated NNT: 114(93-169)**	
			Major life threatening bleeding*(27)*	1.52%/y vs 1.87%/y **SS less major life threatening bleedings with dabigatran: RR 0.81 (95%CI 0.67-0.99), p = 0.04** *estimated NNT/2y: 143(81-2674)*	
			Major non life threatening bleeding	1.88%/y vs 1.76%/y NS: RR 1.07 (95%CI 0.89-1.29), p=0.47	
			GI-bleeding	1.51%/y vs 1.02%/y **SS more GI-bleedings with dabigatran: RR 1.50 (95%CI 1.19-1.89), p<0.001** *estimated NNH/2y: 102(258-55)*	
			AE's		
			SS more dyspepsia 11.3% vs 5.8% (p<0.001)		

11.2.4 Clinical evidence profile. Dabigatran 110mg 2x/d vs 150mg 2x/d

Ref	n / Population	Comparison	Outcomes		Methodological
		Dabigatran 2x150mg vs Dabigatran 2x110mg	**Efficacy**		
			Stroke (ischemic or hemorrhagic) or systemic embolism (PE)	Dabigatran 150mg:1.11%/y Dabigatran 110mg: 1.53%/y **150mg Superior: RR 0.73 (95%CI 0.58-0.91), p = 0.005**	
			Ischemic or unspecified stroke	Dabigatran 150mg:0.92%/y Dabigatran 110mg: 1.34%/y **150mg Superior: RR 0.69 (95%CI 0.54-0.88), p=0.002**	
			Hemorrhagic stroke	Dabigatran 150mg: 0.10%/y Dabigatran 110mg: 0.12%/y NS: RR 0.85 (95%CI 0.39-1.83), p=0.67	
			Mortality	Dabigatran 150mg: 3.64%/y Dabigatran 110mg: 3.75%/y NS: RR 0.97 (95%CI 0.85-1.11), p=0.66	
			Myocardial infarction	Dabigatran 150mg: 0.74%/y Dabigatran 110mg:0.72%/y NS: RR1.02 (95%CI 0.76-1.38), p=0.88	
			Harms		
			Bleeding outcomes		
			Major bleeding (PO)	Dabigatran 150mg 3.11%/y vs 110mg 2.71%/y RR 1.16 (95%CI 1.00–1.34), p=0.052 NS	
			Intracranial	Dabigatran 150mg 0.30%/y vs 0.23%/y 110mg NS: RR 1.32 (95%CI 0.80-2.17), p=0.28	
			Major life threatening bleeding	1.45%/y vs 1.22%/y NS: RR 1.19 (95%CI 0.96-1.49), p=0.11	

			Major non life threatening bleeding	1.88%/y vs 1.66%/y NS: RR 1.14 (95%CI 0.95-1.39), p=0.17	
			Minor Bleeding	Dabigatran 150mg 14.84%/y vs 14.84%/y 110mg **SS more minor bleeding with 150 mg: RR 1.16 (95%CI 1.08-1.24), p<0.001**	
			Major or minor bleeding	Dabigatran 150mg 16.42%/y vs 14.62%/y 110mg **SS more major or minor bleeding with 150 mg: RR 1.16 (95%CI 1.09-1.23), p<0.001**	
			GI-bleeding	1.51%/y vs 1.12%/y **SS more GI-bleeding with 150mg: RR 1.36 (95%CI 1.09-1.70), p=0.007**	
			AE's		
			No statistical analysis		

Major bleeding was defined as a reduction in the hemoglobin level of at least 20 g per liter, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. Life-threatening bleeding was a subcategory of major bleeding that consisted of fatal bleeding, symptomatic intracranial bleeding, bleeding with a decrease in the hemoglobin level of at least 50 g per liter, or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or necessitating surgery. All other bleeding was considered minor.

Intracranial hemorrhage consisted of hemorrhagic stroke and subdural or subarachnoid hemorrhage

11.2.5 Subgroup analysis according to age. Dabigatran 110 mg 2x/d vs warfarin

Reference	n	subgroup Age	Outcome	Results dabigatran 110 bid vs warfarin RR(95%CI)	Remarks
Eikelboom 2011(43)	10855	<75y	Stroke/SE	0.93 (0.70–1.22)	Prespecified analysis: NO Stratified at randomization: NO Baseline characteristics of different subgroups: NR <u>age groups <75 y vs ≥75 y</u> also significant interaction for **extracranial bleeding** (SS lower rate with dabi 110 in age <75, but NS difference with dabi 110 in age ≥75y, compared to warfarin (HR 0.72(0.57 to 0.90) and 1.20(0.97 vs 1.48) respectively), p=0.001
	7258	≥75 y	Stroke/SE	0.88 (0.66–1.17)	
				P for interaction 0.81 NS	
	10855	<75y	Major bleeding	**0.62 (0.50–0.77)**	
	7258	≥75 y	Major bleeding	**1.01 (0.83–1.23)**	
				P for interaction <0.001 **SS**	
Eikelboom 2011(43)	2971	<65y	Major bleeding	**0.82%/y vs 2.43%/y**	Prespecified analysis: unclear Stratified at randomization: NO
	7884	65 to 74y	Major bleeding	**2.29%/y vs 3.25%/y**	
	7258	≥75 y	Major bleeding	**4.43%/y vs 4.37%/y**	
				P for interaction <0.0003 **SS**	

Reference	n	subgroup Age	Outcome	Results dabigatran 110 bid vs warfarin RR(95%CI)	Remarks
Lauw 2017(44)	10855	<75	Stroke/SE	0.93 (0.70 to 1.22)	Prespecified analysis: NO stratified at randomization: NO Baseline characteristics of different subgroups: SS different for most major characteristics also significant interaction for **extracranial bleeding, but not for intracranial bleeding**
	4231	75-79	Stroke/SE	1.08 (0.73 to 1.60)	
	2305	80-85	Stroke/SE	0.75 (0.46 to 1.23)	
	722	≥85	Stroke/SE	0.52 (0.21 to 1.29)	
				p for interaction 0.394 **NS**	
	10855	<75	Major bleeding	**0.62 (0.50 to 0.77)**	
	4231	75-79	Major bleeding	0.93 (0.71 to 1.21)	
	2305	80-85	Major bleeding	1.18 (0.84 to 1.65)	
	722	≥85	Major bleeding	1.01 (0.59 to 1.73)	
				P for interaction <0.006 **SS**	

Author's conclusion (Lauw 2017) "Effects of dabigatran compared with warfarin on stroke prevention and intracranial bleeding are consistent across all age groups. Effects of dabigatran on extracranial major bleeding are age dependent."

Remark of literature group: The above statement made by the authors involves patients with a renal function CrCl >=30ml/min (because patients with CrCl<30 ml/min were excluded)

11.2.6 Subgroup analysis according to age. Dabigatran 150 mg 2x/d vs warfarin

Reference	n	subgroup Age	Outcome	Results dabigatran 150 bid vs warfarin RR(95%CI)	Remarks
Eikelboom 2011(43)	10855	<75y	Stroke/SE	**0.63 (0.46–0.86)**	Prespecified analysis: unclear stratified at randomization: NO <u>age groups <75 y vs ≥75 y</u> also significant interaction for **extracranial bleeding** (SS lower rate with dabi 150 in age <75, but SS higher rate with dabi 150 in age ≥75y, compared to warfarin (HR 0.78(0.63 to 0.98) and 1.39(1.13 vs 1.70) respectively), p<0.001
	7258	≥75 y	Stroke/SE	**0.67 (0.49–0.90)**	
				P for interaction 0.81 NS	
	10855	<75y	Major bleeding	**0.70 (0.57–0.86)**	
	7258	≥75 y	Major bleeding	1.18 (0.98–1.42)	
				P for interaction <0.001 **SS**	
	2971	<65y	Major bleeding	**0.89%/y vs 2.43%/y**	Prespecified analysis: unclear stratified at randomization: NO
	7884	65 to 74y	Major bleeding	**2.6%/y vs 3.25%/y**	
	7258	≥75 y	Major bleeding	**5.1%/y vs 4.37%/y**	
				P for interaction <0.0001 **SS**	

Author's conclusion (Eikelboom 2011): 'There was a significant treatment-by-age interaction, such that dabigatran 110 mg twice a day compared with warfarin was associated with a lower risk of major bleeding in patients aged <75 years (1.89% versus 3.04%; P<0.001) and a similar risk in those aged ≥75 years (4.43% versus 4.37%; P=0.89; P for interaction <0.001), whereas dabigatran 150 mg twice a day compared with warfarin was associated with a lower risk of major bleeding in those aged <75 years (2.12% versus 3.04%; P<0.001) and a trend toward higher risk of major bleeding in those aged ≥75 years (5.10% versus 4.37%; P<0.07; P for interaction <0.001). The interaction with age was evident for extracranial bleeding, but not for intracranial bleeding, with the risk of the latter being consistently reduced with dabigatran compared with warfarin irrespective of age.'

Remark of literature group: The above statement made by the authors involves patients with a renal function CrCl >=30ml/min (because patients with CrCl<30 ml/min were excluded)

Reference	n	subgroup Age	Outcome	Results dabigatran 150 bid vs warfarin RR(95%CI)	Remarks
Lauw 2017(44)	10855	<75	Stroke/SE	0.63 (0.46 to 0.86)	Prespecified analysis: NO stratified at randomization: NO Baseline characteristics of different subgroups: SS different for most major characteristics also significant interaction for **extracranial bleeding, but not for intracranial bleeding**
	4231	75-79	Stroke/SE	0.65 (0.42 to 1.01)	
	2305	80-85	Stroke/SE	0.67 (0.41 to 1.10)	
	722	≥85	Stroke/SE	0.70 (0.31 to 1.57)	
				p for interaction 0.498 **NS**	
	10855	<75	Major bleeding	**0.70 (0.57 to 0.86)**	
	4231	75-79	Major bleeding	1.04 (0.81 to 1.35)	
	2305	80-85	Major bleeding	**1.41 (1.02 to 1.94)**	
	722	≥85	Major bleeding	1.22 (0.74 to 2.02)	
				P for interaction <0.001 **SS**	

Authors conclusion??

11.2.7 Subgroup analysis according to renal function. Dabigatran 110 mg 2x/d vs warfarin: eGFR (Cockroft-Gault)

Reference	n	subgroup eGFR (ml/min)	Outcome	Results dabigatran 110 bid vs warfarin RR(95%CI)	Remarks
Hijazi 2014(50)	3554	<50 (NB < 30 excluded)	Stroke/SE	0.85 (0.59–1.24)	Prespecified analysis: yes stratified at randomization: NO Baseline characteristics of different subgroups: SS different for age, type of AF, CHADS2 risk factors, CHADS2 score Eikelboom 2011(43) produced similar results for major bleeding according to eGFR (Cockroft-Gault) (NS, but with different numbers) Because the subgroup analyses in the present study were exploratory, the P values were not adjusted for multiple comparisons and should be interpreted with caution
	8533	50-79	Stroke/SE	0.93 (0.70–1.23)	
	5844	≥80	Stroke/SE	0.84 (0.54–1.32)	
				P for interaction 0.9108 NS Similar findings with CKD-EPI equation and MDRD	
	3554	<50(NB<30 excluded	Major bleeding	0.99 (0.77–1.28)	
	8533	50-79	Major bleeding	**0.76 (0.62–0.94)**	
	5844	≥80	Major bleeding	**0.61 (0.44–0.84)**	
				P for interaction 0.06 NS <u>With CKD-EPI equation:</u> slightly different numbers, **p for interaction 0.0012,** **SS** (less major bleeding with dabi 110 vs warfarin with better renal function) <u>With MDRD equation</u> **p for interaction <0.05**	

Authors conclusion??

11.2.8 Subgroup analysis according to renal function. Dabigatran 150 mg 2x/d vs warfarin: eGFR (Cockroft-Gault)

Reference	n	subgroup eGFR (ml/min)	Outcome	Results dabigatran 150 bid vs warfarin RR(95%CI)	Remarks
Hijazi 2014(50)	3554	<50 (NB<30 excluded)	Stroke/SE	**0.56 (0.37–0.85)**	Prespecified analysis: YES stratified at randomization: NO Baseline characteristics of different subgroups: SS different for age, type of AF, CHADS2 risk factors, CHADS2 score Eikelboom 2011(43) produced similar results for major bleeding according to eGFR (Cockroft-Gault) (NS, but with different numbers) Based on the Cockcroft-Gault equation, patients with eGFR ≥80 mL/min had annual major bleeding rates of 1.98% compared with 3.30% in patients with eGFR 50 to <80 mL/min and 5.48% in patients with eGFR <50 mL/min.
	8533	50-79	Stroke/SE	**0.68 (0.50–0.92)**	
	5844	≥80	Stroke/SE	0.67 (0.42–1.09)	
				P for interaction 0.7522 NS	
	3554	<50(NB<30 excluded	Major bleeding	1.01 (0.79–1.30)	
	8533	50-79	Major bleeding	0.91 (0.75–1.11)	
	5844	≥80	Major bleeding	0.84 (0.62–1.13)	
				P for interaction 0.6393 NS <u>CKD-EPI equation</u> **fewer major bleeds occurred with dabigatran 150 mg than with warfarin in patients with eGFR ≥80 mL/ min** **HR 0.41; 95% CI 0.27–0.62** **P for interaction=0.005** <u>MDRD equation</u> **p for interaction also <0.05**	

Author's conclusion: "The major findings from this prespecified RE-LY analysis were that dosages of 110 and 150 mg of dabigatran twice daily displayed an efficacy relative to warfarin that was consistent with the overall trial across the range of renal function with regard to the primary outcome of stroke or systemic embolism. With regard to the primary safety outcome of major bleeding, dabigatran 110 mg displayed a lower risk and dabigatran 150 mg a similar risk compared with warfarin, irrespective of renal function. However, when GFR was estimated with the CKD-EPI equation, a significantly greater relative reduction in major bleeding risk was displayed for both doses of dabigatran in patients with eGFR ≥80 mL/min."

11.2.9 Post hoc analysis according to worsening renal function over time. Dabigatran 110 mg or 150 mg 2x/d vs warfarin.

Reference	n	Outcome	Results dabigatran vs warfarin RR(95%CI)	Remarks
Bohm 2014(53)	16490 (5060 at 30 months time point)	eGFR (CKD-EPI) change from baseline	- at 30 months: SS greater decline with warfarin (–3.68 +/- 0.24 ml/min) compared with dabigatran 110 mg (–2.57 +/- 0.24 ml/min; p < 0.0009 vs warfarin) and compared with dabigatran 150 mg (–2.46 +/- 0.23 ml/min; p < 0.0002 vs warfarin) - ns at all previous time points	- post hoc analysis - observational data from clinical trial - note: similar results when only patients that had been followed for 30 months were included note: association is not proof of causality
		decrease in GFR>25%	less likely with dabigatran 110 mg HR 0.81 (95%CI 0.69 to 0.96]; p <0.017) and less likely with dabigatran 150 mg HR: 0.79 (95% CI 0.68 to 0.93]; p < 0.0056) than with warfarin in the observation period >18 months	note: no information on other observation periods, no information on number of patients no information on other baseline characteristics note from the literature group: association is not proof of causality
			Patients with poor international normalized ratio control (TTR <65%) exhibited a faster decline in GFR. A more pronounced decline in GFR was associated with previous warfarin use and with the presence of diabetes	note from the literature group: association is not proof of causality

11.2.10 Subgroup analysis according to different levels of center's mean TTR. Dabigatran 110 mg 2x/d vs warfarin

Reference	n	Subgroup mean TTR	Outcome	Results dabigatran 110 mg vs warfarin HR(95%CI)	Remarks
Wallentin 2010(101)	1497	<57·1%	Stroke/SE	1·00 (0·68–1·45)	Prespecified analysis: YES Stratified at randomization: stratified per centre Baseline characteristics of different subgroups: SS differences between cTTR subgroups for almost all characteristics; although well balanced between intervention and control group
	1524	57·1–65·5%	Stroke/SE	0·81 (0·56–1·17)	
	1474	65·5–72·6%	Stroke/SE	0·89 (0·58–1·36)	
	1482	>72·6%	Stroke/SE	0·92 (0·59–1·45)	
				P for interaction 0·89 NS	
	1497	<57·1%	Major bleeding	0·65 (0·48–0·89)	
	1524	57·1–65·5%	Major bleeding	0·82 (0·63–1·06)	
	1474	65·5–72·6%	Major bleeding	0·83 (0·62–1·11)	
	1482	>72·6%	Major bleeding	0·90 (0·67–1·21)	
				P for interaction 0.50 NS	

11.2.11 Subgroup analysis according to different levels of centre's mean TTR. Dabigatran 150 mg 2x/d vs warfarin

Reference	n	subgroup mean TTR	Outcome	Results dabigatran 150 mg vs warfarin HR(95%CI)	Remarks
Wallentin 2010(101)	1509	<57·1%	Stroke/SE	0·57 (0·37–0·88)	Prespecified analysis: YES Stratified at randomization: stratified per centre Baseline characteristics of different subgroups: SS differences between cTTR subgroups for almost all characteristics; although well balanced between intervention and control group
	1526	57·1–65·5%	Stroke/SE	0·50 (0·33–0·77)	
	1484	65·5–72·6%	Stroke/SE	0·69 (0·44–1·09)	
	1514	>72·6%	Stroke/SE	0·95 (0·61–1·48)	
				P for interaction 0.20 NS	
	1509	<57·1%	Major bleeding	0·71 (0·52–0·96)	
	1526	57·1–65·5%	Major bleeding	0·81 (0·62–1·05)	
	1484	65·5–72·6%	Major bleeding	1·13 (0·87–1·48)	
	1514	>72·6%	Major bleeding	1·16 (0·88–1·54)	
				P for interaction 0.03 **SS**	

the cTTR was estimated by averaging TTR for individual warfarin-treated patients calculated by the Rosendaal method.

Author's comments:
"In a multivariate analysis, the most important baseline characteristic associated with the variability in iTTR was cTTR (data not shown). Other factors contributing to improved iTTR were time in the study, previous use of warfarin, and male sex, whereas factors associated with poorer iTTR were smoking, heart failure, amiodarone use, and insulin treatment (data not shown). Several of these patient- related factors that determine iTTR might also have affected the response to dabigatran (eg, amiodarone use, time in study, and smoking), although not necessarily in the same direction; thus we only used the structural factor cTTR as the basis for the model when comparing the effect of INR control on outcomes."

"Limitations: cTTR might not appropriately represent INR control of individual patients and might not represent the full effect of INR control on outcome. Also, cTTR does not show the effect of good and poor treatment response, treatment adherence to dabigatran, or the effect of treatment discontinuations. Finally, cTTR is a post- randomisation variable and thus is also probably a marker of differences in overall care between centres, which might not be fully compensated for in the multivariate analyses."

Author's conclusion: "The benefits of 150 mg dabigatran at reducing stroke, 110 mg dabigatran at reducing bleeding, and both doses at reducing intracranial bleeding versus warfarin were consistent irrespective of centres' quality of INR control. For all vascular events, non-haemorrhagic events, and mortality, advantages of dabigatran were greater at sites with poor INR control than at those with good INR control. Overall, these results show that local standards of care affect the benefits of use of new treatment alternatives."

11.3 Edoxaban 60mg/d or 30mg/d vs warfarin in atrial fibrillation

11.3.1 Clinical evidence profile

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Giugliano 2013 ENGAGE AF-TIMI 48 Giugliano 2013(28) Design: non-inferiority RCT DB PG Duration of follow-up: median 2.8y	n= 21,105 Mean age: 72 40% ≥ 75y Mean $CHADS_2$ score: ? $CHADS_2$ 2-3/ 77.5% $CHADS_2$ 4-6/ 22.5% Prior stroke/TIA: 28% Type 2 diabetes: 36% Congestive heart failure: 57% Hypertension requiring treatment: 94% CrCL <50ml/min: 19% previous use of VKA: 59% <u>Inclusion:</u> 21 years of age or older and a score of 2 or higher on the CHADS2 risk assessment, and anticoagulation	Edoxaban 60mg/d vs Edoxaban 30 mg/d vs Warfarin (INR 2.0 to 3.0) <u>Remarks</u> dose reduction at randomization: (in 25.3% of participants) if eGFR 30 - 50 ml/min, ≤60 kg, or concomitant use of verapamil or quinidine or	Adherence		
			TTR in warfarin group	mean 64.9% +/- 18.7%	
			INR 1.8 – 3.2	83.1% of treatment period	
			No drug interruption (>3d)	Edoxaban 60: 37.4% Edoxaban 30: 38.2% Warfarin: 34.5% p<0.001 for comparisons each dose of edoxaban vs warfarin	
			Efficacy		
			Stroke or systemic embolism (PO)	<u>mITT , treatment period</u> Edoxaban 60: 1.18% /y Edoxaban 30: 1.61% /y Warfarin: 1.50% /y Edoxaban 60 vs warfarin **HR 0.79 (97.5% CI 0.63 – 0.99)** **p for non-inferiority <0.001, SS** Edoxaban 30 vs warfarin **HR 1.07 (97.5% CI 0.87 – 1.31)** **p for non-inferiority 0.005, SS** <u>ITT, overall period</u> Edoxaban 60: 1.57% /y Edoxaban 30: 2.04% /y Warfarin: 1.80% /y	RANDO: Adequate (computer response system) ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost to follow-up: <1% Permanent discontinuation of study drug: Edoxaban 60: 34.4% Edoxaban 30: 33.0% Warfarin: 34.5% Drop-outs and Exclusions: • Described: yes • Balanced across groups: mostly balanced ITT: see definitions below this table SELECTIVE REPORTING:YES

	therapy planned for the duration of the trial <u>Exclusion</u> atrial fibrillation due to a reversible disorder; an estimated creatinine clearance of less than 30 ml per minute; a high risk of bleeding; use of dual antiplatelet therapy; moderate-to severe mitral stenosis; other indications for anticoagulation therapy; acute coronary syndromes, coronary revascularization, or stroke within 30 days before randomization; and an inability to adhere to study procedures	dronedarone. Randomization was stratified according to CHADS2 score of 2 or 3 versus a score of 4, 5, or 6 and status with respect to the need for a reduction in the edoxaban dose		Edoxaban 60 vs warfarin HR 0.87 (97.5% CI 0.73 – 1.04) p for superiority 0.08 ; NS Edoxaban 30 vs warfarin HR 1.13 (97.5% CI 0.96 – 1.34) p for superiority 0.10; NS	protocol stated analyses according to ITT, mITT and per-protocol for primary and secondary endpoints. These were not all reported. Other important methodological remarks: - wide non-inferiority margin (preserving only 50% of the effect of warfarin vs placebo) - confusing analyses (different populations and different time windows – see definitions below) - multiple changes of protocol (eg. endpoints) - multicenter trial, with high number of centers and low number of patients per center - patients with high risk of bleeding excluded. Definition? - list of prespecified subgroup analyses is vague ('*including but not limited to…*') Sponsor: Daiichi Sankyo Pharma Development
			Stroke, systemic embolism or death from CV causes (including bleeding) (SO)	<u>ITT, overall period</u> Edoxaban 60:3.85 %/y Edoxaban 30:4.23 %/y Warfarin: 4.43 %/y **Edoxaban 60 vs warfarin** **HR 0.87 (0.78–0.96)** **p<0.005** **SS** Edoxaban 30 vs warfarin HR 0.95 (0.86–1.05) p= 0.32 NS	
			Major adverse cardiac events (myocardial infarction, stroke, systemic embolic event, or death due to cardiovascular cause (including bleeding) (SO)	<u>ITT, overall period</u> Edoxaban 60:4.41 %/y Edoxaban 30:4.90 %/y Warfarin: 4.98 %/y Edoxaban 60 vs warfarin **HR 0.88 (0.81–0.97)** **p<0.01** SS	

				Edoxaban 30 vs warfarin HR 0.98 (0.90–1.08) p=0.69 NS	
			Stroke, systemic embolic event, or death (SO)	<u>ITT, overall period</u> Edoxaban 60: 5.01 %/y Edoxaban 30: 5.23 %/y Warfarin: 5.57 %/y Edoxaban 60 vs warfarin **HR 0.90 (0.82–0.98)** **SS** Edoxaban 30 vs warfarin HR 0.94 (0.86–1.02) NS	
			Death, any cause	<u>ITT, overall period</u> Edoxaban 60: 3.99 %/y Edoxaban 30: 3.80 %/y Warfarin: 4.35 %/y Edoxaban 60 vs warfarin HR 0.92 (0.83–1.01) p<0.08 Edoxaban 30 vs warfarin **HR 0.87 (0.79–0.96)** **p<0.006** *estimated NNT/2y=91 (55 to 288)*	
			Death, cardiovascular causes (problably	<u>ITT, overall period</u> Edoxaban 60: 2.74 %/y Edoxaban 30: 2.71 %/y	

			including bleeding)	Warfarin: 3.17 %/y Edoxaban 60 vs warfarin **HR 0.86 (0.77–0.97)** **p<0.013** Edoxaban 30 vs warfarin **HR 0.85 (0.76–0.96)** **p<0.008**	
			Ischemic stroke	<u>ITT, overall period</u> Edoxaban 60: 1.25 %/y Edoxaban 30: 1.77 %/y Warfarin: 1.25 %/y Edoxaban 60 vs warfarin HR 1.00 (0.83–1.19) p=0.97 NS Edoxaban 30 vs warfarin HR 1.41 (1.19–1.67) **p<0.001** **SS** **more ischemic stroke with edoxaban 30**	
			Haemorragic stroke	<u>ITT, overall period</u> Edoxaban 60: 0.26 %/y Edoxaban 30: 0.16 %/y Warfarin: 0.47 %/y Edoxaban 60 vs warfarin **HR 0.54 (0.38–0.77)**	

				p<0.001 SS less haemorragic stroke with edoxaban 60 Edoxaban 30 vs warfarin **HR 0.33 (0.22–0.50)** **p<0.001** SS less haemorragic stroke with edoxaban 30	
			Fatal stroke	<u>edoxaban 60 0.42%/y</u> <u>edoxaban 30 0.38%/y</u> <u>warfarin 0.45%/y</u> <u>ns</u>	
			Myocardial infarction	<u>ITT, overall period</u> Edoxaban 60: 0.70 %/y Edoxaban 30: 0.89 %/y Warfarin: 0.75 %/y Edoxaban 60 vs warfarin HR 0.94 (0.74–1.19) p=0.60 NS Edoxaban 30 vs warfarin HR 1.19 (0.95–1.49) p=0.13 NS	
			Safety		
			Major bleeding (ISTH definition)	<u>mITT, treatment period</u> Edoxaban 60: 2.75% /y Edoxaban 30: 1.61% /y Warfarin: 3.43% /y	

				Edoxaban 60 vs warfarin **HR 0.80 (95%CI 0.71-0.91)** **p<0.001;** **SS less major bleeding with edoxaban 60 mg** *estimated NNT/2y=74 (51 to 161)* Edoxaban 30 vs warfarin **HR 0.47 (95%CI 0.41 - 0.55)** **p<0.001;** **SS less major bleeding with edoxaban 30 mg** *estimated NNT/2y=28 (25 to 33)*
			Any intracranial bleeding	mITT, treatment period Edoxaban 60: 0.39 %/y Edoxaban 30: 0.26 %/y Warfarin: 0.85 %/y **Edoxaban 60 vs warfarin** **HR 0.47 (0.34–0.63)** **p <0.001** **SS** *estimated NNT/2y=109 (90 to 159)* E**doxaban 30 vs warfarin** **HR 0.30 (0.21–0.43)** **p<0.001** **SS** *estimated NNT/2y=85 (75 to 104)*
			Gastro-intestinal bleeding	mITT, treatment period Edoxaban 60: 1.51 %/y Edoxaban 30: 0.82 %/y Warfarin: 1.23 %/y

				Edoxaban 60 vs warfarin **HR 1.23 (1.02–1.50)** **p=0.03** **SS more GI bleeding with edoxaban 60** *estimated NNH/2y=179 (2033 to 82)* Edoxaban 30 vs warfarin **HR 0.67 (0.53–0.83)** **p <0.001** **SS less GI bleeding with edoxaban 30** *estimated NNT/2y=122 (87 to 239)*	
			Fatal bleeding	Edoxaban 60 mg 0.21%/y Edoxaban 30 mg 0.13%/y Warfarin 0.38%/y SS less fatal bleeding with both doses of edoxaban compared to warfarin estimated NNT/2y edox 60 mg: 295 estimated NNT/2y edox 30mg: 200	
			On-treatment Adverse Events (excluding bleeding) Leading to drug interruption/ discontinuation	Edoxaban 60 mg 31.9% Edoxaban 30 mg 32.4% Warfarin 35.4% NT	

Definitions

Modified ITT

patients who underwent randomization and received at least one dose of the study drug during the treatment period

ITT

All randomized subjects whether or not they receive a single dose of randomized study drug.

Safety analysis (from statistical analysis plan)
All randomized subjects who receive at least one dose of randomized study drug

Treatment period
the period between administration of the first dose of the study drug and either 3 days after the receipt of the last dose or the end of the double-blind therapy (whichever came first), with interval censoring of events during study-drug interruptions that lasted more than 3 days.
(for both efficacy and safety analyses)

Overall study period (from statistical analysis plan)
from the initial dose of study drug date to the clinical study end date Visit

Primary efficacy analysis
= non-inferiority testing: modified ITT population – treatment period
Superiority testing
ITT population – overall study period
Safety analysis
Modified ITT - treatment period

Non-inferiority
the upper boundary of the one-sided 97.5% confidence interval for the hazard ratio of the primary efficacy end point comparing edoxaban with warfarin could not exceed 1.38, which was an estimate that preserved at least 50% of the benefit of warfarin over placebo

Sensitivity analyses planned but not reported.

Major bleeding
The definition of major bleeding is based on published guidance from the International Society on Thrombosis and Haemostasis (ISTH) with minor modifications for hemoglobin (Hgb) decrease and blood transfusion requirements.

ISTH definition(116)

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.

11.3.2 Subgroup analysis according to age. Edoxaban 30mg or 60 mg/d vs warfarin.

Reference	n	subgroup Age	Outcome	Results edoxaban vs warfarin event rate (%/y) HR (95%CI)	Remarks
Giugliano 2013(28)	12631	<75y	Stroke/SE	high dose edoxaban 1.35%/y vs 1.48%/y low dose edoxaban 1.71%/y vs 1.48%/y	Prespecified analysis: YES Stratified at randomization: NO Baseline characteristics of different subgroups: Older patients were more likely to be female, with lower body weight and reduced creatinine clearance, leading to higher rates of edoxaban dose reduction (10%, 18%, and 41% for the 3 age groups, P<0.001)
	8474	>=75y	Stroke/SE	high dose 1.91%/y vs 2.31%/y low dose 2.55%/y vs 2.31%/y	
				P for interaction high dose= 0.59 NS P for interaction low dose p= 0.87 NS	
	12594	<75y	Major bleeding	high dose 2.02%/y vs 2.62%/y low dose 1.23%/y vs 2.62%/y	
	8432	>=75y	Major bleeding	high dose 4.01%/y vs 4.83%/y low dose 2.26%/y vs 4.83%/y	
				P for interaction high dose= 0.57 NS P for interaction low dose p= 0.95 NS	
Kato 2016(45)		<65y	Stroke/SE	HR 0.94(0.65 - 1.37)	note: post hoc analyses for <80y vs >= 80y and for <85y vs >=85y showed no significant interactions.
		65-77y	Stroke/SE	HR 0.89(0.68 – 1.16)	
		>=75y	Stroke/SE	HR 0.83(0.66 – 1.04)	

				P for interaction 0.84 NS	low number of patients of >85y.
		<65y	Major bleeding	HR 0.81(0.58 – 1.12)	note: patients with criteria for dose reduction who were >=75 y had a lower rate of major bleeding compared to patients >=75y that did not meet dose reduction criteria (HR 0.58(0.43-0.77) vs 1.06 (0.84 – 1.33) respectively, p for interaction 0.0012)
		65-77y	Major bleeding	HR 0.75 (0.60-0.94)	
		>=75y	Major bleeding	0.83 (0.70-0.99)	
				P for interaction 0.78 NS	

Author's conclusions (Kato 2016) *"Stroke or systemic embolic event (1.1%, 1.8%, and 2.3%) and major bleeding (1.8%, 3.3%, and 4.8%) rates with warfarin increased across age groups (P_{trend}<0.001 for both). There were no interactions between age group and randomized treatment in the primary efficacy and safety outcomes. In the elderly (≥75 years), the rates of stroke/ systemic embolic event were similar with edoxaban versus warfarin (hazard ratio 0.83 [0.66–1.04]), while major bleeding was significantly reduced with edoxaban (hazard ratio 0.83 [0.70–0.99])"*

11.3.3 Subgroup analysis according to renal function: eGFR (Cockroft-Gault). Edoxaban 60 mg/d vs warfarin.

Reference	n	subgroup eGFR	Outcome	Results **high dose** edoxaban vs warfarin HR (95%CI)	Remarks
Bohula 2016(51)	2740	<=50ml/min (NB <30 ml/min excluded)	Stroke/SE	HR 0.87; (0.65–1.18)	Prespecified analysis: YES stratified at randomization: NO Baseline characteristics of different subgroups: Baseline characteristics were well matched(P>0.05) except for differences in the rate of dose reduction for CrCl of 30-50 mL/min (HDER, 78% versus warfarin, 81%) and low body weight (29% versus 33%) within the CrCl of 30 to 50 mL/min subgroup, BMI (30 versus 29 kg/m2) in the CrCl >50 mL/min subgroup, and median age (73 versus 72 years) in the CrCl >50 to 95 mL/min subgroup. exploratory analyses suggested an apparent decrease in relative efficacy to prevent arterial thromboembolism in the upper range of CrCl, but P for interaction was 0.08. Consistent results on bleeding in all ranges of CrCl.
	11331	>50 ml/min	Stroke/SE	HR 0.87; (0.72–1.04)	
				P for interaction 0.94 NS	
	2740	<=50ml/min (NB <30 ml/min excluded)	Major bleeding	HR 0.76 (0.58–0.98)	
	11331	>50 ml/min	Major bleeding	HR 0.82 (0.71–0.95)	
				P for interaction 0.62 NS	

11.3.4 Subgroup analysis according to center level TTR. Edoxaban 30mg or 60 mg/d vs warfarin.

Reference	n	subgroup mean cTTR	Outcome	Results edoxaban vs warfarin	Remarks
Giugliano 2013(28)	9974	>66.4%	Stroke/SE	high dose 1.41%/y vs 1.54%/y low dose 1.0%/y vs 1.54%/y	Prespecified analysis: YES stratified at randomization: NO Baseline characteristics of different subgroups: NR
	10679	<=66.4%	Stroke/SE	high dose 1.73%/y vs 2.07%/y low dose 2.17%/y vs 2.07%/y	
				P for interaction high dose p=0.57 low dose p= 0.24 NS	
	9952	>66.4%	Major bleeding	high dose 3.15%/y vs 3.51%/y low dose 1.62%/y vs 3.51%/y	
	10628	<=66.4%	Major bleeding	high dose 2.33%/y vs 3.35%/y low dose 1.49%/y vs 3.35%/y	
				P for interaction high dose p= 0.06 low dose p= 0.76 NS (trend for less bleeding with edoxaban high dose compared to warfarin with cTTR<66.4)	

11.4 Rivaroxaban 20 mg/d vs warfarin in atrial fibrillation

11.4.1 Clinical evidence profile

Ref	n / Population	Comparison	Outcomes		Methodological
Patel 2011(29) (ROCKET AF trial) Design: RCT, P non-inferiority 707 days mean follow up	n= 14.264 -mean age 73 -mean CHADS score 3.5 (100% CHADS≥2) 13% $CHADS_2$ =2 44% $CHADS_2$ =3 29% $CHADS_2$=4 13% $CHADS_2$ =5 Prior stroke/TIA: 55% Type 2 diabetes: 40% Congestive heart failure: 62% Hypertension requiring treatment: 91% CrCL median 67ml/min previous use of VKA: 62% <u>Inclusion</u> - non-valvular atrial	Rivaroxaban 15- 20mg/d (according to renal function) vs Warfarin INR 2-3 <u>Renal insufficiency:</u> CrCl<30ml/min -> excluded CrCl 30-49ml/min -> 15mg rivaroxaban CrCl≥50ml/min -> 20mg rivaroxaban	Adherence		RANDO: 2/2 low risk of bias ALLOCATION CONCEALMENT low risk of bias BLINDING: 2/2 double blind - lost to follow up <1% treatment discontinuation 23.7% rivaroxaban 22.2% warfarin per-protocol population: all patients who received at least one dose of a study drug, did not have a major protocol violation, and were followed for events while receiving a study drug or within 2 days after discontinuation safety population: patients who received at least one dose of a study drug and
			TTR in warfarin group	mean 55% median 58%; interquartile range 43 to 71	
			INR 1.8 – 3.2	**not reported**	
			No drug interruption (>3d)	**not reported**	
			Other adherence parameter	**not reported**	
			Efficacy		
			Stroke (ischemic or hemorrhagic) or systemic embolism (PO)	Per protocol Rivaroxaban: 1.7%/y vs warfarin:2.2%/y **SS: HR 0.79 (95%CI 0.66 – 0.96) p<0.001 for non-inferiority** ITT: Rivaroxaban: 2.1%/y vs warfarin: 2.4%/y **SS : HR 0.88 (95%CI 0.74 – 1.03)** **p<0.001 for non-inferiority**, p = 0.12 for superiority	
			Ischemic stroke	Rivaroxaban 1.34% vs warfarin 1.42% NS: HR 0.94; 95%CI 0.75-1.17, p=0.581	
			Hemorrhagic stroke	**Rivaroxaban 0.26% vs warfarin 0.44%** **HR 0.59 (95%CI 0.37-0.93)**	

	fibrillation - moderate to high risk of stroke (prior stroke/TIA, or at least 2 risk factors: heart failure, hypertension, ≥75 y, diabetes) <u>Exclusion</u> - high bleeding risk - severe renal insufficiency (CrCl<30ml/min) or liver failure			**p=0.024** **SS less hemorrhagic stroke with rivaroxaban** *estimated NNT/2y: 278(181-11364)*	were followed for events, regardless of adherence to the protocol, while they were receiving the assigned study drug or within 2 days after discontinuation ITT: all patients who underwent randomization and were followed for events during treatment or after premature discontinuation Key secondary efficacy end points were also tested for superiority in the as-treated safety population. - Other important methodological remarks? a non-inferiority margin of 1.46 with a one-sided alpha level of 0.025 -low TTR in warfarin- arm: 55% vs 63-73% in other trials - BMJ reported that a defective point of care device was used in the warfarin arm of the
			Fatal stroke	rivaroxaban 0.42%/y vs warfarin 0.59%/y NS	
			Mortality	Rivaroxaban 1.87% vs 2.21% warfarin NS: HR 0.85 (95%CI 0.70 – 1.02) p=0.073 (safety population)	
			Myocardial infarction	Rivaroxaban 0.91% vs 1.12% warfarin NS: HR 0.81 (95%CI 0.63 – 1.06) p=0.121	
			Harms		
			Bleeding outcomes		
			Intracranial	Rivaroxaban 0.5% vs 0.7% warfarin **HR 0.67 (0.47–0.93)** **(p=0.02)** *estimated NNT/2y=250 (135 to 1021)*	
			Major or nonmajor clinically relevant bleeding (PO)	rivaroxaban 14.9%/y Warfarin 14.5%/y HR 1.03 (0.96–1.11) p=0.44 NS	
			Major bleeding*	3.6%/y vs 3.4%/y HR 1.04 (0.90–1.20) (NS: p=0.58)	
			Fatal bleeding	**0.2%/y vs 0.5%/y** **HR 0.50 (0.31–0.79)** **(SS: p=0.003)** *estimated NNT/2y: 167*	

					trial(Cohen 2016(30))
			Nonmajor clinically relevant bleeding**	11.8%/y vs 11.4%/y (NS: p=0.35)	- Sponsor: Johnson and Johnson, Bayer Healthcare
			GI-bleeding	**3.15%/y vs 2.16% /y** **(SS: p<0.001)** *estimated NNH/2y=51*	
			AE's		
			Epistaxis (10.14% vs 8.55%, SS: p<0.05) and hematuria (4.16% vs 3.420%, SS: p<0.05) SS more frequent in rivaroxaban group No SS differences in non-bleeding adverse events		

* Major bleeding was defined as clinically overt bleeding associated with any of the following: fatal outcome, involvement of a critical anatomic site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), fall in hemoglobin concentration >2 g/dL, transfusion of >2 units of whole blood or packed red blood cells, or permanent disability.

** Non-major clinically relevant bleeding was defined as overt bleeding not meeting criteria for major bleeding but requiring medical intervention, unscheduled contact (visit or telephone) with a physician, temporary interruption of study drug (i.e., delayed dosing), pain, or impairment of daily activities.

11.4.2 Subgroup analysis according to age. Rivaroxaban 20mg/d vs warfarin.

Reference	n	subgroup Age	Outcome	Results Rivaroxaban vs warfarin HR (95%CI)	Remarks
Halperin 2014(46)	8035	<75y	Stroke/SE	0.95 (0.76–1.19)	Prespecified analysis: YES stratified at randomization: NO Baseline characteristics of different subgroups: elderly had lower median BMI, were more likely to be female, had a higher mean CHADS2 socre, less heart failure, more hypertension, less diabetes mellitus, lower median CrCl… note: **Older patients randomized to rivaroxaban had higher rates of the combined end point of major or clinically relevant nonmajor bleeding**, than those assigned to warfarin, whereas there was no difference by treatment in rates of bleeding among younger patients **(interaction P=0.009).** This interaction was restricted to extracranial bleeding and driven primarily by **gastrointestinal bleeding, which was more frequent among elderly patients in the rivaroxaban group** than in the warfarin group. Rates of hemorrhagic stroke were similar in elderly and younger patients and consistent with the overall trial results
	6229	>=75y	Stroke/SE	0.80 (0.63–1.02)	
				P for interaction 0.3131 NS	
	8035	<75y	Major bleeding	0.96 (0.78–1.19)	
	6229	>=75y	Major bleeding	1.11 (0.92–1.34)	
				P for interaction 0.3357 NS	

Author's abstract: "older participants had more primary events (2.57% versus 2.05%/100 patient-years; P=0.0068) and major bleeding (4.63% versus 2.74%/100 patient-years; P<0.0001). Stroke/systemic embolism rates were consistent among older and younger patients, as were major bleeding. Hemorrhagic stroke rates were similar in both age groups; there was no interaction between age and rivaroxaban response. Conclusions—Elderly patients had higher stroke and major bleeding rates than younger patients, but the efficacy and safety of rivaroxaban relative to warfarin did not differ with age, supporting rivaroxaban as an alternative for the elderly."

11.4.3 Subgroup analysis according to renal function: eGFR (Cockroft-Gault). Rivaroxaban 20 mg/d vs warfarin.

Reference	n	subgroup eGFR	Outcome	Results rivaroxaban vs warfarin HR (95%CI)	Remarks
Fox 2011(52)	2950	CrCl 30–49 mL/min	Stroke/SE	per protocol HR 0.84 (0.57–1.23)	Prespecified analysis: YES stratified at randomization: NO Baseline characteristics of different subgroups: patients with moderately impaired renal function were older, had higher CHADS2 scores, higher prevalence of heart failure, peripheral vascular disease and prior myocardial infarction; lower body mass indices, less frequent history of stroke or transient ischaemic attack, and were less likely to be diabetic note: efficacy outcome stroke/SE: similar results **in ITT population** note **primary safety endpoint (major +clinically relevant nonmajor bleeding**): p value for interaction 0.4496: NS
	11277	CrCl ≥50 mL/min	Stroke/SE	per protocol HR 0.78 (0.63–0.98)	
				P for interaction 0.76 NS	
	2950	CrCl 30–49 mL/min	Major bleeding	HR0.95 (0.72–1.26)	
	11277	CrCl ≥50 mL/min	Major bleeding	HR 1.07 (0.91–1.26)	
				P for interaction 0.48 NS	

Patients with CrCl 30-45 had dose adjustment of rivaroxaban: 15mg instead of 20 mg

Author's conclusions:
"Patients with AF and moderate renal insufficiency have higher rates of stroke and bleeding than those with normal renal function. There was no evidence of heterogeneity in treatment effect across dosing groups. Dose adjustment in ROCKET-AF yielded results consistent with the overall trial in comparison with dose-adjusted warfarin."

11.4.4 Post hoc analysis according to worsening renal function over time (Cockroft-Gault). Rivaroxaban 20mg/d vs warfarin.

Reference	n	subgroup	Outcome	Results rivaroxaban vs warfarin HR (95%CI)	Remarks
Fordyce 2016(54)	3320	WRF	Stroke/SE	0.50(0.27-0.93)	Prespecified analysis: NO stratified at randomization: NO Baseline characteristics of different subgroups: see below **note: the interaction test for stroke risk showed no statistical significance when eGFR was calculated with MDRD (p=0.095) or with CKD-EPI (p=0.28)**
	9292	SRF	Stroke/SE	0.97(0.76-1.24)	
				P for interaction 0.05 NS (borderline)	
	3320	WRF	Major and clinically relevant nonmajor bleeding	1.06(0.80-1.39)	
	9292	SRF	Major and clinically relevant nonmajor bleeding	0.98(0.89-1.18)	
				P for interaction 0.61 NS	

WRF= worsening renal function (>20% CrCl decrease from baseline during study period) SRF= stable renal function

Baseline characteristics: compared with patients with SRF, patients with WRF experienced a greater incidence of hypertension (93% versus 90%), diabetes mellitus (43% versus 39%), previous myocardial infarction (18% versus 16%), and congestive heart failure (65% versus 61%) but were less likely to have an actual history of previous stroke, transient ischemic attack, or non–central nervous system embolism (52% versus 56%).

Author's abstract: *"There was a small, statistically significant decline in mean±SD CrCl among patients receiving warfarin (−4.3±14.6 mL/min) compared with patients receiving rivaroxaban (−3.5±15.1 mL/min; P<0.001).*
There was no statistically significant difference in the primary efficacy outcome (stroke or non–central nervous system embolism) between patients with WRF and those with SRF (adjusted HR, 1.25; 95% CI, 0.89–1.75; P=0.19). However, WRF patients had a higher incidence of vascular death (adjusted HR, 1.47; 95% CI, 1.05–2.06; P=0.026) and all-cause mortality (HR 1.49 (1.12 to 1.98), p=0.0067)"

Author's conclusion: *"WRF patients who were randomized to receive rivaroxaban had a reduction in stroke or systemic embolism compared with those taking warfarin (1.54 versus 3.25 events per 100 patient-years) that was not seen in patients with stable renal function who were randomized to receive rivaroxaban (P=0.050 for interaction). There was no difference in major or nonmajor clinically relevant bleeding among WRF patients randomized to warfarin versus rivaroxaban."*
Remark by reviewer from the literature group: this interaction was only apparent with Cockroft-Gault calculation.

11.4.5 Subgroup analysis according to center level TTR. Rivaroxaban 20mg/d vs warfarin.

Reference	n	subgroup mean TTR	Outcome	Results rivaroxaban vs warfarin HR(95%CI)	Remarks
Piccini 2014(102)	3424	< 50.6%	Stroke/SE	0.70 (0.47, 1.04)	Prespecified analysis: YES stratified at randomization: NO Baseline characteristics of different subgroups: see below
	3553	50.7% -58.5%	Stroke/SE	0.90 (0.64, 1.26)	
	3492	58.6% - 65.7%	Stroke/SE	0.88 (0.62, 1.25)	
	3502	65.7% -100.0%	Stroke/SE	0.73 (0.50, 1.06)	
				P for interaction 0.709 NS	
	3514	< 50.6%	Major and clinically relevant nonmajor bleeding	0.80 (0.66, 0.98)	
	3516	50.7% -58.5%	Major and clinically relevant nonmajor bleeding	0.96 (0.81, 1.14)	
	3506	58.6% - 65.7%	Major and clinically relevant nonmajor bleeding	1.03 (0.87, 1.22)	
	3528	65.7% -100.0%	Major and clinically relevant nonmajor bleeding	1.25 (1.10, 1.41)	
				P for interaction 0.001 SS	

Author's conclusions
"Centers with the highest cTTRs by quartile had lower-risk patients as reflected by lower CHADS2 scores (P<0.0001) and a lower prevalence of prior stroke or transient ischemic attack (P<0.0001). Sites with higher cTTR were predominantly from North America and Western Europe. The treatment effect of rivaroxaban versus warfarin on the primary endpoint was consistent across a wide range of cTTRs (P value for interaction=0.71). The hazard of major and non-major clinically relevant bleeding increased with cTTR (P for interaction=0.001), however, the estimated reduction by rivaroxaban compared with warfarin in the hazard of intracranial hemorrhage was preserved across a wide range of threshold cTTR values."

11.5 Rivaroxaban 15mg/d vs warfarin in Japanese patients with atrial fibrillation

11.5.1 Clinical evidence profile

Ref	n / Population	Comparison	Outcomes		Methodological
Hori 2012(31) Design: RCT, P DB non-inferiority follow up planned duration 2.5y	Japanese patients n= 1280 -mean age 71.1 -mean CHADS score 3.25 16.6% $CHADS_2$ =2 83.4% $CHADS_2$ ≥3 Prior stroke/TIA: 64% Type 2 diabetes: 38% Congestive heart failure: 41% Hypertension requiring treatment: 80% CrCL 30-49ml/min 22.1% CrCL 50-80ml/min 531.3% previous use of VKA: 90% <u>Inclusion</u> ≥20 y non-valvular AF history of prior ischemic stroke, TIA or systemic	Rivaroxaban 15mg/d vs Warfarin INR 2-3 <u>Renal insufficiency:</u> 10 mg/d if CrCl 30–49 ml/min ≥70y INR 1.6-2.6	Adherence		RANDO: not described ALLOCATION CONCEALMENT not described BLINDING: double blind - lost to follow up <1% - treatment discontinuation not reported per-protocol population: all patients who received at least one dose of a study drug, did not have a major protocol violation, and were followed for events while receiving a study drug or within 2 days after discontinuation safety population:
			TTR in warfarin group	all patients 65% ≥70y 74% <70y 51.8%	
			INR 1.8 – 3.2		
			No drug interruption (>3d)		
			proportion of days a patient took study medication (%of total treatment duration)	**>99%**	
			Efficacy		
			Stroke (ischemic or hemorrhagic) or systemic embolism (PO)	Per protocol Rivaroxaban: 1.2%/y vs warfarin:2.61%/y HR 0.49 (95%CI 0.24 – 1.0)	
			Ischemic stroke	**HR 0.40; (95%CI 0.17-0.96)** **SS**	
			Hemorrhagic stroke	HR 0.73 (95%CI 0.16-3.25) NS	
			Mortality	Too few events occurred to provide a robust statistical evaluation	
			Myocardial infarction	Too few events occurred to provide a robust statistical evaluation	
			Harms		
			Bleeding outcomes		

	embolism or ≥2 of the following: congestive heart failure and/or left ventricular ejec- tion fraction ≤35%, hypertension, age ≥75 years, or diabetes mellitus. <u>Exclusion</u> • mitral valve stenosis; Prosthetic heart valve; Planned cardioversion • atrial myxoma or left ventricular thrombus or active endocarditis. • History of major surgery or trauma within 30 days • History of significant gastrointestinal bleeding within 6 m • History of intracranial bleeding, intraocular bleeding, spinal bleeding, or atraumatic intra-articular bleeding; Chronic hemorrhagic disorder • Scheduled invasive procedure, including major surgery • hypertension: SBP ≥180 mmHg or DBP ≥100		Intracranial		patients who received at least one dose of a study drug, while they were receiving the assigned study drug or within 2 days after discontinuation ITT: all patients who underwent randomization and were followed for events during treatment or after premature discontinuation - Other important methodological remarks? non-inferiority trial for safety (bleeding risk). Non-inferiority criterion would be met if the upper boundary of the 95% CI for the HR of rivaroxaban to warfarin did not exceed 2.0. This margin was chosen
			Major or nonmajor clinically relevant bleeding (PO)	Rivaroxaban 18.04%/y vs warfarin 16.42%/y **HR 1.11 (95% CI 0.87–1.42)** **rivaroxaban non-inferior to warfarin**	
			Major bleeding*	3.00%/y vs 3.59%/y HR 0.85 (95%CI 0.50-1.43) NS	
			Fatal bleeding	**1 patient vs 3 patients**	
			Nonmajor clinically relevant bleeding**	15.42%/y vs 12.99%/y HR 1.20 (95% CI 0.92–1.56) NS	
			GI-bleeding		
			AE's		
			discontinuation due to AE **13.1% rivaroxaban** **15.0% warfarin**		

	mmHg • Stroke with severe residual disability ≤3 months or any stroke ≤14 days, • antiplatelet drugs (except for ≤100 mg/day acetylsalicylic acid [ASA]; thienopyridines or cilostazol) or fibrinolytic therapy within 10 days chronic use of NSAID, strong cytochrome P450 3A4 inhibitor or P450 3A4 inducer • CrCl<30 ml/min • significant liver disease			based on studies in Asian patients with AF, which demonstrated at least a 2-fold increase in bleeding risk with warfarin treatment at INRs ≥2.6 compared with <2.6 The study was not powered to test efficacy hypotheses - Sponsor: Johnson and Johnson, Bayer Healthcare

* Major bleeding: Clinically overt bleeding that was associated with a fall in hemoglobin ≥20 g/L, transfusion of ≥2 units of packed red blood cells or whole blood, or involved a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal hemorrhage), or had a fatal outcome.

** Non-major clinically relevant bleeding: Clinically overt bleeding not meeting the criteria for major bleeding, but requiring medical intervention, unscheduled consultation with a physician, temporary discontinuation of study treatment, pain, or impairment of daily activities

No significant differences in principal safety outcome rates were observed between the rivaroxaban and warfarin treatment groups, either in patients with moderate renal impairment (HR 1.22; 95% CI 0.78–1.91) or in patients with mild or no renal impairment and baseline CrCl ≥50 ml/min (HR 1.07; 95% CI 0.80–1.43; interaction P-value=0.628)

12 Evidence tables. Meta-analyses in atrial fibrillation

12.1 MA in total study population with AF

12.1.1 Description of included MAs

Ref Study type	Main inclusion criteria	Endpoints/analyses	Comments
Ruff 2014(32)	AF phase III	-efficacy -safety -subgroups (age, CrCl, TTR)	4 trials J-ROCKET excluded AMSTAR score 3 (Van Brabandt 2017)
Jia 2014(33)	AF follow-up>1y	-efficacy -safety -separate analyses for high-dose and low-dose regimens -the high-dose groups of RE-LY (150 mg twice daily) and ENGAGE AF-TIMI 48 (60 mg twice daily) were combined with the single dose studies ARISTOTLE, ROCKET-AF, and J-ROCKET.	5 trials J-ROCKET included AMSTAR score 7 (Van Brabandt 2017)
Providencia 2014(34)	AF Phase III	-efficacy -safety -In studies investigating two different doses of DOAC, these were combined into the same treatment arm and then compared with warfarin. -includes ximelagatran, but sensitivity analysis without this DOAC provided -separate analysis for DTI and FXaI -separate analysis for once-daily and twice-daily	7 trials Ximelagatran included J-ROCKET included AMSTAR score 3 (Van Brabandt 2017)
Liew 2014(117)	AF follow-up>1y	-total mortality -cardvasc mortality	4 trials also NNTs reported

		-bleeding mortality -intracranial bleeding -All doses combined	J-ROCKET not included
Caldeira 2015 (118)	AF VTE phase III J-ROCKET included	Gastrointestinal bleeding separate analysis for AF/VTE available	5 trial AF 7 trials VTE
Gomez-Outes 2016(119)	AF Phase III follow-up >1y	-mortality -vascular mortality -other causes -separate analysis for dose available	4 trials J-ROCKET not included

12.1.2 Results of included meta-analyses

	Stroke/SE RR (95%CI)	Ischemic stroke	Hemorrhagic stroke	mortality	MI	major bleeding	Intracranial bleeding	Gastrointestinal bleeding
Ruff 2014(32)	'high dose' **0·81 (0·73–0·91)** low dose 1·03 (0·84–1·27)	'high dose' 0·92 (0·83-1·02) **low dose** **1·28 (1·02–1·60)**	'high dose' **0·49 (0·38-0·64)**	'high dose' **0.90 (0.85-0.95)**	High dose 0.97(0.78-1.20)	'high dose' 0.86 (0.73-1.00) low dose 0·65 (0·43–1·00)NS	**'high dose'** **0·48 (0·39-0·59)** **SS**	**'high dose'** 1.25 (1.01-1.55) low dose similar (appendix)
Jia 2014(33)	all doses **0.86(0.75–0.99)** high dose **0.80 (0.71–0.91)** low dose 1.03 (0.84-1.27)			high dose **0.90(0.85–0.95)** **low dose** **0.89 (0.83-0.96)**	high dose 0.97(0.85-1.11) low dose **1.25(1.04–1.50)**	all doses **0.78 (0.64–0.94)** **high dose** **0.86 (0.74–0.99)** low dose 0.63 (0.36-1.04)	high dose 0.48 (0.41-0.56) low dose 0.31(0.24-0.41)	high dose low dose 0.85(0.72–1.00)
Providencia 2014(34) (analysis without Ximelagatran)	all doses **0.82 (0.74-0.91)**	all doses 0.98 (0.83-1.17**)**		all doses **0.90 (0.85-0.94)**	all doses 1.01 (0.83-1.23)	all doses **0.80 (0.66-0.97)**	all doses **0.44 (0.35-0.55)**	all doses 1.08 (0.85-1.37)
Providencia FXAI only	**0.83 (0.72-0.95)**		**0.89 (0.84-0.95)**	**0.89 (0.84-0.95)**	0.94 (0.78-1.12)	0.78 (0.61-1.01)	**0.47 (0.36-0.62)**	1.00 (0.74-1.36)
Liew 2014(117)				**all doses** **ARR (total trial duration)** **0.76% (0.39–1.13)** **NNT = 132**			all doses (total trial duration) NNT=118	
Gomez Gomez-Outes 2016(119)				**all doses** risk difference -0.42%/y(0.66-0.18)				
Caldeira 2015 (118)								similar to Providencia 2014

12.2 Meta-analyses in elderly patiens with AF

12.2.1 Description of included meta-analyses

Ref Study type	Main inclusion criteria	Endpoints/analyses	Comments
Sharma 2015(48)	AF VTE	safety no MA because of heterogeneity	we have all this information from publications in subgroup analyses. No MA because of heterogeneity.
Sadlon 2016(47)	AF VTE phase III trials	stroke/SE major + clinically relevant nonmajor bleeding	4 trials high heterogeneity described
Ruff 2014(32)	AF phase III trials	subgroup analysis <75 vs >= 75 for stroke/SE and major bleeding	4 trials

12.2.2 Results of included meta-analyses

	Stroke/SE	Ischemic stroke	Hemorrhagic stroke	mortality	MI	major bleeding	major and clinically relevant nonmajor bleeding	Gastrointestinal bleeding
Sadlon 2016(47)	>=75y, apixaban +rivaroxaban +high dose dabigatran/edoxaban							
	OR 0.71 **95% CI 0.62–0.82**						OR0.98, 95% CI 0.90–1.06	
	>=75y, apixaban +rivaroxaban +LOW dose dabigatran/edoxaban							
	OR 0.84, **95% CI 0.73–0.96**						OR 0.88, 95%CI 0.80–0.96 high heterogeneity for both analyses, unexplained	
	LOW dose dabigatran/edoxaban							
	NS							
Ruff 2014(32)	<75y vs ≥75y, apixaban +rivaroaban +high dose dabigatran/edoxaban							
	P for interaction 0.38					p for interaction 0.28		

12.3 MA in patients with impaired renal function and AF

12.3.1 Description of included MAs

Ref Study type	Main inclusion criteria	Endpoints/analyses	Comments
Raccah 2016(56)	eCrCL < 50 mL/min and eCrCL 50 to 80 mL/min AF VTE	major bleeding hemorragic stroke	5 Trials J-ROCKET included
Ruff 2014(32)	AF phase III	subgroup analysis CrCl (mL/min) < 50 vs 50-80 vs >80 for stroke/SE and major bleeding	4 trials

12.3.2 Results of included meta-analyses

	Stroke/SE	Ischemic stroke	Hemorrhagic stroke	mortality	MI	major bleeding	major and clinically relevant nonmajor bleeding	Gastrointestinal bleeding
Raccah 2016(56)	eCrCL 50 to 80 mL/min							
			RR 0.43 (95%CI 0.33-0.56)			RR 0.89 [95% CI, 0.81-0.97]		
	eCrCL < 50 mL/min							
			RR 0.42 (95%CI0.30-0.61)			RR 0.86 [95% CI, 0.66-1.12] high heterogeneïty		
Ruff 2014(32)	CrCl (mL/min) < 50 vs 50-80 vs >80							
	p for interaction 0.12					p for interaction 0.57		

13 Evidence tables. DOAC vs DOAC in atrial fibrillation. Observational studies

13.1 Meta-analyses of observational studies

Ref Study type	Setting Population	number of studies	Endpoints	Results
Bai 2017-175(39) SR + MA of observational studies search date oct 2016	**-NVAF** **(4 trials with new users)** **rivaroxaban vs dabigatran**	**6** Lip 2016(37) Graham 2016 (120) Gorst-rasmussen 2016(41) Noseworthy 2016(35) Chan 2016(121) Hernandez 2017(122)	**Stroke/SE**	**Rivaroxaban vs dabigatran** **all doses** HR 1.02 (95% CI 0.91–1.13) NS similar results in sensitivity analysis with only new users similar results in sensitivity analysis with low dose vs low dose and high dose vs high dose
			Mortality (Chan, Gorst-Rasmussen, Graham, Hernandez)	**Rivaroxaban vs dabigatran** **all doses** **HR 1.23 (95% CI 1.12–1.33)** **SS higher with rivaroxaban** similar results in sensitivity analysis with low dose vs low dose and high dose vs high dose
			Myocardial infarction (Chan, Graham)	**Rivaroxaban vs dabigatran** **all doses** HR 0.81 (95% CI 0.43–1.19) NS only results for high dose available
			Major bleeding (Chan, Hernandez, Graham, Lip, Noseworthy)	**Rivaroxaban vs dabigatran** **all doses** **HR 1.38 (95% CI 1.27–1.49)** **SS** similar results in sensitivity analysis with low dose vs low dose and high dose vs high dose

			GE bleeding (Chan, Graham, Hernandez)	**Rivaroxaban vs dabigatran** **all doses** **HR 1.33 95% CI, 1.18–1.48** similar results in sensitivity analysis with low dose vs low dose and high dose vs high dose
			Intracranial bleeding (Chan, Graham, Noseworthy)	**Rivaroxaban vs dabigatran** **all doses** HR 1.22 95% CI, 0.85–1.59 NS similar results in sensitivity analysis with low dose vs low dose and high dose vs high dose

Ref **Study type**	**Setting** **Population**	**number of studies**	**Endpoints**	**Results**
Deitelzweig 2017(38) SR of real-world studies (published articles and congress abstracts) no MA search date nov 2016	**- NVAF** **- DOAC or warfarin** **- any observational study design** **- risk of bias assessment: yes**	7(2 full articles, 5 abstracts)	**Major bleeding**	**apixaban vs dabigatran** *Six studies (lip 2016 + noseworthy 2016 abstracts) reported that apixaban was associated with a numerically lower risk of MB compared to dabigatran, but the difference did not reach statistical significance in five of the studies.* *One study (abstract) reported a similar risk of MB for apixaban and dabigatran.* HRs for apixaban versus dabigatran ranged between 0.50 and 1.01 (range of 95% CIs: 0.36–1.28)
		7(2 full articles, 5 abstracts)	**Major bleeding**	**apixaban vs rivaroxaban** ***All studies reported that apixaban was associated with a significantly lower risk of MB compared to rivaroxaban*** **HR 0.39–0.74 (range of 95% CIs: 0.28–0.85)** Non-industry-sponsored studies reported a larger treatment effect for this comparison compared to industry-sponsored studies
		4 (3 full articles, 1 abstract)	**Major bleeding**	**dabigatran vs rivaroxaban** *Three studies reported that dabigatran was associated with a statistically significant reduced risk of MB, while the remaining study reported no significant difference* *HR: 0.67–0.95 (range of 95% Cis 0.58–1.35).* The final study was the only industry-funded study.

Authors' risk of bias assessment ((38))*: "Overall, a majority of studies had a low risk of selection bias, since most used appropriate propensity score matching or multivariate analysis to adjust for baseline characteristics. Furthermore, most studies were rated positively for reporting bias, since most studies pre-specified and reported all relevant outcomes.*

However, studies generally scored poorly for performance bias, detection bias, and attrition bias. Poor ratings in these domains were due primarily to limitations in the data available to authors, with limited information reported about the background care of patients, as well as limitations in the way outcomes and confounding factors were assessed. Studies also frequently did not report patient attrition; many studies reported that patients' records should be complete for inclusion in the study, and did not report how many patients were excluded on this basis and whether this varied between groups"

references included in the above SR's	country population	n	comparison	Main results
Graham 2016 (120) retrospective cohort included in Deitelzweig 2017(38) and Bai 2017-175(39)	**USA** medicare AF oac naïve >65y **mean follow up 110 days**	118 891	rivaroxaban 20 vs dabigatran 150	IPTW-adjusted cohorts (Inverse probability of treatment weighting) *In this observational study, rivaroxaban use was associated with increased intracranial and major extracranial bleeding events compared with dabigatran use.*
Lip 2016(37) Retrospective cohort included in Deitelzweig 2017(38) and Bai 2017-175(39)	**USA** claims databases NVAF **OAC naïve** **mean 0.5y follow-up** **major bleeding outcomes (= bleeding requiring hospitalization)** **13.5 % apixaban 2.5 mg** **10.6 % dabigatran 75 mg,** **19.6 % rivaroxaban 15 mg**	7 438 apixaban 17 801 rivaroxaban 4 661 dabigatran	apixaban vs dabigatran vs rivaroxaban vs warfarin	Propensity score matching (PSM) was used to balance age, sex, region, baseline comorbidities, and comedications **<u>major bleeding, total population</u>** rivaroxaban vs apixaban **HR: 1.82; 95 % CI:1.36–2.43** **SS more major bleeding with rivaroxaban** dabigatran vs apixaban HR: 1.41; 95 % CI: 0.93–2.14 NS rivaroxaban vs dabigatran HR: 1.05; 95 % CI: 0.74–1.49) NS **<u>major bleeding, standard dose users only</u>** rivaroxaban vs apixaban **HR 1.77 (95%CI 1.29 vs 2.45)** **SS more major bleeding with rivaroxaban**

				dabigatran vs apixaban HR 0.88 (95%CI 0.64-1.53) NS rivaroxaban vs dabigatran **HR 1.65 (95 % CI:1.15–2.36)** **SS more major bleeding with rivaroxaban** another publication by Lip(123), from the same database, with a smaller sample size, was excluded by the SR by Deitelzweig 2017 Deitelzweig 2017(38),
Noseworthy 2016(35) Retrospective cohort included in Deitelzweig 2017(38) and Bai 2017-175(39)	**USA** database NVAF **DOAC naïve (probably)** **1/3 not VKA naïve** median age 70 to 73 years, median CHA2DS2-VASc score=4, median HAS-BLED score = 2. 23-29% low dose rivaroxaban 10-13% low dose dabigatran 18% low dose apixaban	13 084 31 574 13 130	apixaban vs dabigatran dabigatran vs rivaroxaban apixaban vs rivaroxaban	propensity-score-matched cohorts sensitivity analysis at 6 months was with overall results sensitivity analysis of initiaters after jan 2013 was consistent with overall study results **<u>stroke or systemic embolism</u>** rivaroxaban vs dabigatran HR 1.00 (95% CI, 0.75-1.32) NS Sensitivity analysis adjusting for dose: NS apixaban vs dabigatran HR, 0.82 (95% CI, 0.51-1.31) NS Sensitivity analysis adjusting for dose: NS apixaban vs rivaroxaban HR 1.05 (95% CI, 0.64-1.72) NS Sensitivity analysis adjusting for dose: NS

	follow-up unspecified			**<u>Major bleeding</u>** Apixaban vs dabigatran **HR 0.50 (95% CI, 0.36-0.70)** **P < .001** **SS less major bleeding with apixaban** sensitivity analysis adjusting for dose: similar results Apixaban vs rivaroxaban HR 0.39 (95% CI 0.28-0.54) P < .001 **SS less major bleeding with apixaban** sensitivity analysis adjusting for dose: similar results **rivaroxaban vs dabigatran** **HR 1.30 (95% CI, 1.10-1.53)** **P < 0.01** **SS** **SS more major bleeding with rivaroxaban** Sensitivity analysis adjusting for dose HR 1.18 (1.00, 1.40) p=0.05 (borderline significance) **intracranial bleeding** apixaban vs dabigatran HR 0.65 (95% CI, 0.25-1.65) P = 0.36 NS apixaban vs rivaroxaban HR 0.56 (95% CI,0.21-1.45)

				P = 0.23 NS rivaroxaban vs dabigatran **HR 1.79 (95% CI, 1.12-2.86)** **P < .05** **SS higher rate with rivaroxaban**
Chan 2016(121) included in Bai 2017-175(39)	**Taiwan** National Health Insurance Research Database (NHIRD) **not oac naïve** February 1, 2013 to December 31, 2013	9837	low dose rivaroxaban vs low dose dabigatran (vs warfarin)	Endpoints: ischemic stroke or systemic embolism, ICH, hospitalization for GI bleeding, acute myocardial infarction (AMI), all hospitalizations for bleeding, and all-cause mortality.
Hernandez 2017(122) included in Bai 2017-175(39)	**USA** medicare data mean follow-up <1y **not OAC naive**	13 121 4386	rivaroxaban 20 vs dabigatran 150 rivaroxaban 15 vs dabigatran 75	Endpoints: stroke, other thromboembolic events, bleeding, discontinuation or switch of an anticoagulant, death sensitivity analysis on VKA naïve patients done
Adeboyeje 2016(124) retrospective cohort included in Deitelzweig 2017(38)	USA database AF doac naïve mean 70y	44 057	apixaban vs dabigatran vs rivaroxaban vs warfarin	Abstract

Amin 2015(125) retrospective cohort included in Deitelzweig 2017(38)	USA database AF doac naïve	36 260	apixaban vs dabigatran vs rivaroxaban vs warfarin	Abstract
Deitelzweig 2015(126) retrospective cohort included in Deitelzweig 2017(38)	USA database AF doac naïve	24 573	apixaban vs dabigatran vs rivaroxaban vs warfarin	Abstract
Tepper 2015(127) Retrospective cohort included in Deitelzweig 2017(38)	**USA** Claims database **unclear whether oac naïve**	60 277	apixaban vs dabigatran vs rivaroxaban	Abstract
Lin 2015(128) retrospective cohort included in Deitelzweig 2017(38)	**USA** electronic health record data AF doac naïve	35 757	apixaban vs dabigatran vs rivaroxaban vs warfarin	Abstract

13.2 COHORT studies

The following studies were not included in the above SRs/MAs

Ref Study type	Setting Population	number of participants	Endpoints	Results
Lamberts 2017(36) retrospective cohort	-**Denmark** -National registries -NVAF - newly initiated OAC (no OAC <6 months) -mean age 73y aug 2011 – dec 2015 **apixaban, dabigatran, rivaroxaban** apixaban and rivaroxaban initiators were older and less often male, with higher CHA2DS2-VASc and HAS-BLED scores, compared to dabigatran and warfarin initiators - low dosage apixaban 37.8%; rivaroxaban 27.4%, dabigatran 40.4% - mean follow-up 403 days	**54 321**	**Major bleeding** (first hospitalization associated with a code for bleeding)	**Crude incidence rates** **apixaban 3.6%pt/y** **rivaroxaban 4.3% pt/y** **dabigatran 2.9% pt/y** **rivaroxaban vs apixaban** **HR 1.49 (95%CI 1.27–1.77]** **SS less bleeding with apixaban** **dabigatran vs apixaban** **HR 1.17 (95%CI 1.00–1.38)** **SS less bleeding with apixaban (borderline significance)** Findings were similar when restricted to the first 30 days after OAC initiation Cox regression models adjusted for age, sex, calendar year, variables in the CHA2DS2-VASc and HAS-BLED scores, and switch of OAC treatment **rivaroxaban vs dabigatran** no statistical analysis

Ref Study type	Setting Population	number of participants	Endpoints	Results
Lai 2017(40) retrospective cohort propensity-score matched cohort	**- Taiwan** -National Health Insurance claims database - AF - new users - 86% of patients in the dabigatran group received 110 mg; 75% of rivaroxaban patients received 15 mg, 21% received 20mg, 4% received 10 mg - mean follow up 10.8m - more prior ischemic strokes in dabigatran users	15 234 (9200 propensity-matched cohort)	**Mortality**	**Rivaroxaban vs dabigatran** **propensity-matched cohort** **HR 1.44 (95%CI 1.17-1.78)** **SS higher mortality with rivaroxaban**
			Ischemic stroke	**Rivaroxaban vs dabigatran** **propensity-matched cohort** HR 0.95 (95%CI 0.74 to 1.23) NS
			Intracranial hemorrhage	**Rivaroxaban vs dabigatran** **propensity-matched cohort** HR 1.26 (95%CI 0.71 to 2.25) NS
			Myocardial infarction	**Rivaroxaban vs dabigatran** **propensity-matched cohort** HR 1.11 (95%CI 0.61 to 2.01) NS
			Gastrointestinal bleeding requiring transfusion	**rivaroxaban vs dabigatran** propensity-matched cohort **HR1.41 (95%CI 1.02-1.95)** **SS** Note: NS in full cohort analysis

Ref Study type	Setting Population	number of participants	Endpoints	Results
Gorst-rasmussen 2016(41) Prospective cohort Propensity-adjusted Cox regression	**- Denmark** - nationwide health registries - NVAF - new-users of dabigatran, rivaroxaban, warfarin Rivaroxaban users were older and with more comorbidities than warfarin and dabigatran users follow-up median 1.08y	22 358	**Mortality**	**Rivaroxaban 15 vs dabigatran 110** **HR 1.43 (95%CI 1.13-1.81)** **SS** **Rivaroxaban 20 vs dabigatran 150** **HR 1.52 (95%CI 1.06-2.19)** **SS** **SS higher mortality with rivaroxaban** (possibly due to residual confounding)
			Stroke	**Rivaroxaban 15 vs dabigatran 110** HR 0.76(95%CI 0.47-1.23) NS **Rivaroxaban 20 vs dabigatran 150** HR 0.97 (95%CI 0.66-1.42) NS
			Any bleeding	**Rivaroxaban 15 vs dabigatran 110** HR 1.28 (95%CI 0.82-2.01) NS **Rivaroxaban 20 vs dabigatran 150** **HR 1.81 (95%CI 1.25 – 2.62)** **SS more bleeding with rivaroxaban 20**

14 Evidence tables. DOAC vs standard treatment in VTE

14.1 Apixaban vs enoxaparin/warfarin in VTE

14.1.1 Pivotal trial

Study details	n/Population	Comparison	Outcomes		Methodological
Agnelli 2013-AMPLIFY (61) Design: Non-inferiority DB PG RCT Setting: 358 centers - 28 countries Duration of follow-up: 6 months	n= 5395 Mean age: 57y Index event: (DVT 66%; PE 25%;DVT+PE 9%) Previous VTE:16% Current malignancy: 3% Recent surgery,recent trauma, immobilized: NR Pretreatment (LMWH, heparin, fondaparinux): 86.5% apix; 85.7% standard. Duration of pretreatment: • Up to 24h: 55.3% apix, 54.2% standard • Up to 48h: 30.4% apix, 30.5% standard) CrCl ≤50ml/min 6% TTR (VKA): mean 61% <u>Inclusion</u> ≥ 18 years ; objectively confirmed, symptomatic proximal	Apixaban 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months (n=2691) vs conventional therapy (subcutaneous enoxaparin 1mg/kg every 15 hours for at least 5 days, and warfarin begun concomitantly) for 6 months (n=2704)	TTR (2.0-3.0) in warfarin group	61% (above 3.0 16%; below 2.0 23%)	RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: 95 % in safety analysis 97 % in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes discontinued treatment: 14% apixaban 15% enox+warf (71) ITT: "all efficacy analyses included data for patients in the intention-to-treat population for whom the
			Adherence in apixaban group	adherence to therapy was 80% or more in 96% of the patients.	
			Efficacy		
			Recurrent symptomatic VTE or death related to VTE (PO) DVT confirmed by compression ultrasound or venography. PE confirmed by CT scan or pulmonary angiogram or ventilation/perfusion lung scan	All patients (DVT+PE): Apixaban: 2.3% Enox+warf: 2.7% RR= 0.84 (0.60 to 1.18), **p-value for non-inferiority < 0.001** The difference in risk (apixaban minus conventional therapy) was −0.4 percentage points (95% CI, −1.3 to 0.4; **P<0.001 for non-inferiority)** In patients with DVT at enrollment: Apixaban: 38/1698 (2.2%) Enox+warf: 47/1736 (2.7%) RR=0.83 (0.54 to 1.26) In patients with PE at enrollment: Apixaban: 21/900 (2.3%) Enox+warf: 23/886 (2.6%) RR=0.90 (0.50 to 1.61)	
			Fatal PE	Apixaban: <0.1% Enox+warf: 0.1%	

	deep-vein thrombosis or pulmonary embolism (with or without deep-vein thrombosis). Proximal deep-vein thrombosis was defined as thrombosis involving at least the popliteal vein or a more proximal vein. <u>Exclusion</u> active bleeding, high risk of bleeding, or other contra-indications to treatment with enoxaparin and warfarin; cancer and long-term treatment with LMWH planned; DVT or PE was provoked in the absence of a persistent risk factor for recurrence; <6 months of anticoagulant treatment planned; another indication for long-term anticoagulation therapy, dual antiplatelet therapy, treatment with aspirin > 165 mg daily, or treatment with potent inhibitors of cyt P-450 3A4; received more than two doses of a once-daily LMWH regimen, fondaparinux, or a vit K antagonist; >3 doses of a twice-daily LMWH regimen; > 36 hours of continuous intravenous heparin; hemoglobin level < 9 mg per deciliter, platelet count <100000 per mm2, serum creatinine level >2.5 mg per deciliter (220 µmol per liter), or a calculated creatinine clearance of less than 25 ml per min.			NT	outcome status at 6 months was documented. The effect of missing outcome data was evaluated with the use of a sensitivity analysis". Power: adequate SELECTIVE REPORTING: no per protocol analysis for non-inferiority no sensitivity analysis for non-inferiority testing Remark from Cochrane Robertson 2015(71): The AMPLIFY Study in-appropriately excluded a number of randomised patients from the intention-to-treat (ITT) analysis (for apixaban, 2 609 out of 2 691 patients were analysed in the 'ITT' analysis). Furthermore, a large number of patients within each treatment group were classified as discontinuing the study for "other reasons" with no given explanations and therefore we deemed the risk of attrition bias to be unclear Other important methodological remarks: -The criteria for non-inferiority required that the upper limits of the 95% confidence intervals
			Death for which PE could not be ruled out	Apixaban: 0.4% Enox+warf: 0.5% NT	
			Nonfatal PE with or without DVT	Apixaban: 1.0% Enox+warf: 0.9% NT	
			DVT only	Apixaban: 0.8% Enox+warf: 1.3% NT	
			VTE or death from cardiovascular cause	Apixaban: 2.3% Enox+warf: 2.9% RR=0.80 (0.57 to 1.11), NS, p=0.18	
			VTE or death from any cause	Apixaban: 3.2% Enox+warf: 3.9% RR=0.82 (0.61 to 1.08), NS, p=0.16	
			VTE, VTE-related death, or major bleeding	Apixaban: 2.8% Enox+warf: 4.5% **RR=0.62 (0.47 to 0.83), SS, p=0.001 in favour of apixaban**	
			Death during intended treatment period	Apixaban: 1.5% Enox+warf: 1.9% RR=0.79 (0.53 to 1.19) NS	
			Safety		
			Major bleeding (PO) (major if overt and associated with a decrease in Hb >=2g/dl, required the transfusion of 2 or more units of blood, occurred into a critical site, or contributed to death)	Apixaban: 0.6% Enox+warf: 1.8% **RR=0.31 (0.17 to 0.55), SS, p<0.001 in favour of apixaban** *estimated NNT/6m: 84 (67-124)*	
			Clinically relevant non-major bleeding (overt bleeding not meeting the criteria for major bleeding	Apixaban: 3.8% Enox+warf: 8.0% **RR=0.48 (0.38 to 0.60), SS in favour of apixaban**	

			but associated with medical intervention, contact with physician, interruption of study drug, or discomfort or impairment in activities of daily life)	*estimated NNT/6m: 24 (21-32)*	were below prespecified margins for both the relative risk (<1.80) and the risk difference (<3.5 percentage points) The non-inferiority margin for a relative risk of 1.8 required that apixaban preserve at least 70% of the relative reduction in the risk of recurrent venous thromboembolism associated with conventional therapy -If non-inferiority was shown, testing for superiority was to be performed according to a prespecified hierarchy of outcomes Sponsor: Pfizer and Bristol-Myers Squibb

14.1.2 Prespecified subgroup analysis according to age

Subgroups according to Age <65y vs 65-74y vs >=75y	
number of patients >=75y: 759	
Recurrent VTE	P value for interaction 0.3427 NS
Major bleeding	P value for interaction 0.8174 NS

14.1.3 Prespecified subgroup analysis according to renal function

Subgroups CrCl at randomization Normal: CrCL >80 versus Mild: 50<CrCL≥80 versus Moderate:30<CrCL≤50/Severe: CrCL≤30	
number of patients with CrCL<=50ml/min: 338	
Recurrent VTE	P value for interaction 0.8757 NS
Major bleeding	P value for interaction 0.3606 NS

14.1.4 Prespecified subgroup analysis according to cTTR

Results are shown in a graph, but no statistical test reported (in supplementary appendix of original article)

14.1.5 Subgroup analysis early time course

Reference	n	subgroup	Outcome	Results apixaban vs warfarin	Remarks
Raskob 2016(129) (analysed Agnelli 2013 – AMPLIFY)	5337	day 7	Recurring symptomatic VTE or death related to VTE	RR: 0.79 (0.43 – 1.46) NS	Prespecified analysis: YES stratified at randomization: Not applicable Baseline characteristics of different subgroups: numbers appear roughly similar, no p-testing
	5319	day 21		RR: 0.83 (0.51 – 1.36) NS	
	5265	day 90		RR: 0.80 (0.54 – 1.17) NS	
	5244	day 180		RR: 0.84 (0.60 – 1.18) NS	
	5337	day 7	DVT without symptomatic PE	RR : 0.83 (0.40 – 1.72) NS	
	5319	day 21		RR : 0.86 (0.48 – 1.52) NS	
	5265	day 90		RR : 0.74 (0.47 – 1.19) NS	
	5244	day 180		RR: 0.83 (0.54 – 1.26) NS	
	5337	day 7	Major bleeding	RR: 0.19 (0.06 – 0.65) **SS favours apixaban**	
	5319	day 21		RR: 0.19 (0.08 – 0.50) **SS favours apixaban**	
	5265	day 90		RR: 0.29 (0.15 – 0.57) **SS favours apixaban**	
	5244	day 180		RR: 0.31 (0.17 – 0.55) **SS favours apixaban**	

Author's abstract:
"Efficacy of apixaban was non-inferior at each time point, with no excess of early recurrences. The reduced bleeding risk associated with apixaban began early during the course of treatment."

14.1.6 Japanese patients

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Nakamura 2015 AMPLIFY-J (62) Design: RCT DB non-inf Phase III Duration of follow-up: 24 weeks	n=80 Mean age: 62.5 Index event: DVT 55%; PE 45%; DVT + PE 0% Recent surgery: NR Recent trauma: NR Immobilized: NR CrCL <50ml/min: 7.5% (n = 6) <u>Inclusion:</u> Japanese patients, ≥20 years of age and who had objectively confirmed, symptomatic proximal DVT or PE (with or without DVT) <u>Exclusion:</u> - had had thrombectomy - used fibrinolytc agent - active bleeding - high risk of bleeding - another indication for long-term anticoagulation therapy	UFH / warfarin (dose adapted to PT-INR 1.5 – 2.5) n = 40 vs apixaban 10 mg b.i.d. for 7 days then 5 mg b.i.d. for 23 weeks n = 40 <u>remarks</u> enoxaparin does not have an indication for VTE treatment in japan so UFH/warfarin was used	Adherence		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: unknown Personnel: unknown Assessors: yes, independent adjudication committee POWER CALCULATION: No FOLLOW-UP: Drop-outs and Exclusions: • Described: yes • Balanced across groups: no (but numbers low, 6 vs 3) ITT: Yes, all subjects who received at least one dose of medication Efficacy analysis on FAS SELECTIVE REPORTING:
			TTR in warfarin group	INR 1.5 – 2.5: 70%	
			Treatment compliance (not further defined)	≥80%	
			Permanent discontinuation of study drug	Apixaban: 3 UFH/warfarin: 6	
			Efficacy		
			recurrent symptomatic VTE	Apixaban : 0 UFH/warfarin : 0	
			recurrent symptomatic PE	Apixaban:0 UFH/warfarin: 1/39	
			Safety		
			Adjudicated composite of major bleeding (during treatment) and CRNM (PO)	Apixaban: 3 / 40 (7.5%) UFH/warfarin: 11/39 (28.2%) No p-values given	
			Major bleeding	Apixaban: 0/40 (0%) UFH/warfarin: 2/39 (5.13%)	

	- dual antiplatelet therapy - treatment with aspirin >&§(mg daily - >2 doses of fondaparinux - continuous infusion of UFH >36h >2 doses of oral vitamin K antagonist before first admission of the study drug - hemoglobin <9g/dl - platelet count >100,000/mm3 - creatinine clearance <25 ml/min				Other important methodological remarks: mean body weight higher in apixaban group (64.64kg) compared to UFH/warfarin (58.14kg) For the primary endpoint, the relative risk, 95% CI and p-value were calculated as post-hoc analysis Sponsor: Pfizer and Bristol-Meyers Squibb

14.2 Dabigatran vs enoxaparin/warfarin in symptomatic VTE

14.2.1 Meta-analysis

Ref	Comparison	N/n	Outcomes	Result
Schulman 2014 (63) pooled analysis of RE-COVER I and RE-COVER II Design: MA* duration 6 months	Dabigatran vs Vitamin K antagonist	N= 2 n= 5107 Schulman 2011 Schulman 2009	**Venous thromboembolism or related death**	2.4% vs 2.2% RR: 1.09 (95%CI, 0.76 to 1.57) NS
			Major bleeding (= clinically overt and associated with a fall in the hemoglobin level of at least 20 g per liter, resulted in the need fortransfusion of 2 or more units of red cells, involved in a critical site, or was fatal)	1.4% vs 2.0% RR: 0.73 (95%CI, 0.48 to 1.11) NS
			All cause mortality	1.8% vs 1.8% RR: 1.00 (95%CI, 0.67 to 1.51) NS

* Characteristics of included studies: see below

14.2.2 Included trial: RE-COVER I

Study details	n/Population	Comparison	Outcomes		Methodological
Schulman 2009-RE-COVER I (64) Design: RCT - DB Double dummy Non inferiority trial Setting: 228 clinical centers in 29 countries Duration of follow-up: 6 months	n= 2564 Mean age: 55y Index event: DVT 69% PE 21% DVT+PE 10% Previous VTE : 25% Current malignancy: 61% Recent surgery:NR Recent trauma: NR Immobilized:NR <u>Inclusion</u> Patients 18 years of age or older who had acute, symptomatic, objectively verified proximal deep-vein thrombosis of the legs or pulmonary embolism Before randomization, the diagnosis of venous thromboembolism was established with the use of compression ultrasonography or venography of leg veins and	Dabigatran (2x150 mg /d)+ warfarin-like placebo versus warfarin + dabigatran-like placebo (dose-adjusted to achieve an INR of 2.0 to 3.0) initially given parenteral anticoagulation therapy for a median of 9 days (interquartile range, 8 to 11)	Adherence		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: 84.4% in safety analysis 88.8 % in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes Early discontinuation of study drug: Dabigatran 16.0% warfarin 14.5% ITT: modified intention-to-treat for efficacy (since patients who did not receive any study drug were excluded from all analyses, as was prespecified in the protocol) Per protocol-analysis for safety (on the basis of the patient's
			TTR in warfarin group	59.9% (66% during the last month)	
			Adherence to dabigatran intake (or placebo) (pill intake >80% <120%)	Dabigatran: 98% Warfarin: 97.5%	
			Efficacy		
			Venous thromboembolism (6-month incidence of recurrent symptomatic, objectively confirmed) and related deaths (PO) confirmed by compression ultrasonography or venography of leg veins and ventilation–perfusion lung scanning, angiography, or spiral computed tomography of pulmonary arteries.	<u>modified intention-to-treat</u> Dabigatran: 30/1274 (2.4%) Warfarin: 27/1265 (2.1%) HR: 1.10 (CI 0.65 to 1.84) **P<0.001 for the prespecified non-inferioritymargin** ARD=0.4% (95%CI −0.8 to 1.5) **P<0.001 for the prespecified non-inferiority margin**	
			Symptomatic deep-vein thrombosis	No. of subjects Dabigatran: 16/1274 (1.3%) Warfarin: 18/1265 (1.4%) HR: 0.87 (CI 0.44 to 1.71) NS	
			Symptomatic nonfatal pulmonary embolism	No. of subjects Dabigatran: 13/1274 (1%)	

	ventilation–perfusion lung scanning, angiography, or spiral computed tomography of pulmonary arteries. <u>Exclusion</u> duration of symptoms longer than 14 days, pulmonary embolism with hemodynamic instability or requiring thrombolytic therapy, another indication for warfarin therapy, recent unstable cardiovascular disease, a high risk of bleeding, liver disease with an aminotransferase level that was two times the local upper limit, an estimated creatinine clearance of < 30 ml per minute, a life expectancy of less than 6 months, a contraindication to heparin or to radiographic contrast material, pregnancy or risk of becoming pregnant, or a requirement for long-term antiplatelet therapy (≤100 mg of acetylsalicylic acid daily was acceptable).			Warfarin: 7/1265 (0.6%) HR: 1.85(CI 0.74 to 4.64) NS	actual treatment with the study drug) Power: adequate SELECTIVE REPORTING:unclear Non-inferiority margin: '90% power to exclude a hazard ratio of 2.75 and an absolute increase in risk of 3.6 percentage points for the primary outcome with dabigatran, at a one-sided alpha level of 0.025. These non-inferiority margins were estimated to correspond to preservation of 57% (for assessment of hazard ratio) and 75% (for assessment of difference in risk) of the lower boundary of the 95% confidence interval for the efficacy of warfarin as compared with no anticoagulation, as assessed in four studies that compared discontinuing warfarin therapy at 4 to 6 weeks with continuing it for 3 to 6 months' Note: this is quite a large margin for non-inferiority
			Death related to venous thromboembolism	No. of subjects Dabigatran: 1/1274 (0.1%) Warfarin:3/1265 (0.2%) HR: 0.33(CI 0.03 to 3.15) NS	
			All deaths	No. of subjects Dabigatran:21/1274 (1.6%) Warfarin:21/1265 (1.7%) HR: 0.98(CI 0.53 to 1.79) NS	
			Safety		
			Major bleeding event Bleeding was defined as major if it was clinically overt and if it was associated with a fall in the hemoglobin level of at least 20 g per liter, resulted in the need for transfusion of 2 or more units of red cells, involved a critical site, or was fatal	No. of subjects Dabigatran: 20/1274 (1.6%) Warfarin: 24/1265 (1.9%) HR: 0.82(CI 0.45 to 1.48) NS	
			Major or clinically relevant non-major bleeding event Less severe bleeding episodes were classified as minor and were subcategorized as clinically relevant bleeding or nuisance bleeding.	No. of subjects Dabigatran: 71/1273 (5.6%) Warfarin:111/1265 (8.8%) **HR: 0.63(CI 0.47 to 0.84)** **p=0.002** **SS in favor of dabigatran** *estimated NNT/6m: 32 (22-71)*	
			Any bleeding event	No. of subjects Dabigatran:205/1273 (16.1%) Warfarin:277/1265 (21.9%) HR: 0.71(CI 0.59 to 0.85) **SS in favor of dabigatran**	

				estimated NNT/6m: 18 (12-31)	
			Acute coronary syndrome	Dabigatran:0.4% Warfarin:0.2% NS	Sponsor: Boehringer Ingelheim
			Other adverse events No. of subjects/total treatment period	Any event : Dabigatran:5/1273 (0.4%) Warfarin:3/1266 (0.2%) P= 0.51 NS Serious event: Dabigatran:165/1273 (13.0%) Warfarin:150/1266 (11.8%) P= 0.43 NS Events with an incidence of at least 3% NS except **Dyspepsia:** **Dabigatran:39/1273 (3.1%)** **Warfarin:9/1266 (0.7%)** **SS P<0.001**	

14.2.3 Included trial: RE-COVER II

Study details	n/Population	Comparison	Outcomes		Methodological
Schulman 201-RE-COVER II(65) Design: RCT - DB Double dummy Non inferiority trial 208 sites 31 countries Duration of follow-up: 6 months	n= 2589 Mean age: 55y Index event: DVT 68% PE 23% DVT+PE 8% Previous VTE : 19% vs 16% p=0.02 Current malignancy: 3.9% Recent surgery:NR Recent trauma: NR Immobilized:NR <u>Inclusion</u> Patients 18 years of age or older who had acute, symptomatic, objectively verified proximal deep-vein thrombosis of the legs or pulmonary embolism Before randomization, the diagnosis of venous thromboembolism was established with the use of compression ultrasonography or venography of leg veins and	Dabigatran (2x150 mg /d)+ warfarin-like placebo versus warfarin + dabigatran-like placebo (dose-adjusted to achieve an INR of 2.0 to 3.0) initially given parenteral anticoagulation therapy for a mean of 9.5 days (SD 4)	Adherence		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes Early discontinuation of study drug: Dabigatran 14.7% warfarin 14.1% ITT: No modified intention-to-treat for efficacy (since patients who did not receive any study drug were excluded from all analyses, as was prespecified in the protocol) Per protocol-analysis for safety (on the basis of the patient's actual treatment with the study drug)
			TTR in warfarin group	56.9% (+/-21.9%) below the therapeutic range 24% of the time and above the therapeutic range 19% of the time	
			Adherence to dabigatran intake (or placebo) (pill intake >80% <120%)	Dabigatran: 97.7% Warfarin: 98.3%	
			Efficacy		
			Venous thromboembolism (6-month incidence of recurrent symptomatic, objectively confirmed) and related deaths (PO) confirmed by compression ultrasonography or venography of leg veins and ventilation–perfusion lung scanning, angiography, or spiral computed tomography of pulmonary arteries.	<u>modified intention-to-treat</u> Dabigatran: 2.3% Warfarin: 2.2% HR 1.08 (95%CI 0.64–1.80) **P<0.001 for the prespecified non-inferioritymargin** ARD=0.4% (95%CI −0.8 to 1.5) **P<0.001 for the prespecified non-inferiority margin**	
			Symptomatic deep-vein thrombosis	Dabigatran: 2.0% Warfarin: 1.3% HR: 1.48 (95%CI 0.80–2.74)	

	ventilation–perfusion lung scanning, angiography, or spiral computed tomography of pulmonary arteries. <u>Exclusion</u> duration of symptoms longerthan 14 days, pulmonary embolism with hemodynamic instability or requiring thrombolytic therapy,another indication for warfarin therapy, recent unstable cardiovascular disease, a high risk of bleeding, liver disease with an aminotransferase level that was three times the local upper limit, an estimated creatinine clearanceof < 30 ml per minute, a life expectancy of less than 6 months, a contraindication to heparin or to radiographic contrast material, pregnancy or risk of becoming pregnant, or a requirement for long-term antiplatelet therapy (≤100 mg of ASA daily was acceptable).			NS	
			Symptomatic nonfatal pulmonary embolism	Dabigatran: 0.5% Warfarin: 1% HR: 0.54 (95%CI 0.21–1.35) NS	Power: adequate SELECTIVE REPORTING:unclear
			Death related to pulmonary embolism	Dabigatran: 0.2% Warfarin:0.0% NT	
			All deaths	Warfarin:1.9% HR: 0.98 (0.56–1.71) NS	Non-inferiority margin: '90% power to exclude a hazard ratio of 2.75 and an absolute increase in risk of 3.6 percentage points for the primary outcome with dabigatran, at a one-sided alpha level of 0.025. Note: this is quite a large margin for non-inferiority Sponsor: Boehringer Ingelheim
			Safety		
			Major bleeding event Bleeding was defined as major if it was clinically overt and if it was associated with a fall in the hemoglobin level of at least 20 g per liter, resulted in the need for transfusion of 2 or more units of red cells, involved a critical site, or was fatal	Dabigatran: 1.2% Warfarin: 1.7% HR: 0.69(CI 0.36 to 1.32) NS	
			Major or clinically relevant non-major bleeding event Less severe bleeding episodes were classified as minor and were subcategorized as clinically relevant bleeding or nuisance bleeding.	Dabigatran: 5.0% Warfarin:7.9% **HR: 0.62(CI 0.45 to 0.84)** **SS in favor of dabigatran** *estimated NNT/6m: 35 (23-80)*	
			Any bleeding event	Dabigatran:15.6% Warfarin:22.1% **HR: 0.67 (0.56–0.81)** **SS in favor of dabigatran** *estimated NNT/6m: 16 (11-24)*	
			Acute coronary syndromes	Dabigatran:0.3% Warfarin:0.2% NS	

14.2.4 Subgroup analysis according to baseline PE or DVT

Reference	n	subgroup	Outcome	Results dabigatran vs warfarin	Remarks
Goldhaber 2016 (66) Schulman 2014 (RECOVER I & RECOVER II) (63)	1602	patients with PE as index event	recurrent VTE or VTE related death	Dabigatran : 2.9% Warfarin : 3.1% HR : 0.93 (0.53 – 1.64) NS	Prespecified analysis: YES stratified at randomization: YES, according to absence or presence of symptomatic PE at baseline Baseline characteristics of different subgroups: "mostly similar but among those with PE as the index event there was a higher proportion of women, a higher prevalence of risk factors for VTE recurrence (thrombophilia, recent prolonged immobilisation), and a lower proportion of current smokers."
	3505	patients with baseline DVT alone	recurrent VTE/VTE-related death	Dabigatran: 2.6% Warfarin: 2.1% HR: 1.20 (0.78 – 1.86) NS	
				p for interaction: 0.4848 NS	
	1527	patients with PE as index event	Major bleeding even	Dabigatran : 0.5% Warfarin : 1.0% HR : 0.50 (0.15 – 1.67) NS	
	unknown	patients with baseline DVT alone	Major bleeding	Dabigatran : 1.2% Warfarin : 1.9% HR : 0.62 (0.35 – 1.08) NS	
				p for interaction : 0.7598 NS	

Authors conclusion: "COX regression analysis showed no statistically significant interaction, indicating similar treatment effects regardless of index event"

14.2.5 Subgroup analysis according to age (RE-COVER I + II)

Subgroups age 18-<40; 40-<50; 50-<65; 65-<75y	
Number of patients >=75y: 529	
Recurrent VTE	P for interaction = 0.37 NS

14.2.6 Subgroup analysis according to baseline renal function (RE-COVER I+II)

Subgroups CrCl at randomization CrCL >=80 ; 50- <80 ; 30-<50; <30	
number of patients with CrCL<50ml/min: 267	
Recurrent VTE	P value for interaction 0.80 NS

14.3 Dabigatran versus warfarin after at least 3 months of continued anticoagulant treatment

Study flow	**Group**	At least 3 months of treatment for VTE Participants at increased risk					**6 months**					
RE-MEDY	Active						Dabigatran	Dabigatran	Dabigatran	Dabigatran	Dabigatran	Dabigatran
	Control						Warfarin	Warfarin	Warfarin	Warfarin	Warfarin	Warfarin
		At least 6 months of treatment for VTE					**6 months**					
RE-SONATE	Active						Dabigatran	Dabigatran	Dabigatran	Dabigatran	Dabigatran	Dabigatran
	placebo						Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

Study details	n/Population	Comparison	Outcomes		Methodological
Schulman 2013-RE-MEDY *(76)* Design: DB PG non-inferiority and superiority RCT Setting: Patients from 265 sites in 33 countries Duration of follow-up: 36m	n= 2866 Mean age: 55y Index event: DVT 65%; PE 32%; DVT + PE 12% patients had completed at least 3 initial months of therapy. Current malignancy: 4% Recent surgery: NR Recent trauma: NR Immobilized: 7% <u>Inclusion</u> at least 18 years; objectively	Dabigatran 2x150mg/d (n=1435) + placebo (sham INR) vs Warfarin (target INR 2 to 3) + placebo (n=1431) for 6-36 months (≠protocol: initial duration 18months)	Adherence		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: unclear Personnel: unclear Assessors: yes FOLLOW-UP: Lost-to follow-up: <1% Drop-out and Exclusions: 6.5% • Described: yes • Balanced across groups: yes ITT: No, modified (exclusion of patients who did not receive any dose of the study drug)
			TTR	median of 65.3% of the time	
			Adherence to dabigatran or dabigatran-placebo (pill count >80%<120%)	Dabigatran:98% Warfarin: 98.2%	
			Efficacy		
			Recurrent or fatal VTE (PO) (clinically suspected recurrent DVT had to be objectively verified using pre-specified imaging studies)	Dabigatran: 26/1430 (1.8%) Warfarin: 18/1426 (1.3%) HR= 1.44 (95% CI 0.78 to 2.64), NS p for non-inferiority = 0.01	
			Symptomatic DVT	Dabigatran: 17/1430 (1.2%) Warfarin: 13/1426 (0.9%) HR= 1.32 (95% CI 0.64 to 2.71), NS,	

	confirmed, symptomatic, proximal deep-vein thrombosis or pulmonary embolism that had already been treated with an approved anticoagulant or received dabigatran in one of two previous clinical trials of short-term treatment of venous thromboembolism (RE-COVER and RE-COVER II studies). Considered to be at increased risk for recurrent venous thromboembolism on the basis of the site investigator's assessment . DVT confirmed by venous compression ultrasonography (CUS)or venography. PE confirmed by ventilation-perfusion (VQ), or lung scan, or pulmonary angiography, or spiral (helical) CT. In case of death, autopsy is an additional way to confirm VTE. Exclusion: Symptomatic DVT or PE at screening; primary PE with suspected origin other that leg limbs; actual or anticipated use of vena cava filter; interruption of anticoagulant therapy for 2 or more weeks during the 3-	Randomization was stratified according to the presence or absence of active cancer and according to the index diagnosis (DVT or PE) The required duration of initial treatment before trial enrollment was 3 to 12 months (≠ protocol: duration of treatment 3 to 6 months)		p=0.46	Power: adequate SELECTIVE REPORTING: no *"The sample size was determined on the basis of an expected rate of the primary efficacy outcome of 2.0% in both groups with a power of 85% to exclude a hazard ratio of 2.85 (the non-inferiority margin for the hazard ratio) and an absolute increase in the risk of recurrent venous thromboembolism of 2.8 percentage points at 18 months (the non-inferiority margin for the risk difference), at a one-sided alpha level of 0.025. To meet these specifications, we estimated that we would need to enroll 2000 patients"* Other important methodological remarks: -the prespecified non-inferiority margin for the hazard ratio of 2.85 for the PO is large, since it allows an increase in risk by a factor of nearly 3 to be accepted as non-inferior -The upper limit of the 95% CI for the hazard ratio of the PO
			Symptomatic nonfatal PE	Dabigatran: 10/1430 (0.7%) Warfarin: 5/1426 (0.4%) HR= 2.04 (95% CI 0.70 to 5.98), NS, p=0.19	
			Death related to VTE	Dabigatran: 1/1430 (0.1%) Warfarin: 1/1426 (0.1%) HR= 1.01 (95% CI 0.06 to 16.2), NS, p=0.99	
			All deaths	Dabigatran: 17/1430 (1.2%) Warfarin: 19/1426 (1.3%) HR= 0.90 (95% CI 0.47 to 1.72), NS, p=0.74	
			Safety		
			Major bleeding (defined as clinically overt and associated with a fall of the hemoglobin level of 20 g/L or required transfusion of at least 2 units of red cells or, involved a critical organ or was fatal)	Dabigatran: 13/1430 (0.9%) Warfarin: 25/1426 (1.8%) HR= 0.52 (95% CI 0.27 to 1.02), NS, p=0.06	
			Clinically relevant non-major bleeding (At least one of the following criteria had to be fulfilled: spontaneous skin hematoma of at least 25 cm; spontaneous nose bleed > 5 minutes duration ; macroscopic hematuria, lasting more than 24 hours ; spontaneous rectal bleeding (more than	NR	

	6 months of treatment for the prior VTE; patients who in the investigator's opinion should not be treated with warfarin; allergy to warfarin or dabigatran; excessive risk of bleeding; known anaemia ; need of anticoagulant treatment ; recent unstable cardiovascular disease; elevated AST or ALT > 2x ULN; liver disease expected to have any potential impact on survival; developed transaminase elevations upon exposure to ximelagatran; severe renal impairment; pregnant, nursing or of childbearing potential who refuse to use a medically acceptable form of contraception		spotting on toilet paper); gingival bleeding for more than 5 minutes; bleeding leading to hospitalization and/or requiring surgical treatment; Bleeding leading to a transfusion of less than 2 units of whole blood or red cells; any other bleeding considered clinically relevant by the investigator)		(2.64) was close to the predefined non-inferiority margin (2.85), and the CI gives boundaries for the event rate with dabigatran as low as 1.0% and as high as 3.4%. Sponsor: Boehringer Ingelheim
			Major or clinically relevant bleeding event	Dabigatran: 80/1430 (5.6%) Warfarin: 145/1426 (10.2%) **HR= 0.54 (95% CI 0.41 to 0.71), SS, p<0.001 in favour of dabigatran** *estimated NNT/mean study duration: 22(17-34)*	
			Any bleeding event	Dabigatran: 277/1430 (19.4%) Warfarin: 373/1426 (26.2%) **HR= 0.71 (95% CI 0.61 to 0.83), SS, p<0.001 in favour of dabigatran** *estimated NNT/mean study duration: 15(10-23)*	
			Adverse event	Dabigatran: 1029/1430 (72.0%) Warfarin: 1010/1426 (70.8%) p=0.53	
			Adverse event leading to discontinuation of study drug	Dabigatran: 145/1430 (10.1%) Warfarin: 126/1426 (8.8%) p=0.26	
			Serious adverse event	Dabigatran: 227/1430 (15.9%) Warfarin: 224/1426 (15.7%) p= 0.97	

			Acute coronary syndrome:	<u>During treatment</u> Dabigatran: 13/1.430 (0.9%) Warfarin: 3/1.426 (0.2%) **p= 0.02 in favour of warfarin** *estimated NNH/mean study duration: 143* <u>Within 30d after treatment</u> Dabigatran: 1/1430 (0.1%) Warfarin: 3/1426 (0.2%) p-value NR	

14.4 Edoxaban versus warfarin in VTE

Study details	n/Population	Comparison	Outcomes		Methodological
Hokusai-VTE 2013 (67) Design: DB RCT non-inf Duration of follow-up: 12 months	n=8292 Mean age: 55.8 y Index event: DVT only: 59.7%, PE: NR DVT+PE: NR, Recent surgery: NR Recent trauma: NR Immobilized: NR Prior VTE: 18.5% CrCL <50ml/min: 6.5% <u>Inclusion:</u> over 18 years objectively diagnosed, acute, symptomatic deep-vein thrombosis involving the popliteal, femoral, or iliac veins or acute, symptomatic pulmonary embolism (with or without deep-vein thrombosis).	edoxaban 60mg or 30 mg 1x/day vs warfarin **All patients received initial therapy with open-label enoxaparin or unfractionated heparin for at least 5 days (median 7 days). Edoxaban (or placebo) was started after dis-continuation of initial heparin.** Treatment with edoxaban or warfarin was to be continued for at least 3 months	Adherence		RANDO: Adequate (interactive web-based system) ALLOCATION CONC: Adequate BLINDING : Participants: unclear, states double blind Personnel: unclear, states double blind Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: 99.4% in safety analysis 99.4% in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: mITT: all patients who underwent randomization and received at least one dose of the study drug
			TTR in warfarin group	63.5%	
			% adherent (taking 80% of doses or more)	E: 99% W: NR	
			Permanent discontinuation of study drug	5%	
			Efficacy		
			Recurrent symptomatic thromboembolism (composite of deep-vein thrombosis or nonfatal or fatal pulmonary embolism)	<u>overall study period</u> E: 130/4118 (3.2%) W: 146/4122 (3.5%) HR: 0.89 (0.70 – 1.13) p<0.001 for non-inferiority **NS** **on-treatment period** **1.6% vs 1.9%** **HR 0.82 (95%CI 0.60–1.14)** **patients with index DVT** **on-treatment period** **0.96 (0.64–1.42)** **patients with index PE** **on-treatment period** **0.60 (0.34–1.08)**	

	Exclusion contraindications to heparin or warfarin, had received treatment for more than 48 hours with therapeutic doses of heparin, had received more than one dose of a vitamin K antagonist, had cancer for which long-term treatment with lowmolecular-weight heparin was anticipated, had another indication for warfarin therapy, continued to receive treatment with aspirin at a dose of more than 100 mg daily or dual antiplatelet therapy, or had creatinine clearance of less than 30 ml per minute.	in all patients and for a maximum of 12 months. The duration was determined by the treating physician on the basis of the patient's clinical features and patient preference. 40% of patients were treated for 12 months remarks patients with CrCL <50 ml/min and body weight <60kg received 30mg of edoxaban stratification according to the			SELECTIVE REPORTING: no Other important methodological remarks: The primary analysis included all efficacy outcomes from randomization through the end of 12 months or study closure (overall study period), regardless of the duration of the patient's study treatment. In addition, the primary efficacy outcome was evaluated for the on-treatment period — the time during which the patients were receiving the study drug or within 3 days after the study drug was stopped or interrupted. with respect to the primary efficacy outcome, an upper limit of the confidence interval for the hazard ratio of 1.5 and a two-sided alpha level of 0.05. This margin corresponds to retention of at least 70% of the treatment effect of warfarin.
			Fatal PE	E: 4/4118 W: 3/4122 No analysis	
			Nonfatal PE with or without DVT	E: 49/4118 W: 59/4122 no analysis	
			DVT alone	E: 57/4118 W: 63/4122 no analysis	
			Mortality	overall study period 3.2% vs 3.1% no analysis	
			Safety		
			Clinically relevant bleeding (major or non-major)	E: 349/4118 (8.5%) W: 423 /4122 (10.3%) **HR: 0.81 (0.71 – 0.94)** **p=0.004 for superiority** **SS** *estimated NNT/treatment duration: 56 (34-162)*	
			Major bleeding	E: 56/4118 (1.4%) W: 66 / 4122 (1.6%) HR: 0.84 (0.59 – 1.21) NS	

		qualifying diagnosis (deepvein thrombosis or pulmonary embolism), presence or absence of temporary risk factors, and the dose of edoxaban.			Sponsor: Daiichi-Sankyo

Among patients who qualified for the 30-mg dose of edoxaban, recurrent venous thromboembolism occurred in 22 of 733 patients (3.0%) receiving edoxaban, as compared with 30 of the 719 patients (4.2%) receiving warfarin (hazard ratio, 0.73; 95% CI, 0.42 to 1.26).
Among patients who qualified for the 30-mg dose of edoxaban, clinically relevant bleeding occurred in 58 of 733 patients (7.9%) who received edoxaban, and in 92 of the 719 patients (12.8%) who received warfarin (hazard ratio, 0.62; 95% CI, 0.44 to 0.86). Major bleeding occurred in 11 patients (1.5%) in the edoxaban group and in 22 patients (3.1%) in the warfarin group (hazard ratio, 0.50; 95% CI, 0.24 to 1.03).

14.4.1 Prespecified subgroup analysis according to age

Subgroups < 75Y vs >= 75 y number of patients >= 75y: 1104	
Recurrent VTE	P value for interaction 0.0586 NS
Major bleeding	P value for interaction 0.9305 NS

14.4.2 Prespecified subgroup analysis according to renal function

Subgroups CrCl at randomization (IXRS) 30-50 ml/min vs > 50 ml/min number of patients with CrCl >=50ml/min = 541

Recurrent VTE	P value for interaction 0.1581 NS
Major bleeding	P value for interaction 0.5926 NS

14.4.3 Prespecified subgroup analysis according to cTTR

Subgroups <60% vs >=60%	
Recurrent VTE	P for interaction 0.9136 NS
Major bleeding	P for interaction 0.0174 ss less bleeding with edoxaban if cTTR <60% NS if cTTR>= 60%

14.5 Rivaroxaban vs enoxaparin/VKA in DVT

Study details	n/Population	Comparison	Outcomes		Methodological
Einstein DVT 2010 (68) Design: OL RCT non-inferiority Duration of follow-up: variable	n=3449 Mean age: 56.1 Type 2 diabetes: CrCL <50ml/min: 7% Previous VTE: 19.3% intended duration of treatment 3 mo: 11.9% 6 mo: 62.8% 12 mo: 25.3% <u>Inclusion:</u> - having acute, symptomatic, objectively confirmed proximal DVT, without symptomatic pulmonary embolism <u>Exclusion</u> - receive therapeutic doses of LMWH, fondaparinux or unfractioned heparin for more than 48 hours - received more than a	VKA – acenocoumarol or warfarin (dose adjusted to maintain an INR between 2.0 to 3.0) vs rivaroxaban 15 mg 2x/d for the first 3 weeks then 20 mg 1x/d <u>remarks</u> patients asigned to standard therapy received subcutaneous enoxaparin, 1.0 mg /kg of body weight 2x/d and starting warfarin or acenocoumarol within 48h.	Adherence		RANDO: Adequate (computerized voice response system) ALLOCATION CONC: open study Adequate BLINDING : Participants: no, open Personnel: no, open Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: 99.4% in safety analysis 100% in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: Yes (also for non-inferiority testing) SELECTIVE REPORTING: no Other important methodological remarks: Intended treatment duration (3. 6 or 12 months) determined by
			TTR in warfarin group	57.7%	
			No drug interruption (>3d)	NR	
			Permanent discontinuation of study drug	Rivaroxaban: 11.3% VKA: 14.2%	
			Efficacy		
			PO : symptomatic recurrent VTE (composite of DVT, non-fatal PE or fatal PE)	RIV: 36 (2.1%) VKA: 51 (3.0%) HR: 0.68 (0.44 – 1.04) **p<0.001** **SS for non-inferiority**	
			Fatal PE	RIV: 1 VKA: 0	
			Mortality	RIV: 38 (2.2) VKA: 49 (2.9%) HR: 0.67 (0.44 – 1.02) p = 0.06 NS	
			Safety		
			First clinically relevant bleeding	RIV: 139 (8.1%) VKA: 138 (8.1%)	

	single dose of a vitamin K antagonist before randomization - treated with thrombectomy - vena cava filter - treated with fibrinolytic agent for the current episode of thrombosis - contraindication to enoxaparin, warfarin or acenocoumarol - creatinine <30 ml/min - clinically significant liver disease or ALT more than 3x the upper limit of the normal range - bacterial endocarditis - active bleeding or a high risk of bleeding -systolic pressure >180 mmHg or diastolic blood pressure <110 mmHg - childbearing potential without proper contraception, pregnancy or breastfeeding - use of strong CYP3A4 inhibitors	Enoxaparine was discontinued when the INR was 2.0 or more for 2 consecutive days In the standard therapy group, median duration of enoxaparin treatment was 8 days stratification by country. The intended treatment duration was determined by the treating physician	(major or clinically relevant non-major bleeding)	HR: 0.97 (0.76 – 1.22) p=0.77 NS	treating physician Non-inferiority margin : a margin of 2.0 for the upper limit of the 95% confidence interval for the observed hazard ratio at a two-sided alpha level of 0.05. This margin corresponds to maintenance of at least 50% of the proven efficacy of standard therapy. Termination of study was event-driven Sponsor: Bayer Schering Pharma and Ortho- McNeil
			Major bleeding	RIV: 14 (0.8%) VKA: 20 (1.2%) HR: 0.65 (0.33 – 1.30) p = 0.21 NS	

14.6 Rivaroxaban versus enoxaparin/VKA in PE

Study details	n/Population	Comparison	Outcomes		Methodological
EINSTEIN PE 2010 (69) Design: OL RCT non-inferiority Duration of follow-up: depends on intended duration of treatment (3, 6 or 12 months)	n=4832 Mean age: 57.7 Prior VTE: 19.55% CrCL <50ml/min: 8.3% previous use of VKA: nr <u>Inclusion:</u> - acute, symptomatic pulmonary embolism with objective confirmation, with or without symptomatic deep-vein thrombosis <u>Exclusion</u> - received therapeutic doses of LMWH, fondaparinux or unfractioned heparin for more than 48 hours - received more than a single dose of a vitamin K antagonist before randomization - treated with thrombectomy	Rivaroxaban 15 mg 2x/d for the first 3 weeks then 20 mg 1x/d vs Enoxaparin at 1,0 mg per kg bodyweight 2x/d then warfarin or acenocoumarol until INR between 2.0 and 3.0 In the standard therapy group, median duration of enoxaparin treatment was 8 days <u>remarks</u>	Adherence		RANDO: Adequate (computer voice-response system) ALLOCATION CONC: Adequate BLINDING : Participants: no, open label Personnel: no, open label Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: 99.7% in safety analysis 99.9% in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: Yes SELECTIVE REPORTING: Other important methodological remarks: - intended duration of treatment determined by physician before
			TTR in warfarin group	62.7%	
			No drug interruption (>3d)	NR	
			Permanent discontinuation of study drug	RIV: 10.7% VKA:12.3%	
			Efficacy		
			Symptomatic recurrent venous thromboembolism (fatal PE, non-fatal PE or DVT)	RIV : 50 (1.2%) VKA : 44 (1.8%) HR : 1.12 (0.75 – 1.68) **p = 0.003 for non-inferiority** **SS**	
			Mortality	RIV: 10 VKA: 6	
			Safety		
			First episode of major or clinically relevant non-major bleeding	RIV: 249 (10.3%) VKA: 274 (11.4%) HR: 0.90 (0.76 – 1.07) NS	
			Major bleeding	RIV: 26 (1.1%) VKA: 52 (2.2%)	

	- vena cava filter - treated with fibrinolytic agent for the current episode of thrombosis - contraindication to enoxaparin, warfarin or acenocoumarol - another indication for vitamin K antagonist - creatinine clearance <30 ml/min - liver disease or ALT level more than 3x the upper limit of the normal range - bacterial endocarditis - active bleeding or high risk of bleeding - systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mmHg - childbearing potential without proper contraceptive measures, pregnancy, breastfeeding - concomitant use of a strong CYP3A4 inhibitor or inducer			HR: 0.49 (0.31 – 0.79) **p=0.003** **SS** *estimated NNT/treatment duration: 91(66-217)*	randomization using a non-inferiority margin of 2.0 for the upper limit of the 95% confidence interval for the observed hazard ratio, with a two-sided alpha level of 0.05 Sponsor: Bayer Healthcare and Janssen Pharmaceuticals

14.6.1 Prespecified subgroup analyses age, CrCl

Presented in graph. No p values for interaction reported

14.6.2 Prespecified subgroup analysis according to baseline renal function

Reference	n	subgroup	Outcome	Results rivaroxaban vs warfarin/acenocoumarol	Remarks
Bauersachs 2014(73)	5569	(>=80ml/min)	Recurrent venous thromboembolism	1.8% vs 1.9% (HR 0.95; 95% CI 0.65–1.41)	Prespecified analysis: YES, but pooling of two EINSTEIN studies wasn't prespecified stratified at randomization: YES Baseline characteristics of different subgroups: median age : 58y % female: 45.5% median weight: 80 kg
	2037	(50-79 ml/min)	Recurrent venous thromboembolism	2.4% vs 3.1% HR : 0.77 (0.45 – 1.30)	
	636	(30-49 ml/min)	Recurrent venous thromboembolism	3.4% vs 3.2% HR : 1.05 (0.44 – 2.47)	
				p interaction : 0.72 NS	
	5569	(>=80ml/min)	Major bleeding	0.8% vs 1.0% HR 0.79 (95% CI 0.46–1.36)	
	2037	(50-79 ml/min)	Major bleeding	1.4% vs 3.0% HR: 0.44 (0.24 – 0.84)	
	636	(30-49 ml/min)	Major bleeding	0.9% vs 3.9% HR : 0.23 (0.06 – 0.81)	
	21	(<30 ml/min)	Major bleeding	RIV : 0 VKA : 1 no statistical analysis	
				P interaction : 0.034 SS	
	5569	(>=80ml/min)	First major or clinically relevant non-major bleeding	8.7% vs 8.8% 0.98 (95% CI 0.82–1.18)	
	2037	(50-79 ml/min)		10.7% vs 12.3% HR: 0.85 (0.65 – 1.09)	
	636	(30-49 ml/min)		11.6% vs 13.9% HR: 0.77 (0.49 – 1.19)	
	21	(<30 ml/min)		RIV:2/9 VKA: 1/11 no statistical testing	
				P interaction: 0.29. NS	

Author's conclusion: 'Patients with symptomatic VTE and renal impairment are at increased risk of recurrent VTE. Renal impairment increased the risk of major bleeding in enoxaparin/VKA-treated patients but not in rivaroxaban-treated patients.'1. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. The New England journal of medicine 2013;369: 799-808.
2.

15 Evidence tables. Meta-analyses. DOAC vs VKA in the prevention of recurrent VTE

15.1 Included meta-analyses

Ref Study type	Main inclusion criteria	Endpoints/analyses	Comments
Dentali 2015(70)	DVT PE RCTs	- initial/long term therapy - efficacy (recurrent VTE or death-related VTE) and in the safety (major bleeding) -analysis for PE, DVT and both	search date may 2014 RECOVER 2009 (dabigatran) RECOVER II 2014 (dabigatran) EINSTEIN-DVT 2010 (rivaroxaban) EINSTEIN-PE 2012 (rivaroxaban) HOKUSAI 2013 (edoxaban) AMPLIFY 2013(apixaban)
Cochrane Robertson 2015 (72)	DVT RCTs DTI and FXaI	- initial/long term therapy - efficacy and safety - separate analysis for DTI - separate analysis for FXaI	search date jan 2015 includes ximelagatran for DTI. includes Phase II studies FXaI studies: Botticelli DVT (apixaban) Einstein-DVT dose (rivaroxaban) Einstein-DVT (rivaroxaban) ODIXa-DVT(rivaroxaban) Piazza 2014(edoxaban) AMPLIFY (apixaban) Einstein-PE (rivaroxaban) Hokusai-VTE (edoxaban)
Cochrane Robertson 2015(71)	PE RCTs DTI and FXaI	- initial/long term therapy - efficacy and safety - separate analysis for DTI - separate analysis for FXaI	search date jan 2015 includes ximelagatran for DTI. includes Phase II studies AMPLIFY (apixaban) Einstein-PE (rivaroxaban) Hokusai-VTE (edoxaban)

15.2 Results of meta-analyses

Ref	Comparison	N/n	Outcomes	Result
Dentali 2015(70) SR + MA	DOAC vs standard treatment in initial/extended treatment of VTE	N=6 n=26 848	**recurrent VTE or death related to VTE**	All 0.92(95%CI 0.80-1.07) NS
		RECOVER 2009 RECOVER II 2014 EINSTEIN-PE 2012 HOKUSAI 2013 AMPLIFY 2013		PE RR 0.90 (95%CI 0.72-1.13) NS
		RECOVER 2009 RECOVER II 2014 EINSTEIN-DVT 2010 HOKUSAI 2013 AMPLIFY 2013		DVT 0.93 (95%CI 0.75-1.16) NS
		N=6 n=26 848	**major or clinically relevant non-major bleeding**	All **RR 0.64 (95%CI 0.47-0.86)** **SS less bleeding with DOACs**
		RECOVER 2009 RECOVER II 2014 EINSTEIN-PE 2012 HOKUSAI 2013 AMPLIFY 2013		PE **0.49 (95%CI 0.26-0.95)** **SS less bleeding with DOACs** **high heterogeneity**
		RECOVER 2009 RECOVER II 2014 EINSTEIN-DVT 2010 HOKUSAI 2013 AMPLIFY 2013		DVT 0.74(95%CI 0.51-1.06) NS
Limitations according to the authors: - not all the included RCTs provide separate data according to different clinical presentations for the outcome of major bleeding complications, and, therefore, no definitive conclusion can be drawn for this outcome. - in pooled studies, patients were not randomized according to their clinical presentations. Thus, differences in the baseline characteristics in different groups cannot be excluded. However, given the large sample size of studies included in our meta-analysis, this is extremely unlikely. - the funnel plot for major bleeding is asymmetrical with a lack of studies on the right part of the plot, suggesting that unpublished studies likely to demonstrate an increased risk of MB with NOACs were not included in our meta-analysis (but extensive search was made for unpublished material). - patients with hemodynamically unstable PE were excluded from studies included in our meta-analysis.				

Ref	Comparison	N/n	Outcomes	Result
Cochrane Robertson 2015 (72)	FXaI vs standard anticoagulation in DVT patients	N=8 n=16356 Botticelli DVT Einstein-DVT dose Einstein-DVT ODIXa-DVT Piazza 2014 AMPLIFY Einstein-PE Hokusai-VTE	Recurrent venous thromboembolism	OR 0.89 (95%CI 0.73, 1.07) NS
		N=7 n=16272 Botticelli DVT Einstein-DVT dose Einstein-DVT ODIXa-DVT AMPLIFY Einstein-PE Hokusai-VTE	Recurrent deep vein thrombosis	**OR 0.75 (95%CI 0.57, 0.98)** **SS less recurrent DVT in FXaI**
		N=5 10377 Botticelli DVT Einstein-DVT dose Einstein-DVT ODIXa-DVT AMPLIFY	All cause mortality	OR 0.84 (95%CI 0.64, 1.11) NS
		N=8 n=16645	Major bleeding	**OR 0.57 (95%CI 0.43, 0.76)** **SS less major bleeding with FXaI**

Note: Includes also phase II studies. Pooling of FXaI and DTI separately can be interesting to evaluate (when compared to results in DTI and results in all individual DOACs), but the interpretation of these meta-analyses is limited by not including all available FXaI for each outcome, due to lack of data from the individual trials

Ref	Comparison	N/n	Outcomes	Result
Cochrane Robertson 2015(71)	FXaI vs standard anticoagulation in PE patients	6295 (3 RCTs) AMPLIFY Einstein-PE Hokusai-VTE	Recurrent venous thromboembolism	OR 0.85 (0.63 to 1.15) NS GRADE (by Cochrane authors) ⊕⊕⊕⊕ HIGH
		4509 (2 RCTs) Einstein-PE Hokusai-VTE	Recurrent PE	OR 1.08 (0.46 to 2.56) NS GRADE (by Cochrane authors) ⊕⊕⊕ MODERATE (due to statistical heterogeneity) (see note)
		4817 (1 RCT) Einstein-PE	All cause mortality	OR 1.16 (0.79 to 1.70) NS GRADE (by Cochrane authors) ⊕⊕⊕ MODERATE (due to only 1 study included) (see note)
		4507 (2 RCTs) Einstein-PE Hokusai-VTE	Major bleeding	OR 0.97 (0.59 to 1.62) NS GRADE (by Cochrane authors) ⊕⊕⊕⊕ HIGH (see note)

Note:

- GRADE performed by Cochrane authors. We (the literature group for the consensus conference) **suggest downgrading 1 additional point for the 3 last outcomes** because of not including all FXaI. There is also an argument to be made for downgrading due to imprecision (confidence interval includes clinically relevant benefit and clinically relevant harm). Comparisons also need to be made with other meta-analyses to see if the results are consistent.

16 Evidence tables. LMWH vs VKA in VTE

16.1 Meta-analysis

Ref	Comparison	N/n	Outcomes	Result**
Nice 2012 {NICE National Institute for Health an Care Excellence, 2012 (update 2015) Design: SR + MA Search date: aug 2011	LMWH vs VKA in the continuation phase of treatment	N= 16 n= 2953 (Beckman 2003, Cesarone 2003, Das 1996; Daskalopoulos 2005, Deitcher 2006, Gonzalez-Fajardo 1999, Hamann 1998, Hull 2006, Lee 2003, Lopaciuk 1999, Lopez-Beret 2001, Meyer 2002, Perez-de Llano 2010, Pini 1994, Romera 2009, Veiga 2000)	**All cause mortality – all patients**	LMWH:247/1499 (16.5%) VKA:239/1454 (16.4%) RR:0.99(95%CI 0.85 to 1.15) NS Absolute effect: 2 fewer per 1000 (95% CI 25 fewer to 25 more)
		N=11 n= 1872 (Cesarone 2003, Das 1996, Daskalopoulos 2005, Gonzalez-Fajardo 1999, Hamann 1998, Hull 2006, Lopaciuk 1999, Lopez-Beret 2001, Pini 1994, Romera 2009, Veiga 2000)	**All cause mortality - subgroup: DVT**	LMWH:69/933 (7.4%) VKA:63/939 (6.7%) RR:1.1 (95%CI 0.79 to 1.51) NS Absolute effect: 7 more per 1000 (95% CI 14 fewer to 34 more)
		N=2 n=162 (Beckman 2003, Perez-de Llano 2010)	**All cause mortality - subgroup PE**	LMWH:4/92 (4.3%) VKA:0/70 (0.0%) RR: 3.28(95%CI 0.38 to28.33) NS Absolute effect: Not estimable
		N=3 n=919 (Deitcher 2006, Lee 2003, Meyer 2002)	**All cause mortality - subgroup: DVT or PE**	LMWH: 174/474 (36.7%) VKA: 176/445 (39.6%) RR: 0.94 (95%CI 0.79 to 1.11) NS Absolute effect: 24 fewer per 1000 (95% CI 83 fewer to 44 more)
		N=11 n=1538 (Beckman 2003, Das 1996; Daskalopoulos 2005,	**All cause mortality - subgroup: Non cancer**	LMWH: 42/776 (5.4%) VKA: 33/762 (4.3%) RR: 1.23 (95%CI 0.8 to 1.9)

		Gonzalez-Fajardo 1999, Hamann 1998, Lopaciuk 1999, Lopez-Beret 2001, Perez-de Llano 2010, Pini 1994, Romera 2009, Veiga 2000)		NS Absolute effect: 10 more per 1000 (95% CI 9 fewer to 39 more)
		N=7 n=1415 (Cesarone 2003, Deitcher 2006, Hull 2006, Lee 2003, Lopez-Beret 2001, Meyer 2002, Romera 2009)	**All cause mortality - subgroup: Cancer patients**	LMWH: 205/723 (28.4%) VKA: 206/692 (29.8%) RR: 0.95 (95%CI 0.81 to 1.11) NS Absolute effect: 15 fewer per 1000 (95% CI 57 fewer to 33 more)
		N= 5 n= 689 (Beckman 2003, Daskalopoulos 2005, Gonzalez-Fajardo 1999, Perez-de-Llano 2010, Romera 2009)	**VTE related mortality**	LMWH: 4/354 (1.1%) VKA: 2/335 (0.6%) RR: 1.35 (95%CI 0.31 to 5.92) NS Absolute effect: 2 more per 1000 (95% CI 4 fewer to 29 more)
		N=3 n=527 (Daskalopoulos 2005, Gonzalez-Fajardo 1999, Romera 2009)	**VTE related mortality - subgroup: DVT**	LMWH: 2/262 (0.76%) VKA: 2/265 (0.75%) RR: 1.02 (95%CI 0.18 to 5.84) NS Absolute effect: 0 more per 1000 (95% CI 6 fewer to 37 more)
		N=2 n=162 (Beckman 2003, Perez-de-Llano 2010)	**VTE related mortality - subgroup: PE**	LMWH: 2/92 (2.2%) VKA: 0/70 (0.0%) RR: 2.56 (95%CI 0.13 to 50.95) NS Absolute effect: Not estimable
		N= 16 n= 2916 (Beckman 2003, Das 1996, Daskalopoulos 2005, Deitcher 2006, Gonzalez-Fajardo 1999, Gonzalez-Fajardo 2008, Hamann 1998, Hull 2006, Lee 2003, Lopaciuk 1999, Lopez-Beret 2001, Meyer 2002, Perez-de Llano 2010, Pini 1994, Romera 2009, Veiga 2000)	**Recurrent VTE rates - all**	**LMWH: 116/1482 (7.8%)** **VKA: 166/1434 (11.6%)** **RR: 0.68 (95%CI 0.54 to 0.85)** **SS in favour of LMWH** Absolute effect: 37 fewer per 1000 (95% CI 17 fewer to 53 fewer)
		N=11 n= 1845	**Recurrent VTE rates - all - subgroup: DVT**	**LMWH: 79/922 (8.6%)** **VKA: 107/923 (11.6%)**

		(Das 1996, Daskalopoulos 2005, Gonzalez-Fajardo 1999, Gonzalez-Fajardo 2008, Hamann 1998, Hull 2006, Lopaciuk 1999, Lopez-Beret 2001, Pini 1994, Romera 2009, Veiga 2000)		**RR: 0.74 (95%CI 0.56 to 0.97)** **SS in favour of LMWH** Absolute effect: 30 fewer per 1000 (95% CI 3 fewer to 51 fewer)
		N=2 n=162 (Beckman 2003, Perez-de Llano 2010)	**Recurrent VTE rates - all - subgroup: PE**	LMWH: 4/92 (4.3%) VKA: 0/70 (0.0%) RR: 3.28 (95%CI 0.38 to 28.33) NS Absolute effect: Not estimable
		N=3 n=909 (Deitcher 2006, Lee 2003, Meyer 2002)	**Recurrent VTE rates - all - subgroup: DVT or PE**	**LMWH: 33/468 (7.1%)** **VKA: 59/441 (13.4%)** **RR: 0.53 (95%CI 0.35 to 0.79)** **SS in favour of LMWH** Absolute effect: 63 fewer per 1000 (95% CI 28 fewer to 87 fewer)
		N=12 n=1772 (Beckman 2003, Das 1996, Daskalopoulos 2005, Gonzalez-Fajardo 1999, Gonzalez-Fajardo 2008, Hamann 1998, Lopaciuk 1999, Lopez-Beret 2001, Perez-de Llano 2010, Pini 1994, Romera 2009, Veiga 2000)	**Recurrent VTE rates - all - subgroup: Non cancer**	LMWH: 75/897 (8.4%) VKA: 87/875 (9.9%) RR: 0.85 (95%CI 0.63 to 1.13) NS Absolute effect: 15 fewer per 1000 (95% CI 37 fewer to 13 more)
		N=5 n=1144 (Deitcher 2006, Hull 2006, Lee 2003, Lopez-Beret 2001, Meyer 2002)	**Recurrent VTE rates - all - subgroup: Cancer patients**	**LMWH: 41/585 (7%)** **VKA: 79/559 (14.1%)** **RR: 0.5 (95%CI 0.35 to 0.71)** **SS in favour of LMWH** Absolute effect: 71 fewer per 1000 (95% CI 41 fewer to 92 fewer)
		N=15 n=2762 (Beckman 2003, Das 1996, Daskalopoulos 2005, Deitcher 2006, Gonzalez-Fajardo 1999, Hamann 1998, Hull 2006, Lee 2003, Lopaciuk 1999, Lopez-Beret 2001, Meyer 2002, Perez-de Llano 2010, Pini 1994, Romera 2009, Veiga 2000)	**Major bleeding - all patients**	LMWH: 47/1405 (3.3%) VKA: 56/1357 (4.1%) RR: 0.79 (95%CI 0.55 to 1.16) NS Absolute effect: 9 fewer per 1000 (95% CI 19 fewer to 7 more)

		N=11 n=1607 (Beckman 2003, Das 1996, Daskalopoulos 2005, Gonzalez-Fajardo 1999, Hamann 1998, Lopaciuk 1999, Lopez-Beret 2001, Perez-de Llano 2010, Pini 1994, Romera 2009, Veiga 2000)	**Major bleeding - subgroup: Non cancer**	**LMWH: 10/812 (1.2%)** **VKA: 21/795 (2.6%)** **RR: 0.48 (95%CI 0.24 to 0.97)** **SS in favour of LMWH** Absolute effect: **14 fewer per 1000 (95% CI 1 fewer to 20 fewer)**
		N=5 n=1155 (Deitcher 2006, Hull 2006, Lee 2003, Lopez-Beret 2001, Meyer 2002)	**Major bleeding - subgroup: Cancer patients**	LMWH: 37/593 (6.2%) VKA: 35/562 (6.2%) RR: 1 (95%CI 0.64 to 1.58) NS Absolute effect: 0 fewer per 1000 (95% CI 22 fewer to 36 more)
		N=3 n=445 (Daskalopoulos 2005, Perez-de-Llano 2010, Romera 2009)	**Fatal bleeding**	LMWH:1/221 (0.45%) VKA: 1/224 (0.45%) RR: 1.04 (0.07 to 16.18) NS Absolute effect: 0 more per 1000 (95% CI 4 fewer to 68 more)
		N=1 n=102 (Perez-de-Llano 2010)	**Intracranial bleed/haemorrhage**	LMWH: 0/52 (0.0%) VKA: 0/50 (0.0%) RR: - Absolute effect: Not pooled
		N=1 n=165 (Gonzalez-Fajardo 2008)	**PTS**	LMWH: 34/85 (40%) VKA: 31/80 (38.8%) RR: 1.03 (0.71 to 1.51) NS Absolute effect: 12 more per 1000 (95% CI 112 fewer to 198 more)
		N=0 n=/	**Quality of life**	/

16.2 Studies included in meta-analysis

Ref + design	n	Population	Duration	Comparison	Definition of outcomes	Methodology
Beckman 2003 Setting: Brigham and women hospital's Investigational Drug Service Study design: RCT, Parallel design, single institution treatment trial Duration of follow-up: 90 days total. Patients assessed at 2, 4, 8, 12 weeks	60	**Patient group:** Patients with objectively confirmed symptomatic PE **Inclusion criteria:** PE diagnosed by symptoms confirmed by objective methods: ▪ Symptoms included shortness of breath, lightheadedness, and/or chest discomfort ▪ Radiologic confirmation method: **either** ○ High probability ventilation/ perfusion lung scan or positive spiral chest CT with i.v. contrast or positive pulmonary angiography **or** ○ An intermediate ventilation/ perfusion scan in the presence of high clinical suspicion for PE.	90days	Enoxaparin (LMWH)1.5mg/kg (high dose) or 1.0mg/kg (moderate dose) (initial 14 days of 1.0mg) Vs 5 days continuous infusion of unfractionated heparin and concomitant warfarin for 90 days	**Recurrent VTE rates** confirmed by: see symptomatic PE and DVT) **Major bleeding**: defined as bleeding that caused a decrease in Hb level of >2g/dL, intracranial haemorrhage, cardiac tamponade, or haemorrhage that required major surgical intervention. **Symptomatic pulmonary embolism** confirmed by: spiral CT	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Open label study FOLLOW-UP: Drop outs: 7 Those treated with enoxaparin received echocardiogram for risk stratification of PE allowing for early discharge (within 48 hours for those with low risk), those in UFH arm did not receive echocardiogram. All high risk patients in enoxaparin arm and all patients in the UFH/OA arm were hospitalised for at least 120 hrs. ▪ 8% patients in the enoxaparin arm were undergoing chemotherapy whereas 0 in VKA group were undergoing chemotherapy. ITT: yes (Patients who did not completed study were analysed in the study using ITT analysis (according to randomised arm)

						Funding: Aventis and National Institute of Health (NIH)
Daskalopoulos 2005 **Country of study:** Greece **Setting:** Accident and Emergency Department of a district hospital. **Study design:** Open label RCT **Duration of follow-up:** Evaluated at 1.3, 6 and 12 months.	108	**Patient group:** Consecutive symptomatic adult patients with acute proximal lower limb DVT. Age (range): 58.6 (23-95) **Inclusion criteria:** ▪ Onset of symptoms less than one week. ▪ Thrombotic process had to objectively document by means of duplex ultrasound scan. **Exclusion criteria:** ▪ Segmental deep venous thrombosis restricted to infrapopliteal deep veins or calf muscles as determined by duplex ultrasonography; ▪ Symptomatic or clinically suspected PE, history of recently diagnosed DVT or PE; ▪ Patient already under anticoagulant therapy; ▪ Recently performed thrombolysis;	6 months	Tinzaparin sodium in a weight adjusted dose of 175 anti Xa IU/Kg vs Intravenous bolus of 5000IU UFH. Continuous intravenous UFH infusion for 5-7 days. Acenocoumarol commenced on third day. The dose of the drug was adjusted aiming at an INR 2-3. Patients encouraged to ambulate wearing elastic support stockings. UFH treatment discontinued as soon as the INR value reached 2 or more.	Recurrent DVT rates (documented by duplex ultrasound scan) Incidence of PE confirmed at post mortem. Major bleeding overt and associated with a drop in the haemoglobin level of 2g/dlor more, if it required transfusion of two blood units or more, if it was intracranial, intraspinal, intraocular, pericardial, retroperitoneal or associated with death or the treatment had to permanently discontinued. Minor bleeding: hemorrhagic event not considered major	ALLOCATION CONC: unclear RANDO: not stated BLINDING : Participants: no Personnel no Assessors yes FOLLOW-UP: 6 consent withdrawal before initiation of assigned treatment. ITT: no **Funding:** Leo Pharmaceutical, University of Athens.

GonzalezFajardo 1999 and 2008 **Country of study:** Spain **Setting: NR** **Study design:** RCT **Duration of follow-up:** 3, 6 and 12 months and yearly thereafter for 5 years.	165	**Patient group:** Consecutive patients with symptomatic, unilateral, first episode DVT confirmed by venography. Age (mean): 57.4 (14.4) **Inclusion criteria:** Symptomatic, unilateral and first episode DVT confirmed by venography **Exclusion criteria:** ▪ Clinically suspected pulmonary embolism ▪ Two or more previously documented episodes of DVT or pulmonary embolism, Instructed and motivated to wear graduate compression stockings daily during diurnal activities for at least 2 years.	3 months	LMWH – enoxaparin 40mg once daily, started on 8th day [Initial therapy: Enoxaparin 40 mg twice daily for 7 days] vs. Coumarin (not specified which drug in the class was used) INR, 2-3	**Recurrent VTE rates:** confirmed by: see symptomatic DVT and PE. This does not include the recurrent VTE events in those patients that died during follow up, or those lost to follow up. **Post thrombotic syndrome**: classified according to validated Villalta scale **Symptomatic pulmonary embolism:** confirmed by perfusion lung scan, chest radiography, angio-CT **Symptomatic DVT:** confirmed by new clinical signs of DVT, if signs could be confirmed independently by ultrasound scanning at vascular laboratory, phlebography or non-compressibility ofpreviously normal venous segment	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants unclear Personnel unclear Assessors yes FOLLOW-UP: **Drop outs:** 65 at 5 years After 2nd year of follow up 37 patients lost: Group 1: 12 Group 2: 25 (p=0.08) Significant differences in baseline characteristics between groups regarding risk factor for DVT (Cancer p=0.041 and thrombophilia p=0.032) ITT: no Recurrent VTE rates, post thrombotic syndrome, symptomatic PE and symptomatic DVT analysis only includes those patients who did not die and were not lost to follow up.
Van der heijden 2002 *van der Heijden JF, Hutten*	1137	**Patient group:** Symptomatic VTE, all 7 studies included	3 months (2 studies),	**LMWH** Enoxaparin (n=3	**Recurrent VTE rates** definition of	ALLOCATION CONC: Unclear RANDO: Unclear (4 studies)

BA, Buller HR, Prins MH. Vitamin K antagonists or low-molecular-weight heparin for the long term treatment of symptomatic venous thromboembolism. Cochrane database of systematic reviews. 2002(1):CD002001. **Study design:** Cochrane systematic review including 7 RCTS (Hamann 1998, Das 1996, Gonzalez-Fajardo 1999, Lopaciuk 1999, Lopez-Beret 2001, Pini 1994, Veiga 2000) **Duration of follow-up:** 3, 6, and/or 9 months		only patients with DVT **Inclusion:** - Symptomatic VTE ▪Long term treatment of with LMWH or Vit K antagonists **Exclusion:** ▪ Accepted objective tests were not used to confirm diagnosis of deep vein thrombosis (venography, ultrasound, or any sequence of tests that results in a high positive predictive forlue for the diagnosis of symptomatic DVT) or the diagnosis of PE (high probability ventilation perfusion scan or pulmonary angiography)	3-9months (2 studies), 3 or 6 months (3 studies)	studies), Tinzaparin (n=1), dalterparin (n=1), nadroparin (n=1). vs **Vitamin K antagonist (VKA)** 5/7 studies defined that the INR was titrated to between 2 and 3	-Recurrent symptomatic DVT: includes an extension of an intraluminal filling defect on a venogram, -New intraluminal filling defect, -Extension of non-visualization of proximal veins in the presence of a sudden cut-off defect on a venogram seen on at least 2 projections. -Abnormal results of compression US in an area where compression had been normal, or a substantial increase in the diameter of the thrombus during full compression at the popliteal or femoral vein -A change in the results of impedance plethysmography from normal to abnormal, accompanied by a change from negative to positive result on a D-dimer test **Recurrent symptomatic PE**: A -New intraluminal filling defect, an extension of an existing defect, or the sudden cut-off of vessels more than 2.5 mm in diameter on a PA. -Intraluminal filling defect or sudden cut-off of vessels more than 2.5 mm in diameter on PA ▪ Defect of at least 75% of a segment on the perfusion scan with normal ventilation ▪ Where the VQ scan non-diagnostic & no PA, satisfaction of the above criteria for deep venous thrombosis was acceptable.	BLINDING : Participants:no Personnel: no Assessors: yes(All studies were not blinded. Outcome assessors blinded in 3 studies) ITT: unclear All analyses were according to the ITT analysis. When the individual studies did not use ITT, the analyses of this review were on the basis of the data provided by the individual study. **Methodology of review:** **Only include studies if:** ▪ Initial treatment consisted of UFH or LMWH lasting 5- 10 days ▪ Randomised study

					-Autopsy **Major bleeding:** Clinically overt and associated with a fall in hemoglobin level of≥ 2 g/dl ; clinically overt and leading to a transfusion of ≥2 units of packed cells; intracranial; retroperitoneal; leading directly to death; leading to interruption of antithrombotic treatment or (re)operation	
Akl 2008 *Akl EA. Anticoagulation for the long term treatment of venous thromboembolism in patients with cancer. Cochrane database of systematic reviews. 2008((Issue 2)):CD006650.* **Setting:** Outpatients **Study design:** Cochrane systematic review including 6 randomised controlled trials (RCTs) (Cesarone 2003, Deitcher 2006; Hull 2006; Lee 2003; Lopez Beret 2001; Meyer 2002)	1661	Patients with cancer and symptomatic objectively confirmed VTE. **Inclusion:** Patients could be of any age group, with either solid or hematological cancer at any stage of their cancer and respectively of the type of cancer therapy. DVT should have been diagnosed using one of the following objective diagnostic tests: venography, 125I-fibrinogen-uptake test, impedance plethysmography or Doppler ultrasound. Pulmonary embolism should have been diagnosed using one of the following objective diagnostic tests: pulmonary perfusion/ventilation scans, computed tomography or	3-6 months	**LMWH**: Enoxaparin (n=3 studies), Tinzaparin (n=1), dalterparin (n=1), nadroparin (n=1). vs **Vitamin K antagonist (VKA)**		ALLOCATION CONC: Adequate(3)/unclear(3) RANDO: not stated BLINDING : Participants: no/personnel: no/assessors:unclear FOLLOW-UP: ? % in safety analysis 89-100 % in efficacy analysis ITT: Unclear **Funding:** Deitcher 2006 funding from Aventis Pharmaceutical. Hull 2006 funded by Canadian Institute for Health Research, industry grant, Leo Pharmaceutical, Pharmion Pharmaceutical and Dupont Pharmaceutical. Lee 2003 funding from Pharmacia. Meyer 2002

		pulmonary angiography.				funding from Aventis, Assistance Publique, Hospitaux de Paris. 2 remaining studies did not report funding.
Perez-de-Llano 2010 **Country of study:** Spain **Setting:** Initial inpatient then outpatient. 4 hospital centres **Study design:** Randomized multicentre, open-label trial **Duration of follow-up:** Follow up at 1,3 and 6 months	102 **Age (mean):** 72.2 (41.2% over 75)	Consecutive patients with symptomatic acute PE (April 2005-December 2008). Diagnosis of PE objectively confirmed. Majority of patients from a rural area. **Inclusion criteria:** Consecutive patients with symptomatic acute PE. **Exclusion criteria:** ▪ need for indefinite anticoagulation and poor life expectancy (including advanced malignancy)	6 months.	LMWH: Tinzaparin 175 IU/kg once daily Route: subcutaneous **vs** VKA: Acenocoumarol adjusted to target INR 2.0-3.0. Given within 48 hours (range 1-8days) of 1st dose of tinzaparin. Route: oral <u>Initial therapy</u> Tinzaparin stopped when INR>2 on two consecutive days. Median duration of tinzaparin 7 days. Initial dose N/R **For all patients:** Initial treatment with tinzaparin s/c 175anti-Xa	**VTE related mortality=** Haemodynamic shock from initial massive PE Patient satisfaction (not validated) **Recurrent VTE rates:** Symptomatic only. Jugular vein thrombosis day 25. Confirmed by compression US or helical CT as appropriate **Major bleeding**: Clinically overt and associated with decrease Hb level ≥2g/dl, or required transfusion of at least 2 units, or retroperitoneal or intracranial bleed **Minor bleeding:** Epistaxis, gingivitis, haematuria, metrorrhagia, rectorrhagia	ALLOCATION CONC:Unclear RANDO: Unclear BLINDING : No Participants/personnel/assessors Inadequate FOLLOW-UP: **Drop outs: 8** ITT:unclear **Funding:** LEO Pharma (manufacturer of tinzaparin)

				IU/kg once daily		
Romera 2009 **Country of study:** Spain **Setting:** 2 centres. Vascular surgery department then outpatient **Study design:** Randomised, open-label	241	**Patient group:** Consecutive symptomatic proximal DVT or the lower limbs confirmed by duplex ultrasound. January 2002 to January 2005 **Inclusion criteria:** - Over 18 years old - First episode, onset of symptoms less than 2 weeks **Exclusion criteria:** ▪ PE requiring thrombolytic therapy, surgical thrombectomy or vena cava interruption, ▪ Hb <7g/dl, severe renal failure necessitating dialysis, ▪ Pregnancy, history of HIT, surgery within previous 14 days, lumbar puncture within previous 24 hours, receiving anti-coagulant or anti-platlet drugs for other conditions unable to discontinue medication during treatment interval. Those who had received heparin, LMWH or oral-anticoagulant therapy for >2days. Distal DVT.	12 months Duplex scan at 6 and 12 months Treatment for 6 months	LMWH Tinzaparin (Innohep) Dose, and frequency: 175 IU anti-Xa/kg once daily Route: subcutaneous injection vs VKA Acenocoumarol Start time: Day 1 Dose, and frequency: 3mg (initial dose) adjusted to give INR 2-3. Tinzaparin given until INR≥2 on two consecutive days Route: oral	**Recurrent VTE rates at 6 months** Symptomatic, USS, hi prob lung scan, abnormal perfusion scan with documented new DVT, or spiral CT **Recurrent VTE rates at 12 months (inc at 6 months)** Confirmed as above **Major bleeding** overt and associated with ≥2g/dl fall in Hb, resulted in transfusion of 2 or more units of blood, retroperitoneal, into a major joint or intracranial **Symptomatic pulmonary embolism at 6 months** (confirmed by: see above) **Symptomatic DVT at 6 months**(confirmed by: see above) **Symptomatic DVT at 12 months (exc at 6 months)** (confirmed by: see above)	ALLOCATION CONC: Adequate RANDO: unclear BLINDING : open-label Participants:no personnel:no assessors: unclear FOLLOW-UP: Drop outs: 2(died from cancer) ITT:yes **For all patients:** Tinzaparin (innohep, LEO PHarma A/S) subcutaneously 175IU anti-Xa per kg once daily. All patients told to come to hospital immediately if signs or symptoms suggestive of recurrent VTE and given ultrasound. Outpatient at 1,6,12 months for clinical examination and ultrasound Post randomisation cancer subgroup analysis **Funding:** LEO Pharma) , provided funding and performed statistical analysis

17 Evidence tables. Duration of treatment for (prevention of recurrent) VTE

17.1 Meta-analyses about treatment duration

17.1.1 Included meta-analyses

Marik 2015(78)	OAC and aspirin - first unprovoked VTE -clinical equipoise regarding cessation or continuation >=3m initial therapy - >=6 m treatment vs placebo	-extended therapy -VKA vs pla -DOAC vs pla	search date july 2015 Searched only Medline and Cochrane (CENTRAL) analysis for VKA/DOAC/aspirin seperately only 2 trials included for VKA (Kearon 1999 and Couturaud 2015)
Sindet Pedersen 2015(79)	3 m pre-treatment 6 m treatment vs other	extended therapy efficacy and safety	Search date nov 2014 Einstein ext amplify ext re-sonate re-medy wodit Kearon Pooled DOAC trials + Kearon 1999. Similar results as Cochrane Middeldorp 2014 and Marik 2015.
Cochrane Middeldorp 2014(77)	VKA any duration symptomatic VTE vs placebo or no treatment	extended therapy efficacy and safety	search date oct 2013 heterogeneous populations included (PE-DVT-unprovoked-provoked-factor VIII…)

17.1.2 Results from meta-analyses

Ref	Comparison	N/n	Outcomes	Result
ref* Cochrane Middeldorp 2014(77) Design: SR+ MA Search date: oct 2013	long-term (3 m -4y) vs short term (1m -6 m) VKA treatment	N= 10 n= 3536 Agnelli 2001 Agnelli 2003 Eischer 2009 Kearon 1999 Kearon 2004 Levine 1995 Pinede 2001 Ridker 2003 Schulman 1995 Schulman 1997	Recurrent VTE	during prolonged treatment **RR 0.20 (95% CI 0.11 to 0.38)** **SS less recurrent VTE with long term treatment** illustrative comparative risks short term 88/1000 long term 18/1000 (95%CI 10 to 33) HIGH QUALITY OF EVIDENCE
		N=7 n=2639 Agnelli 2001 Agnelli 2003 Eischer 2009 Kearon 2004 Levine 1995 Pinede 2001 Schulman 1995	Recurrent VTE	recurrences after cessation of prolonged treatment (follow-up period) RR 1.28, 95% CI 0.97 to 1.70 NS
		N= 4 n= 1049 Kearon 1999 Levine 1995 Ridker 2003 Kearon 2004	Mortality	RR 0.89 (95% CI 0.66 to 1.21) NS MODERATE QUALITY OF EVIDENCE (low number of studies/events)
		N= 6 n= 1350 Kearon 1999 Levine 1995 Eischer 2009 Ridker 2003	Major bleeding	during entire period after randomisation **RR 2.60 (95% CI 1.51 to 4.49)** **SS more major bleeding with long term treatment** illustrative comparative risks short term 4/1000

		Agnelli 2001 Kearon 2004		long term 15/1000 (95%CI 5 to 43) MODERATE QUALITY OF EVIDENCE (imprecision)
	6 months vs 3 months	N= 4 n= 1113 Agnelli 2001 Agnelli 2003 Kearon 1999 Pinede 2001	Recurrent VTE	period from cessation of VKA in short arm until VKA cessation in long arm **RR 0.10 (95%CI 0.02 to 0.43]** SS **less recurrent VTE with long term treatment**
	12 months vs 3 months	N=3 n= 610 Agnelli 2001 Agnelli 2003 Kearon 1999	Recurrent VTE	period from cessation of VKA in short arm until VKA cessation in long arm RR 0.18 (95%CI 0.07 to 0.45) SS **less recurrent VTE with long term treatment**
	3 months vs 1 months	N=2 n=379 Kearon 2004 Levine 1995	Recurrent VTE	period from cessation of VKA in short arm until VKA cessation in long arm 0.18 (95%CI 0.04 to 0.79)

Ref	Comparison	N/n	Outcomes	Result
Marik 2015(78) Design: SR+ MA Search date: july 2015	warfarin long (24m)vs short (3-6 m) Kearon 1999 Couturaud 2015	N=2 n=533	Recurrent VTE	during the study period **OR 0.09 (95%CI 0.03 to 0.25)** **SS less recurrent VTE with long term treatment**
			Mortality	during the study period OR 0.86 (95%CI 0.20 to 3.61) NS
			Major bleeding	during the study period OR 5.13(95%CI 0.87—30.15) NS
	DOAC long vs short Schulman 2013 (RE-SONATE) Agnelli 2013 (AMPLIFY-EXT) EINSTEIN-EXT 2010	N=3 n=5021	Recurrent VTE	during the study period OR 0.16 (95%CI 0.11 to 0.24) **SS less recurrent VTE with long term treatment**
			Mortality	during the study period OR 0.52 (95%CI 0.10 to 2.66) NS
			Major bleeding	during the study period OR 1.88 (95%CI 0.19 to 18.06) NS

17.1.3 Trials included in the meta-analyses

Treatment durations

OAC both treatment arms
OAC 1 arm/placebo other arm
some OAC/pla some already end of trial

- Trials found in Cochrane Middeldorp 2013(77)

Study	**1 Month**	**2 Month**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Agnelli 2001 (WODIT)	VKA	VKA	VKA																					
Agnelli 2003	VKA	VKA	VKA																					
Eischer 2009	VKA	VKA	VKA	VKA	VKA	VKA																		30 m
Kearon 1999	Warfarin	Warfarin	Warfarin																					
Kearon 2004	Warfarin																							
Levine 1995	Warfarin																							
Pinede 2001	Fluindione	Fluindione	Fluindione																					
Ridker 2003	Warfarin	(trial halted)																						
Schulman 1995	Warfarin																							

Schulman 1997																								indefinitely
Siragusa 2008	VKA																							

- Additional trials, from Marik 2015(78)

Study	**1 M**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Couturaud 2015 PADIS PE	VKA	VKA	VKA	VKA	VKA	VKA																		

Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Schulman 2013 RE-SONATE	dabi					6 to 18m																		additional 6m
												additional 6m												
Agnelli 2013 AMPLIFY-EXT	apix					6 to12m												additional 6 m						
												additional 6 m												
EINSTEIN-EXT 2010	rivarox					6 to 12m												additional 6 m						
												additional 6 m												

Details of included trials

Study	population	comparison	comments/authors' summary
Agnelli 2001(130) WODIT	n=267 idiopathic DVT	VKA 3m vs 1y	no placebo treatment (discontinuation)
Agnelli 2003(131)	n=326 PE unprovoked or reversible risk factors	VKA 3 m vs 6m (temporary risk factors) 3m vs 1 y (unprovoked)	no placebo treatment (discontinuation) Among 165 patients assigned to extended anticoagulant therapy, 15 patients (9.1%) had a recurrence of venous thromboembolism (3.1% per patient-year; average follow-up, 34.9 months), as compared with 18 of 161 patients (11.2%) assigned to discontinue treatment (4.1% per patient-year; average follow-up, 32.7 months); the rate ratio was 0.81 (95% CI, 0.42 to 1.56). All but one of the recurrences occurred after anticoagulant treatment was discontinued
Eischer 2009(132)	n=34 first spontaneous VTE patients with high factor VIII	VKA 6 m vs 30 m	Our findings in a small number of patients indicate that prolonged anticoagulation seems to be effective but that the benefit is not maintained after discontinuation of anticoagulation.
Kearon 1999(133)	n=162 first episode of VTE no known risk factors	Warfarin 3m vs 24 m	A prespecified interim analysis of efficacy led to the early termination of the trial after 162 patients had been enrolled and followed for an average of 10 months Of 83 patients assigned to continue to receive placebo, 17 had a recurrent episode of venous thromboembolism (27.4 percent per patient-year), as compared with 1 of 79 patients assigned to receive warfarin (1.3 percent per patient-year, P<0.001).
Kearon 2004(134)	n=84 first VTE, provoked by transient risk factor	warfarin 1 m vs 3 m	The incidence of recurrent venous thromboembolism after discontinuation of warfarin was 6.8% per patient-year in those who received warfarin for 1 month and 3.2% per patient-year in those who received warfarin for 3 months (rate difference of 3.6% per patient-year; 95% CI - 3.8, 11.0).
Levine 1995(135)	acute proximal DVT	warfarin 1m vs 3 m	During the eight weeks following randomization, nine (8.6%) of the 105 placebo patients developed recurrent VTE compared to one (0.9%) of the 109 warfarin patients, P = 0.009.
Pinede 2001 (136)	n=736 proximal DVT PE	Fluindione 3 m vs 6 m (6w vs 12 w for calf DVT)	There were 23 recurrences of venous thromboembolism in the short treatment group (6.4%) and 26 in the long treatment group (7.4%); the 2 treatment regimens had an equivalent effect. For the

	calf DVT		hemorrhage end point, the difference between the short and the long treatment groups was not significant: 15.5% versus 18.4% for all events (P=0.302), 1.7% versus 2.8% (P=0.291) for major events, and 13.9% versus 15.3% for minor bleeding
Ridker 2003(137)	n=508 idiopathic VTE	warfarin low intensity (INR 1.5-2) median 6.5m vs indefinite?	The trial was terminated early Of 253 patients assigned to placebo, 37 had recurrent venous thromboembolism (7.2 per 100 person-years), as compared with 14 of 255 patients assigned to low-intensity warfarin (2.6 per 100 person-years), a risk reduction of 64 percent (hazard ratio, 0.36 [95 percent confidence interval, 0.19 to 0.67]; P<0.001)
Schulman 1995(138)	n=902 first episode of VTE	VKA 6w vs 6m	After two years of follow-up, there had been 123 recurrences of venous thromboembolism that met the diagnostic criteria, 80 in the six-week group (18.1 percent; 95 percent confidence interval, 14.5 to 21.6) and 43 in the six-month group (9.5 percent; 95 percent confidence interval, 6.8 to 12.2). The odds ratio for recurrence in the six-week group was 2.1 (95 percent confidence interval, 1.4 to 3.1).
Schulman 1997(139)	n=227 second episode of VTE (DVT or PE)	VKA 6m vs indefinitely	After four years of follow-up, there were 26 recurrences of venous thromboembolism that fulfilled the diagnostic criteria, 23 in the group assigned to six months of therapy (20.7 percent) and 3 in the group assigned to continuing therapy (2.6 percent). The relative risk of recurrence in the group assigned to six months of therapy, as compared with the group assigned to therapy of indefinite duration, was 8.0 (95 percent confidence interval, 2.5 to 25.9). There were 13 major hemorrhages, 3 in the six-month group (2.7 percent) and 10 in the indefinite-treatment group (8.6 percent). The relative risk of major hemorrhage in the six-month group, as compared with the indefinite-treatment group, was 0.3 (95 percent confidence interval, 0.1 to 1.1). There was no difference in mortality between the two groups.
Siragusa 2008(140)	n=258 first episode of DVT	VKA stop if no residual vein thrombosis if residual vein thrombosis: 3 m vs 12m VKA	no placebo treatment (discontinuation) Residual thrombosis was detected in 180 (69.8%) of 258 patients; recurrent events occurred in 27.2% of those who discontinued (25/92; 15.2% person-years) and 19.3% of those who continued OAT (17/88; 10.1% person-years). The relative adjusted hazard ratio (HR) was 1.58 (95% confidence interval [CI], 0.85-2.93; P = .145). Of the 78 (30.2%) patients without RVT, only 1 (1.3%; 0.63% person-years) had

			a recurrence. The adjusted HR of patients with RVT versus those without was 24.9 (95% CI, 3.4-183.6; P = .002). One major bleeding event (1.1%; 0.53% person-years) occurred in patients who stopped and 2 occurred (2.3%; 1.1% person-years) in those who continued OAT. Absence of RVT identifies a group of patients at very low risk for recurrent thrombosis who can safely stop OAT

Study	**population**	**comparison**	**Endpoints**	**Results**	
Couturaud 2015 PADIS PE (141)	**-n=371** **-mean 58y** **-first episode of symptomatic PE (unprovoked)** **-6 m previous VKA treatment**	**Warfarin vs placebo for 18 m**	**Recurrent venous thromboembolism or major bleeding**	**during study period (18m)** **3.3% vs 13.5%** **HR 0.22 (95%CI 0.09-0.55)** **SS less events with warfarin** at 42 months (treatment period + follow-up) 20.8% vs 24.0% HR 0.75 95%CI,0.47-1.18 NS	**RANDO: ok** **ALLOCATION CONCEALMENT: ok** **BLINDING: ok** attrition: drop-outs and exclusions described and balanced across groups Early discontinuation of study because steering committee decided that the overall rates of recurrence provided sufficient data Programme Hospitalier de Recherche Clinique (French Department of Health),University Hospital of Brest
			Recurrent VTE	**n= 3 vs n=25** **HR,0.15; 95%CI,0.05-0.43** **SS less recurrent VTE with warfarin**	
			Death unrelated to VTE/major bleeding	HR 1.32 (95% 0.19-9.35) NS	
			Major bleeding	n=4 vs n=1 (HR, 3.96; 95%CI,0.44 to 35.89). NS	

17.2 Additional 6 months of apixaban vs stop after 6-12 months of treatment

Study details	n/Population	Comparison	Outcomes		Methodological
Agnelli 2013 Amplify-EXT (81) Design: RCT DB trial extension Duration of follow-up: median 1 year	n=2486 Mean age: 56.7y Initial diagnosis: DVT 65.4%, PE 34.6%, DVT+PE 0% CrCL <50ml/min: 5.6% Risk factors for recurrent VTE Previous DVT or PE: 12.7% Immobilized : 2.7% <u>Inclusion:</u> objectively confirmed, symptomatic deep-vein thrombosis or pulmonary embolism (with or without deep-vein thrombosis); <u>if they had been treated for 6 to 12 months with standard anticoagulant therapy or had completed treatment with apixaban or</u>	Apixaban 5 mg twice daily (n = 815) vs apixaban 2.5 mg twice daily (n = 842) vs placebo (n = 829) <u>remarks:</u>	Adherence		RANDO: Adequate (interactive voice response system) ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: 99.6% in safety analysis 99.8 % in efficacy analysis Drop-outs and Exclusions: Described: yes Balanced across groups: no ITT: Yes SELECTIVE REPORTING: no Other important methodological remarks: patients who were lost to follow
			No drug interruption (>3d)	NR	
			Permanent discontinuation of study drug	API 5mg: 15.8% API 2.5 mg: 13.5% Placebo: 22.7%	
			Efficacy		
			Symptomatic recurrent thromboembolism (fatal and non-fatal PE and DVT) or death from any cause	Placebo: 96/829 (11.6%) API 2.5: 32/842 (3.8%) API 5: 34/813 (4.2%) API 2.5 vs placebo: **RR: 0.33 (0.22 – 0.48) SS** *estimated NNT/12m: 13(11-17)* API 5 vs placebo: **RR: 0.36 (0.25–0.53) SS** *estimated NNT/12m:14 (12-19)*	
			Symptomatic recurrent VTE or death related to VTE	Placebo: 73 / 829 (8.8%) API 2.5: 14/842 (1.7%) API 5: 14 / 813 (1.7%) API 2.5 vs placebo: **0.19 (0.11–0.33) SS**	

	enoxaparin and warfarin as participants in the AMPLIFY trial - had not had a symptomatic recurrence during prior anticoagulant therapy - clinical equipoise about the continuation or cessation of anticoagulant therapy Exclusion: contraindication to continued anticoagulant therapy or if they required ongoing anticoagulant therapy, dual antiplatelet therapy, or aspirin at a dose higher than 165 mg daily. - hemoglobin level of less than 9 mg per deciliter, a platelet count of less than 100,000 per cubic millimeter, a serum creatinine level of more than 2.5 mg per deciliter (221 µmol per liter) or a calculated creatinine clearance of less than 25 ml per minute, an			API 5 vs placebo: **0.20 (0.11–0.34) SS**	up were counted as having had a primary event * the numbers given in the table do not match the numbers in the text Randomization stratified according to initial diagnosis (DVT or PE) Sponsor: Bristol-Myers Squibb & Pfizer
			Death from any cause	Placebo: 1.7% Api 2.5: 0.8% API 5: 0.5% No statistical testing	
			composite of symptomatic recurrent venous thromboembolism, death related to venous thromboembolism, myocardial infarction, stroke, or death related to cardiovascular disease	Placebo: 83/ 829 (10.0%)* API2.5: 18 / 842 (2.1%)* API 5: 19 / 813 (2.3%)* API 2.5 vs placebo: **RR: 0.21 (0.13–0.35) SS** API5 vs placebo: **RR: 0.23 (0.14–0.38) SS**	
			Safety		
			Major bleeding (during treatment) (ISTH definition)	Placebo: 4 (0.5%) API 2.5:2 (0.2%) Api 5: 1 (0.1%) API2.5 vs placebo: 0.49 (0.09–2.64) **NS** API5 vs placebo:	

	alanine aminotransferase or aspartate aminotransferase level that was more than 2 times the upper limit of the normal range, or a total bilirubin level that was more than 1.5 times the upper limit of the normal range			0.25 (0.03–2.24) **NS**	
			Clinically relevant non-major bleeding	Placebo: 19 (2.3%) API 2.5: 25 (3.0%) API 5: 34 (4.2%) API 2.5 vs placebo: 1.29 (0.72–2.33) **NS** API 5 vs placebo: 1.82 (1.05–3.18) **SS** *estimated NNH/12m: 53 (870-20)*	

17.3 Dabigatran versus placebo after at least 6 months of anticoagulant treatment

Study flow	Group	At least 3 months of treatment for VTE Participants at increased risk					6 months					
RE-MEDY	Active						Dabigatran	Dabigatran	Dabigatran	Dabigatran	Dabigatran	Dabigatran
	Control						Warfarin	Warfarin	Warfarin	Warfarin	Warfarin	Warfarin
		At least 6 months of treatment for VTE					6 months					
RE-SONATE	Active						Dabigatran	Dabigatran	Dabigatran	Dabigatran	Dabigatran	Dabigatran
	placebo						Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

Study details	n/Population	Comparison	Outcomes		Methodological
Schulman 2013-RE-SONATE(76) Design: DB PG superiority RCT Setting: Patients from 147 sites in 21 countries Duration of follow-up: 6 months (= treatment) extended up to 12 months after completion of the study treatment(≠protocol)	n= 1353 Mean age: 56y Index event: DVT 65%; PE 27%; DVT + PE 6% Recent surgery: NR Recent trauma: NR Immobilized: 6% <u>Inclusion</u> at least 18 years; objectively confirmed, symptomatic, proximal deep-vein thrombosis or pulmonary embolism that had already been treated with an approved anticoagulant or received dabigatran in one of two previous clinical trials of short-term treatment of venous thromboembolism (RE-COVER3 and RE-COVER II4 studies). DVT confirmed by venous compression ultrasonography (CUS) or venography. PE confirmed by ventilation-perfusion (VQ), or lung scan, or pulmonary angiography, or	Dabigatran 2x150mg/d (n=685) vs. placebo (n=668) Randomization was stratified according to study center for 6 months The required duration of initial treatment before trial enrollment was 6 to 18 months	Adherence		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: unclear Personnel: unclear Assessors: yes FOLLOW-UP: Lost-to follow-up: <1% Drop-out and Exclusions: 2.6% • Described: yes • Balanced across groups: yes ITT: no, modified (exclusion of patients who did not receive any dose of the study drug) Power: adequate? (1800 patients were needed according to sample size calculation) SELECTIVE REPORTING: no
			Adherence to dabigatran or dabigatran-placebo	Dabigatran: 96.5% Placebo: 96.5%	
			Efficacy (during 6m of treatment)		
			Recurrent or fatal VTE or unexplained death (**PO**) (clinically suspected recurrent DVT had to be objectively verified using pre-specified imaging studies)	Dabigatran: 3/681 (0.4%) Placebo: 37/662 (5.6%) **HR= 0.08 (95% CI 0.02 to 0.25),SS, p<0.001 in favour of dabigatran** *estimated NNT/6m: 20 (19-24)*	
			Symptomatic DVT	Dabigatran: 2/681 (0.3%) Placebo: 22/662 (3.3%) P value NR	
			Symptomatic nonfatal PE	Dabigatran: 1/681 (0.1%) Placebo: 14/662 (2.1%) P value NR	
			Unexplained death	Dabigatran: 0/681 (0%) Placebo: 2/662 (0.3%) P value NR	
				"no cases of objectively verified fatal PE or any other deaths"	
			Safety		
			Major bleeding (defined as clinically overt and associated with a fall of the hemoglobin level of 20 g/L or required transfusion of at least 2 units of red cells or, involved a critical organ or was fatal)	Dabigatran: 2/684 (0.3%) Placebo: 0/659 (0%) HR= not estimable	

	spiral (helical) CT. In case of death, autopsy is an additional way to confirm VTE. <u>Exclusion:</u> < 18 y; indication for vitamin K antagonist other than DVT and/or PE; patients in whom anticoagulant treatment for their index PE or DVT should be continued; active liver disease or liver disease decreasing survival or ALT >3 x ULN; creatinine clearance <30 ml/min; acute bacterial endocarditis; active bleeding or high risk for bleeding; uncontrolled hypertension; intake of another experimental drug < 30 days ; life expectancy <6 months; childbearing potential without proper contraceptive measures, pregnancy or breast feeding; known hypersensivity to dabigatran or any other component of the investigational product; active cancer		**Clinically relevant non-major bleeding** (At least one of the following criteria had to be fulfilled: spontaneous skin hematoma of at least 25 cm; spontaneous nose bleed > 5 minutes duration ; macroscopic hematuria, lasting more than 24 hours ; spontaneous rectal bleeding (more than spotting on toilet paper); gingival bleeding for more than 5 minutes; bleeding leading to hospitalization and/or requiring surgical treatment; bleeding leading to a transfusion of less than 2 units of whole blood or red cells; any other bleeding considered clinically relevant by the investigator)	NR	Sponsor: Boehringer Ingelheim
			Major or clinically relevant bleeding event	Dabigatran: 36/684 (5.3%) Placebo: 12/659 (1.8%) **HR= 2.92 (95% CI 1.52 to 5.60), SS, p=0.001 in favour of placebo** *estimated NNH/6m: 29 (107-12)*	
			Any bleeding event	Dabigatran: 72/684 (10.5%) Placebo: 39/659 (5.9%) **HR= 1.82 (95% CI 1.23 to 2.68), SS, p=0.003 in favour of placebo** *estimated NNH/6m: 22 (74-10)*	
			Acute coronary syndrome	Dabigatran: 1/684 (0.1%) Placebo: 1/659 (0.2%) NT	

17.4 Rivaroxaban vs placebo after 6-12 months treatment for VTE

Study details	n/Population	Comparison	Outcomes		Methodological
EINSTEIN-extension 2010 (68) Continued treatment study Design: double-blind, randomized, event-driven superiority study RCT: DB, PG Setting: unclear Duration of follow-up: treatment duration of 6 or 12 months	n= 1197 Mean age:58 Patients had been treated for 6 to 12 months with acenocoumarol or warfarin or rivaroxaban Previous VTE(DVT/PE): 108 (17.9%) (rivaroxaban) 84 (14.1%) (placebo) <u>Inclusion</u> **objectively** confirmed, symptomatic DVT or pulmonary embolism and had been treated for 6 to 12 months with acenocoumarol or warfarin (in the EINSTEIN studies or from routine care) or rivaroxaban (in the EINSTEIN studies) and if there was equipoise with respect to the need for continued anticoagulation. <u>Exclusion</u> Another indication for a	Rivaroxaban 20 mg 1x/d vs placebo	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: >99% Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT:Yes, for efficacy Safety analysis: all patients that received study drug were analysed Power: adequate SELECTIVE REPORTING: no Sponsor: Bayer Schering Pharma and Ortho- McNeil
			Symptomatic recurrent VTE (PO) (confirmed by with the use of diagnostic criteria for PE: CT scan, pulmonary angiogram, ventilation/perfusion scan; for DVT: compression ultrasound, venography)	**Rivaroxaban: 8/602 (1.3%)** **placebo:42/594 (7.1%)** **HR: 0.18 (95% CI 0.09-0.39 p<0.001)** **SS in favour of rivaroxaban** *estimated NNT/mean study duration: 18(16-23)*	
			Safety		
			First major or clinically relevant non-major bleeding Major bleeding is defined as overt bleeding and: fall in hemoglobin of 2 g/dL or more, or leading to a transfusion of 2 or more units of packed red blood cells or whole blood, or occurring in a critical site or contributing to death Other clinically relevant bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention	**Rivaroxaban: 36/598(6.0%)** **Placebo: 7/590 (1.2%)** **HR: 5.19 (95% CI 2.3 to 11.7);** **p<0.001** **SS in favour of placebo** *estimated NNH/mean study duration: 21 (65-8)*	
			Major bleeding	Rivaroxaban: 4/598 (0.7%) Placebo: 0 (0%)	

	vitamin K antagonist; a creatinine clearance < 30 ml /min; clinically significant liver disease or an ALT >3x; bacterial endocarditis; active bleeding or a high risk of bleeding; systolic BP> 180 mm Hg ordiastolic BP> 110 mm Hg; childbearing potential without proper contraception, pregnancy, or breast-feeding; concomitant use of strong cytochrome P-450 3A4 inhibitors or inducers, ; a life expectancy of less than 3 months.			HR: NA; p=0.11	
			Clinically relevant non-major bleeding	Rivaroxaban: 32/598(5.4%) Placebo: 7 /590 (1.2%)	
			All-cause mortality	Rivaroxaban: 1/598(0.2%) Placebo: 2/590 (0.3%)	
			Vascular events (acute coronary syndrome, ischemic stroke, transient ischemic attack, or systemic embolism)	Rivaroxaban: 3 /598 (0.5%) Placebo: 4 /598(0.7%)	

18 Evidence tables. Bridging

18.1 Meta-analysis

Heparin bridging versus no bridging after interruption of vitamin K antagonists for elective procedures

Reference	N/n	Outcome	Results: bridging vs no bridging OR (95%CI)	Remarks
Siegal 2012(83) Meta-analysis	5 cohort studies 3501 participants	Major bleeding events	Bridging:52/1397 (3.7%) No bridging: 16/2104 (0.8%) **OR 3.60 (1.52 to 8.50) SS in favour of no bridging**	Search: 2001 -2010 in Medline, EMBASE and Cochrane Collaboration databases <u>Included:</u> Studies (observational and interventional) in adult patients, elective invasive procedure or surgery, long-term use of VKA preprocedurally, periprocedural bridging with LMWH in at least some patients studied, reporting of thrombo-embolic and bleeding events. Any indication for anticoagulation
	8 cohort studies 5184 participants	Thromboembolic events	Bridging: 19/1691 (1.1%) No bridging: 32/3493 (0.9%) OR 0.80 (0.42 to 4.54) NS	

Table 35

18.2 **RCTs**

Bridging with LMWH versus placebo after interruption of warfarin in AF

Study details	n/Population	Comparison	Outcomes		Methodological
Douketis 2015(84) BRIDGE Design: RCT DB PG non-inferiority for primary efficacy outcome superiority for primary safety outcome Duration of follow-up: 30 days after the procedure	n= 1884 Mean age: 72 Mean $CHADS_2$ score: 2.3 $CHADS_2$ 2-3/ 63.4% $CHADS_2$ 4-6/ 13.8% Prior stroke/TIA: 18% Diabetes mellitus: 41% Congestive heart failure: 32% Hypertension: 87% mean CrCL: 88 ml/min previous use of VKA: 100% Inclusion: - 18 years of age or older - chronic AF or flutter - received warfarin for at least 3 months - INR therapeutic range of 2.0 to 3.0	bridging LMWH (dalteparin 100 IU/kg body weight) vs SC placebo Remarks Bridging or placebo started from 3 days – 24 hours before the procedure and then for 5 to 10 days after the procedure. Warfarin was stopped 5 days before and resumed within 24 hours after the procedure.	Adherence		RANDO: Adequate (computer response system) ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes POWER CALCULATION: Yes FOLLOW-UP: Lost-to follow-up: 0.3% Drop-out and Exclusions: 3.5% • Described: yes • Balanced across groups: yes ITT: Yes SELECTIVE REPORTING: no Sponsor: grants from the National Heart, Lung, and Blood Institute
			Number of doses taken	Before procedure: 5.0 After procedure: 16.0	
			TTR	not reported	
			Adherence to study-drug protocol (= administration of 100% of protocol-specified doses of study drug)	Before procedure: 86.5% After procedure: 96.5%	
			Efficacy		
			Arterial thromboembolism (Stroke, systemic embolism, or TIA) (PO)	Bridging: 3/895 (0.3%) Placebo: 4/918 (0.4%) MD: 0.1% (95%CI -0.6 to 0.8) p=0.01 for non-inferiority p=0.73 for superiority Placebo is non-inferior to bridging As-treated analysis: Bridging: 3/847 (0.4%) Placebo: 3/875 (0.3%) MD: 0.0% (95%CI -0.7 to 0.7) p=0.0006 for non-inferiority	
			Death	Bridging: 4/895 (0.4%) Placebo: 5/918 (0.5%) p = 0.88 for superiority NS	

	- undergoing an elective invasive procedure requiring interruption of warfarin therapy - at least one $CHADS_2$ stroke risk factor <u>Exclusion</u> - mechanical heart valve - stroke, systemic embolism or TIA within previous 12 weeks - Creatine clearance <30ml/min - platelet count $<100x10^3/mm^3$ - planned cardiac, intracranial or intraspinal surgery		Myocardial infarction	Bridging: 14/895 (1.6%) Placebo: 7/918 (0.8%) p = 0.10 for superiority NS
			Deep-vein thrombosis (symptomatic/ non-symptomatic?)	Bridging: 1/895 (0.1%) Placebo: 0/918 (0%) p = 0.25 for superiority NS
			Pulmonary embolism	Bridging: 1/895 (0.1%) Placebo: 0/918 (0%) p = 0.25 for superiority NS
			Safety	
			Major bleeding (PO)	Bridging: 1/895 (3.2%) Placebo: 0/918 (1.3%) RR: 0.41 (95%CI 0.20 to 0.78) SS in favour of placebo p = 0.005 for superiority
			Minor bleeding	Bridging: 187/895 (20.9%) Placebo: 110/918 (12%) p<0.001 for superiority **SS in favour of placebo**

Table 36

Bridging versus no bridging in AF patients with interruption of warfarin

Reference	n	Outcome	Results: bridging vs no bridging OR (95%CI)	Remarks
Douketis 2014(85) RE-LY SUBSTUDY	1415	Major Bleeding	Bridging:26/383 (6.8%) No bridging: 16/1032 (1.6%) **OR 4.62 (2.45 to 8.72)** **p<0.001** **SS in favour of no bridging**	Prespecified analysis: YES Stratified at randomization: NO Included: Patients with NVAF with a first interruption of warfarin because of an elective surgery/procedure Excluded: - patients having an urgent surgery procedure, surgery/procedure not specified - without interruption before a procedure - an event (major bleeding, any thromboembolism) in the 30 days before the surgery/procedure Bridging defined as: peri-operative use of LMWH or unfractioned heparin Period of observation: 7 days before procedure up until 30 days after Outcomes adjusted for age, sex, CHADS2 score, creatinine clearance, surgery/procedure type (major or minor)
		Stroke and systemic embolism	Bridging: 2/383 (0.5%) No bridging: 2/1032 (0.2%) OR 2.70 (0.38 to 19.3) p= 0.321 NS	
		Any thrombo-embolism	Bridging: 7/383 (1.8%) No bridging: 3/1032 (0.3%) **OR 6.39 (1.64 to 24.8)** **p= 0.007** **SS in favour of no bridging**	

Table 37

19 Evidence tables. Switching

END-OF-TRIAL TRANSITION PLAN for edoxaban ENGAGE AF TIMI (Ruff 2014(88))

1) selection of the oral anticoagulant (VKA or an DOAC) by the treating physician and patient
2) a 14-day transition kit of modified-dose edoxaban for patients randomized to edoxaban (30 mg once daily for patients in whom the edoxaban dose was not reduced before the end-of-trial visit and 15 mg once daily for patients in whom the edoxaban dose had been reduced before the end-of-trial visit, regardless of randomized edoxaban drug assignment) or matching placebo for patients randomized to warfarin
3) early and frequent INR testing (>=3 tests during the first 2 weeks)
4) use of a VKA titration algorithm
At the end-of-trial visit, INR was measured with a point-of-care device and a prescription for the
intended open-label anticoagulant (VKA or DOAC) was provided. The transition kit was provided only to patients who were transitioning to open-label VKA and was continued until an open-label INR >=2 was achieved or until day 14 (whichever occurred first). If the INR was <2.0 during the transition period, the patient continued on the transition kit (up to 14 days) with aggressive titration of open-label VKA dose as recommended by the protocol algorithm.
INR measurements were mandated at days 4 to 6, 7 to 10, and 11 to 14 and as often as needed
through day 30 until the patient was confirmed to be in therapeutic range. Open-label INR testing was not allowed on days 1 to 3 to avoid unblinding so as to maintain the integrity of the trial.
Patients transitioning to a DOAC were not given a transition kit.

Results
Of the 13,642 patients taking the blinded study drug at the end of the trial, 9,304 (68.2%) were transitioned to open-label VKA and 4,258 patients (31.2%) to an DOAC.
In the 13 642 patients, there were 21 strokes evenly distributed across the 3 randomized treatment arms: warfarin 7 (1.90%/year), edoxaban high dose 7 (1.89%/year), edoxaban low dose 7 (1.85%/year). Major bleeding was also similar across the 3 treatment arms: warfarin 11 (2.98%/year), edoxaban high dose 10 (2.69%/year), edoxaban low dose 18 (4.76%/year).
For patients transitioned to VKA and patients transitioned to a DOAC, rates of stroke/SE and major bleeding were also similar across the 3 treatment arms, with no statistically significant differences observed.

Methodological remarks
Observational data from a randomized trial (trial was not designed to test transition plan – no comparator group)

20 Evidence tables. Adherence and persistence in atrial fibrillation. Observational studies

20.1 Adherence rates and persistence rates in atrial fibrillation (Europe)

Ref Study type	Setting Population	number of participants	Endpoints	Results
Forslund 2016(93) prospective cohort	**Sweden** Administrative health data register – Stockholm region NVAF CHA2DS2VASc scores 2–9, First claims of warfarin, dabigatran, rivaroxaban, apixaban (additional analysis of patients with 9months without previous OAC) mean age +/+ 75y age >80y >30% dabigatran users SS younger - **follow up 1 y**	17.741 (14.426 OAC naïve)	**Persistence** **(alive during follow-up and claiming treatment)**	**1 year**, all patients Warfarin 85.0 % Apixaban 85.9 % Dabigatran 74.4 % Rivaroxaban 77.4 % **An analysis in OAC naïve patients revealed almost identical results** warfarin vs apixaban NS Warfarin vs dabigatran p<0.0001 Warfarin vs rivaroxaban p<0.0001 apixaban vs dabigatran p<0.0001 apixaban vs rivaroxaban p=0.004 rivaroxaban vs dabigatran NS Factors significantly associated with lower persistence were female sex and number of drugs, while initiation of treatment from primary care was associated with higher persistence Note: apixaban relatively new in this population
			Percentage of days covered (PDC)>80%	Apixaban 93.5 % Dabigatran 92.0 % Rivaroxaban 95.7 % **SS more adherence with rivaroxaban vs dabigatran p<0.001** NS difference for Rivaroxaban vs apixaban p=0.14
			PDC=100%	apixaban 71.4 % dabigatran 72.7 % rivaroxaban 79.7 %

Ref Study type	Setting Population	number of participants	Endpoints	Results
				Full adherence was significantly higher with rivaroxaban than with dabigatran (p < 0.001) or apixaban (p = 0.004).
Johnson 2016(94) Retrospective cohort	**UK** General practice records (clinical practice research datalink) - newly diagnosed NVAF - OAC naïve (subgroup) -75% VKA users - median 75y - **follow up max 22 m** History of stroke and bleeding was the highest among apixaban (23.7% and 31.6%) and lowest among VKA patients (15.9% and 27.5%)	13.089 OAC naieve dabigatran and apixaban <1000	**Persistence** (No discontinuation (break >60 d) or switch during follow up)	VKA 70.6% apixaban 82.8% dabigatran 62.5% rivaroxaban 67.6% 2/3 of nonpersistence due to discontinuation 1/3 due to switch non-persistence total follow up time VKA vs apixaban HR 0.92 (95% CI 0.68 to1.23) **dabigatran vs apixaban HR 1.67 (1.20 to 2.32)** **rivaroxaban vs apixaban HR 1.41 (1.02 to1.93)** **SS more non-persistence with dabigatran and rivaroxaban vs apixaban** non-persistence at 2 months **VKA vs apixaban HR 0.33 (0.22 to 0.48)** **dabigatran vs apixaban HR 1.65 (1.08 to 2.52)** **SS less non-persistence with VKA and SS more with dabigatran compared to apixaban** non-persistence after 2 months **VKA vs apixaban HR 1.70 (1.08 to 2.66)** **and dabigatran vs apixaban HR 2.10 (1.30 to 3.41)** **SS more non-persistence with VKA and with dabigatran compared to apixaban.** note: very low number of apixaban users, especially at longer follow up times

Ref Study type	Setting Population	number of participants	Endpoints	Results
(Martinez 2016 (95))	**UK** General practice records (clinical practice research datalink) - newly diagnosed NVAF - OAC naïve - OAC commenced <90d after incident AF - mean age 74.2 - DOAC users more likely to be men, less likely to be hypertensive and more likely to have previous stroke/SE	13.221	**Persistence** (based on pattern of repeat prescriptions) (30 day gap allowed) (switching was considered non-persistence)	VKA 63.6 % DOAC 79.2 % (p< 0.0001) note: same database as Johnson 2016 with overlapping time periods

Ref Study type	Setting Population	number of participants	Endpoints	Results
Lamberts 2017(36) retrospective cohort	-**Denmark** -National registries -NVAF - newly initiated OAC (no OAC <6 months) -mean age 73y aug 2011 – dec 2015 apixaban and rivaroxaban initiators were older and less often male, with higher CHA2DS2-VASc and HAS-BLED scores, compared to dabigatran and warfarin initiators - mean follow-up 403 days	54.321	**Non-persistence** (>30 days without repeat prescription = treatment gap for more than 30 days) (Note: switch of treatment within 30 days was not considered to be non-persistence)	OAC 27.2% experienced a break of at least 30 days non-persistence at +/- 3 y (nonswitch users) warfarin 60% apixaban 15% dabigatran 30% rivaroxaban 15% non- persistence **dabigatran vs apixaban HR 1.45 [1.33–1.59]** **warfarin vs apixaban HR 1.22 [1.12–1.33]** **rivaroxaban vs apixaban HR, 1.07 [0.96–1.20]** **SS higher non-persistence with dabigatran and warfarin compared to apixaban** Several sensitivity analyses note: low number of apixaban users at 3y
Gorst-Rasmussen 2015(97) retrospective cohort, single arm	-**Denmark** -National databases -newly diagnosed AF -Dabigatran initiated as first anticoagulant, **and remaining on dabigatran for 1 year** -41.5%>75y	2960	**Proportions of days covered** (PDC)	1y dabigatran 83.9% (SD 27.7) Older people more adherent than younger people. Cha2DS2-VASc ≥2 more adherent than lower scores. History of stroke more adherent than no history of stroke Females more adherent than males High number of cardiovascular prescriptions more adherent than low number of cardiovascular prescriptions
			PDC>80%	dabigatran 76.8%
			Gaps (≥ 1 day)	1.4 gaps/year

Ref Study type	Setting Population	number of participants	Endpoints	Results
Beyer-Westendorf 2016(96) retrospective cohort	**Germany** Primary care practices electronic medical records database NVAF OAC naïve mean age 74y (VKA was predominantly phenprocoumon) DOAC patients more likely to be privately insured	7265(180d) 3785(360d)	**Persistence** (refill gaps of ≤60 days were allowed) (for VKA a main daily dosage of 3mg phenprocoumon was used)	at 180 days rivaroxaban 66.0% dabigatran 60.3% VKA 58.1% **P< 0.001 for rivaroxaban vs VKA** **P < 0.008 for rivaroxaban vs dabigatran** (restart after more than 60 days: rivaroxaban 4.9%, dabigatran 4.0%) Persistence was positively associated with male gender, statutory health insurance, presence of diabetes mellitus, rivaroxaban treatment, and concomitant cardiovascular drug use at 360 days rivaroxaban 53.1% dabigatran 47.3% VKA 25.5% **p< 0.001 for rivaroxaban and dabigatran vs VKA** 14.1% rivaroxaban patients and 11.2% dabigatran patients restarted their index OAC after a gap of more than 60 days Note: no information on switching
			Medication possession ratio (MPR) (proportion of days of medication supplied within a defined time period)	at 180 days High adherence (MPR≥0.80) rivaroxaban 61.4% dabigatran 49.5% rivaroxaban vs dabigatran p<0.001 note: low number of patients (<1000) on dabigatran and rivaroxaban at 360 days

20.2 Impact of adherence or persistence on clinical outcomes in atrial fibrillation

Ref Study type	Setting Population	number of participants	Comparison	Results
YAO 2016 (98) Retrospective cohort	**- USA** - Insurance database - NVAF - initiated warfarin, dabigatran, rivaroxaban, or apixaban - follow-up median 1.1y	**64.661**	not taking anticoagulation >/=1 month versus <1 week	CHA2DS2-VASc score >/=4 risk of stroke when not taking antico for 1-3 months: HR 1.96 3-6 months: HR 2.64 >/=6 months: HR 3.66 (all P<0.001) CHA2DS2-VASc score 2 or 3 risk of stroke when not taking antico for >/=6 months: HR 2.73, P<0.001 In these patients with CHA2DS2-VASc score >/=2, nonadherence was not associated with intracranial hemorrhage. CHA2DS2-VASc score 0 or 1, time not taking anticoagulation was not associated with stroke, but not taking anticoagulation >/=3 months was associated with a significant reduction of bleeding see figure below

Table 5. Survival Analysis, Ischemic Stroke, and Systemic Embolism as the Outcome

Time Not Taking OAC	Hazard Ratio (95% CI)
CHA_2DS_2-VASc score 0 or 1	
<1 wk	Ref
1 wk to 1 mo	0.87 (0.23–3.23)
1–3 mo	1.57 (0.55–4.44)
3–6 mo	1.76 (0.58–.37)
≥6 mo	1.53 (0.60–3.91)
CHA_2DS_2-VASc score 2 or 3	
<1 wk	Ref
1 wk to 1 mo	1.08 (0.64–1.82)
1–3 mo	1.21 (0.74–2.00)
3–6 mo	1.63 (0.96–2.78)
≥6 mo	2.73* (1.76–4.23)
CHA_2DS_2-VASc score ≥4	
<1 wk	Ref
1 wk to 1 mo	1.21 (0.91–1.60)
1–3 mo	1.96* (1.48–2.60)
3–6 mo	2.64* (1.93–3.61)
≥6 mo	3.66* (2.68–5.01)

OAC, oral anticoagulation; CHA_2DS_2-VASc, risk based on the presence of congestive heart failure, hypertension, age ≥75 y, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, sex category. Age, sex, race, annual household income, residence region, HAS-BLED, risk stratification scheme to estimate baseline risk of major hemorrhage based on the presence of hypertension, abnormal renal function, abnormal liver function, stroke, bleeding history or predisposition, age > 65 y, antiplatelet or nonsteroidal anti-inflammatory drug use and alcoholism, Charlson–Deyo comorbidity index, index medication, and switch to nonindex medication were adjusted.
*P<0.001.

Figure 1. From Yao 2016(98) Survival analysis: ischemic stroke and systemic embolism

Ref Study type	Setting Population	Number of participants	Comparison	Results
Shore 2014 (99) Retrospective cohort	**USA** Veterans NVAF newly initiated dabigatran 1st year Compared to non-adherent patients, adherent patients were more likely to be older, white and less likely to have depression, drug abuse, alcohol abuse, clopidogrel use	**5.376**	**Non-adherence (PDC<80%)** **vs** **adherence (PDC >= 80%)**	**combined all-cause mortality and stroke** **HR 1.13 (95% CI 1.07–1.19) per 10% decrease in PDC** **non-fatal bleeding** NS **myocardial infarction** NS

20.3 Impact of TTR on clinical outcomes in atrial fibrillation

Reference	subgroup cTTR	Outcome	Results DOAC vs warfarin	Remarks
Carmo 2017(103) MA of 4 pivotal DOAC trials in AF	cTTR < 60%	Stroke/SE	0.79 [0.68–0.90]	Prespecified analysis: NO stratified at randomization: NO Baseline characteristics of different subgroups: NR For mortality: **also SS interaction when comparing TTR<70% vs TTR>=70% (lower mortality with DOAC when cTTR <70%; similar mortality when cTTR>=70%)** note: - cTTR does not represent individual patient TTR - "Selected thresholds were *roughly* based on the cut-offs of cTTR quartiles whereby they only represent approximate values." - High heterogeneity for bleeding results - Rivaroxaban data not included in CTTR<70% vs >=70% analyses - Mortality analyses did not include edoxaban and rivaroxaban
	cTTR ≥ 60%	Stroke/SE	0.89 [0.79–1.01]	
			P for interaction 0.180	
	cTTR < 65%	Stroke/SE	0.77 [0.68–0.87]	
	cTTR ≥ 65%	Stroke/SE	0.89 [0.77–1.02]	
			P for interaction 0.135	
	cTTR < 70%	Stroke/SE	0.79 [0.72–0.88]	
	cTTR ≥ 70%	Stroke/SE	1.00 [0.82–1.23]	
			P for interaction 0.042	
	cTTR < 60%	Major/CRNM bleeding	0.67 [0.54–0.83]	
	cTTR ≥ 60%	Major/CRNM bleeding	0.83 [0.68–1.00]	
			P for interaction 0.150	
	cTTR < 65%	Major/CRNM bleeding	0.74 [0.63–0.86]	
	cTTR ≥ 65%	Major/CRNM bleeding	0.85 [0.69–1.03]	
			P for interaction 0.288	
	cTTR < 70%	Major/CRNM bleeding	0.71 [0.62–0.82]	
	cTTR ≥ 70%	Major/CRNM bleeding	0.84 [0.64–1.11]	
			P for interaction 0.271	

Ref Study type	Setting Population	Number of participants	Endpoints	Results
Bjorck 2016(104) retrospective cohort	**-Sweden** -AF and antico registries -Specialized centers and primary care - starting warfarin therapy due to NVAF - study duration: max 5 y Patients with >= iTTR 70% had a higher prevalence of stroke or transient ischemic attack at baseline compared with patients with an iTTR < 70%,with almost similar mean CHA2DS2-VASc scores in the 2 groups owing to **more comorbidities in the latter subgroup**	40.449	'Complications'	analysis according to iTTR (<70% vs >=70%) see below **SS lower rate of mortality, major bleeding, any thromboembolism with iTTR>=70% compared to iTTR<70%**
				analysis according to INR variability : high vs low see below **SS lower rate of mortality, major bleeding, any thromboembolism with low INR variability compared to high INR variability**
				For patients with iTTR 70% or greater, the level of INR variability did not alter event rates.
Note. - Observational study. Causality cannot be inferred - Reliability/completeness of data (especially primary care cohort) e.g. reason for warfarin, concomitant diseases - no adjustments for confounders seem to have been made?				

Table 3. Warfarin Treatment Complications in Relation to INR Control[a]

	iTTR				INR Variability			
	<70% (n = 16 703)		≥70% (n = 22 185)		High (n = 21 021)		Low (n = 19 428)	
Characteristic	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)
All-cause mortality	752	4.35 (4.03-4.66)	602	1.29 (1.18-1.39)	923	2.94 (2.75-3.14)	510	1.50 (1.37-1.63)
Any major bleeding	659	3.81 (3.51-4.11)	752	1.61 (1.49-1.73)	955	3.04 (2.85-3.24)	502	1.47 (1.34-1.61)
Intracranial	124	0.72 (0.59-0.85)	157	0.34 (0.28-0.39)	160	0.51 (0.43-0.59)	128	0.38 (0.31-0.44)
Gastrointestinal tract	216	1.26 (1.09-1.43)	260	0.56 (0.49-0.63)	326	1.05 (0.93-1.16)	168	0.50 (0.42-0.57)
Other	368	2.17 (1.94-2.40)	395	0.85 (0.77-0.94)	550	1.79 (1.63-1.94)	241	0.71 (0.62-0.81)
Any thromboembolism	763	4.41 (4.09-4.73)	1 107	2.37 (2.23-2.51)	1 093	3.48 (3.27-3.69)	839	2.46 (2.29-2.63)
Arterial	425	2.52 (2.28-2.76)	645	1.41 (1.30-1.53)	605	1.98 (1.82-2.14)	502	1.51 (1.38-1.65)
Myocardial infarction	323	1.90 (1.69-2.11)	449	0.98 (0.88-1.07)	471	1.53 (1.39-1.67)	323	0.96 (0.85-1.07)
Venous	41	0.24 (0.16-0.31)	43	0.09 (0.06-0.12)	51	0.16 (0.12-0.21)	37	0.11 (0.07-0.14)

Abbreviations: INR, international normalized ratio; iTTR, individual time in therapeutic range.

[a] Results presented in total numbers during the study period and complication per treatment year. High INR variability indicates INR variability greater than or equal to mean INR variability; low INR variability indicates less than mean INR variability.

Figure 2. From Bjorck 2016(104)

21 Evidence tables. Adherence and persistence in the prevention of recurrent VTE. Observational studies

21.1 Adherence rates and persistence rates in the prevention of recurrent VTE (Europe)

ref design	country population	n	Endpoint	Results
Vora 2016 (105) SR + MA of observational studies search date may 2015	**12 observational studies (USA=5, Germany=5, Canada =1, UK=1)** VTE >18y treatment >=3m DOAC or VKA **see below for 1 European study with adequate size (n>1 000)**	71 969 58 940 68 235	Persistence 3m Persistence 6m Persistence 12m	83% (95% CI 78–87) 62% (95%CI 58-66) 31% (95%CI 22-40) note: high heterogeneity - Definition of persistence varied considerably: prespecified gap (>37 days to 90 days) or premature discontinuation of treatment or not specified - Heterogeneity explored but no explanation - Treatment type did not contribute significantly to heterogeneity at 3 months, but it did at 6 months and at 12 months (but very low number of patients on DOAC)
Cohen 2013 (106) (from: Vora 2016 (105)) Retrospective cohort note: conference abstract	**UK** CPRD database (clinical practice research datalink) mean age 63.5 VTE VKA use	8 504 (7 676 in analysis)	Persistence (no treatment gap >56 days)	VTE (complete cohort) 3m 77.4% 6m 50.3% 12m 11.4%
		Subgroup (3 130)		Provoked VTE (noncancer) 3m 76.8% 6m 49.0% 12m 10.3%
		Subgroup (4 546)		Unprovoked VTE 3m 77.8% 6m 51.1% 12 m 11.9%

21.2 Impact of non-adherence or non-persistence on clinical outcomes in the prevention of recurrent VTE

Ref Design	Country Population	n	Comparison	Results
Deitelzweig 2010(107) Retrospective cohort (from: Vora 2016 (105))	**USA** -Integrated Healthcare Information -VTE -VKA, at least 2 prescriptions follow-up for up to 1 y	8 380	**Discontinuation vs no discontinuation**	**VTE recurrence** **HR 1.05 (95%CI 1.04, 1.07)** **p<0.0001** **Major bleeding** **HR 0.93 (95% CI 0.88, 0.99);** **P=0.013**
			Discontinuation < 3 m vs >=3m	**VTE recurrence** **total 10.9% of patients** **HR 1.45 (95% CI 1.18 to 1.77)** **p=0.0003** **Major bleeding** **HR 1.86 (95% CI 1.18, 2.92)** **P=0.007**
Chen 2013(108) Retrospective cohort (From: Vora 2016 (105)**)**	**USA** -Marketscan database -VTE (DVT or PE) -**High- risk patients** (patients with cancer, or noncancer patients who did not have reversible risk factors during the 3-month period prior to the index date) VKA Compliant users, defined by PDC ≥ 0.8, were older than non- compliant users (63.3 years vs. 60.6 years, P < 0.001) Patients who used warfarin	8 040		**2.2% of patients experienced a recurrent VTE following the 1-year warfarin assessment period**
			Discontinuation (<12 m) vs no discontinuation	**VTE recurrence <u>after</u> 12 month warfarin assessment period** 2.5% vs 1.8% **HR 1.48 (95% CI, 1.09–2.01)** **SS** **Sensitivity analysis:** **VTE recurrence within first 12 m + after 12 m** **HR 1.43 (95%CI 1.06-1.92)** **SS**
			Non-compliant (PDC<80%) vs compliant (PDC>=80%)	**VTE recurrence <u>after</u> 12 month warfarin assessment period** **2.5% vs 0.9%** **HR 3.01 (95% CI 1.28-4.97)** **SS** **Sensitivity analysis : VTE recurrence within first 12 m + after 12 m**

	continuously were significantly older than those who discontinued (62.5 years vs. 60.0 years, P < 0.001). Sex distribution was significantly different between the compliant and noncompliant groups, with compliant groups containing a higher proportion of males. 1 y after index date = warfarin assessment period + mean 1 year follow-up after the warfarin assessment period			**HR 2.58 (95%CI 1.62-4.11)** **SS**
			Non-compliant (MPR<80%) vs compliant (MPR>=80%)	**VTE recurrence <u>after</u> 12 month warfarin assessment period** **2.9% vs 1.9%** **HR = 1.60 (95% CI 1.18-2.16)** **SS** **Sensitivity analysis : VTE recurrence within first 12 m + after 12 m** **HR 1.58 (95% CI 1.17 to 2.12)** **SS**

PDC was calculated as the total number of days covered with warfarin supply divided by 365 days.
MPR was calculated as the number of days of supply dispensed during the 1-year warfarin utilization assessment period divided by the number of days between the first and last prescription refill

These 2 measures were chosen because they use different assumptions when evaluating compliance. PDC assumes expected length of therapy to be a full year and considers discontinuation in its calculation. On the other hand, MPR measures only the compliance between the first and last observed refills. It does not consider the time once therapy was discontinued
.

22 Evidence tables. Improving adherence

22.1 Educational and behavioural interventions

Ref Type of work	N/ studies n/ participants	comparison	Outcome	Results
Wong 2013(109) SR + MA Search date feb 2012	4/545 Not only AF VKA	supplemental patient education vs usual care	TTR	MD 2.02% 95% CI - 2.81 to 6.84 NS GRADE very low-quality evidence

22.2 Self-monitoring and self-management of oral anticoagulation (point of care testing)

Ref Type of work	N/ studies n/ participants	comparison	Outcome	Results
Cochrane Heneghan 2016(110) SR + MA Search date july 2015	16/?	**Self-monitoring or self-management vs usual care**	% INR measurements within target range	All studies but one reported improvements in the self-monitoring or self-management groups; six were statistically significant Improvements ranged from 3% to 21%
	18/?		% TTR	Seven studies reported a significant improvement in the time in therapeutic range in the self-monitoring or self-management groups
	18/7594		Thromboembolic events	RR 0.58 (0.45 to 0.74) SS in favour of self-monitoring/self-management GRADE: moderate quality of evidence
			Mortality	While self-management caused a reduction in all-cause mortality (RR 0.55, 95% CI 0.36 to 0.84; participants = 3058; studies = 8); self-monitoring did not (RR 0.94, 95%CI 0.78 to 1.15; participants = 3300; studies = 3) GRADE: moderate quality of evidence
			Major hemorrhage	NS GRADE: moderate quality of evidence

Note: older SRs (e.g. Sharma 2015(111)) reach roughly the same conclusions as Cochrane Heneghan 2016.
Point of care testing (self-management, self-testing or testing with POC device by health care professional) was also the subject of a 2009 KCE report (Gailly 2009 (112))

Ref Type of work	N/ studies n/ participants	comparison	Outcome	Results
Gailly 2009 (112) Health technology assessment (HTA) SR search date jan 2009	2 HTA 24 primary studies	POC versus usual care	TTR	not reported
			Thromboembolic events	**OR 0.43** **95% CI 0.32 to 0.58** **both self-management and self-testing are SS compared to usual care** moderate quality of evidence
			Mortality	**OR 0,59** **95% CI 0.46 to 0.74** Self management SS, but self-testing NS compared to usual care moderate quality of evidence
			Major bleeding	NS moderate quality of evidence
			Patient satisfaction scores, such as overall satisfaction, pain, distress	**in favour of POC**, compared with previous usual care with venous punction (low quality of evidence)
			Criteria for candidates	personal willingness; physical capacity of self testing (motor skills, eyesight) and capacity to complete training and succeed in accurately perform an INR test, manage of quality control issues, use of algorithm and adjustment of dosage, and document INR results and adverse events (low quality of evidence). The percentage of patients able to carry out PST or PSM was estimated to 24% in Canada and to 14% in UK .

22.3 Pharmacist – managed anticoagulation

Ref Type of work	N/ studies n/ participants	Comparison	Outcome	Results
Manzoor 2017(113) SR + MA search date may 2017	3 RCT (22 non-RCT)	Pharmacist-managed anticoagulation services (PMAS) compared with routine medical care (RMC)	Quality of anticoagulation control	Quality of anticoagulation control was better in the PMAS group compared with RMC in 2/3 RCTs
			Hard endpoints	Lower bleeding and thromboembolic events, mainly in non-RCTs

23 Appendix: Search strategies

23.1 Atrial fibrillation – DOAC

(atrial fibrillation[Title/Abstract] OR "Atrial Fibrillation"[Mesh])
AND
(non vitamin K oral anticoagulant*[Title/Abstract] OR new oral anticoagulant*[Title/Abstract] OR direct oral anticoagulant*[Title/Abstract] OR indirect factor Xa inhibit*[TIAB] OR direct thrombin inhibitor*[TIAB] OR dabigatran[TIAB] OR apixaban[TIAB] OR rivaroxaban[TIAB] OR edoxaban[TIAB] OR NOAC[TIAB] OR DOAC[TIAB] OR "Dabigatran"[Mesh] OR "edoxaban" [Supplementary Concept] OR "Rivaroxaban"[Mesh] OR "apixaban" [Supplementary Concept] OR "Factor Xa Inhibitors" [Pharmacological Action] OR "Antithrombins" [Pharmacological Action])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2016/01/01"[Date - Publication] : "2017/07/01"[Date - Publication])

23.2 Venous thromboembolism – DOAC

("Venous Thromboembolism"[Mesh] OR Thromboembolism[TIAB] OR Venous Thrombosis[TIAB] OR vein thrombosis[TIAB] OR dvt[TIAB] OR vte[TIAB] OR Pulmonary Emboli*[TIAB])
AND
(non vitamin K oral anticoagulant*[Title/Abstract] OR new oral anticoagulant*[Title/Abstract] OR direct oral anticoagulant*[Title/Abstract] OR indirect factor Xa inhibit*[TIAB] OR direct thrombin inhibitor*[TIAB] OR dabigatran[TIAB] OR apixaban[TIAB] OR rivaroxaban[TIAB] OR edoxaban[TIAB] OR NOAC[TIAB] OR DOAC[TIAB] OR "Dabigatran"[Mesh] OR "edoxaban" [Supplementary Concept] OR "Rivaroxaban"[Mesh] OR "apixaban" [Supplementary Concept] OR "Factor Xa Inhibitors" [Pharmacological Action] OR "Antithrombins" [Pharmacological Action])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2015/01/01"[Date - Publication] : "2017/07/01"[Date - Publication])

23.3 Venous thromboembolism VKA vs LMWH

("Venous Thromboembolism"[Mesh] OR Thromboembolism[TIAB] OR Venous Thrombosis[TIAB] OR vein thrombosis[TIAB] OR dvt[TIAB] OR vte[TIAB] OR Pulmonary Emboli*[TIAB])
AND
(vitamin K antagonist*[TIAB] OR acenocoumarol[TIAB] OR phenprocoumon[TIAB] OR warfarin[TIAB] OR "4-Hydroxycoumarins"[Mesh])
AND
("Heparin, Low-Molecular-Weight"[Mesh] OR LMWH[TIAB] OR low molecular weight heparin*[TIAB] OR dalteparin[TIAB] OR Enoxaparin[TIAB] OR nadroparin[TIAB] OR tinzaparin[TIAB])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2014/02/01"[Date - Publication] : "2017/07/01"[Date - Publication])

23.4 VTE duration of treatment

("Venous Thromboembolism"[Mesh] OR Thromboembolism[TIAB] OR Venous Thrombosis[TIAB] OR vein thrombosis[TIAB] OR dvt[TIAB] OR vte[TIAB] OR Pulmonary Emboli*[TIAB])
AND
(non vitamin K oral anticoagulant*[Title/Abstract] OR new oral anticoagulant*[Title/Abstract] OR direct oral anticoagulant*[Title/Abstract] OR indirect factor Xa inhibit*[TIAB] OR direct thrombin inhibitor*[TIAB] OR dabigatran[TIAB] OR apixaban[TIAB] OR rivaroxaban[TIAB] OR edoxaban[TIAB] OR NOAC[TIAB] OR DOAC[TIAB] OR "Dabigatran"[Mesh] OR "edoxaban" [Supplementary Concept] OR "Rivaroxaban"[Mesh] OR "apixaban" [Supplementary Concept] OR "Factor Xa Inhibitors" [Pharmacological Action] OR "Antithrombins" [Pharmacological Action]) OR (vitamin K antagonist*[TIAB] OR acenocoumarol[TIAB] OR phenprocoumon[TIAB] OR warfarin[TIAB] OR "4-Hydroxycoumarins"[Mesh])
AND
(Duration[TIAB] OR long-term[TIAB] OR continue*[TIAB] OR short-term[TIAB] OR extended[TIAB])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2013/10/01"[Date - Publication] : "2017/07/01"[Date - Publication])

23.5 Switching DOAC – VKA

(atrial fibrillation[Title/Abstract] OR "Atrial Fibrillation"[Mesh] OR "Pulmonary Embolism"[Mesh] OR "Venous Thromboembolism"[Mesh] OR Thromboembolism[TIAB] OR Venous Thrombosis[TIAB] OR vein thrombosis[TIAB] OR dvt[TIAB] OR vte[TIAB] OR Pulmonary Emboli*[TIAB])
AND
(non vitamin K oral anticoagulant*[Title/Abstract] OR new oral anticoagulant*[Title/Abstract] OR direct oral anticoagulant*[Title/Abstract] OR indirect factor Xa inhibit*[TIAB] OR direct thrombin inhibitor*[TIAB] OR dabigatran[TIAB] OR apixaban[TIAB] OR rivaroxaban[TIAB] OR edoxaban[TIAB] OR NOAC[TIAB] OR DOAC[TIAB] OR "Dabigatran"[Mesh] OR "edoxaban" [Supplementary Concept] OR "Rivaroxaban"[Mesh] OR "apixaban" [Supplementary Concept] OR "Factor Xa Inhibitors" [Pharmacological Action] OR "Antithrombins" [Pharmacological Action])
AND
(change[Title/Abstract] OR changeing*[Title/Abstract] OR switch[Title/Abstract] OR switching[Title/Abstract])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])

23.6 Bridging

(non vitamin K oral anticoagulant*[Title/Abstract] OR new oral anticoagulant*[Title/Abstract] OR direct oral anticoagulant*[Title/Abstract] OR indirect factor Xa inhibit*[TIAB] OR direct thrombin inhibitor*[TIAB] OR dabigatran[TIAB] OR apixaban[TIAB] OR rivaroxaban[TIAB] OR edoxaban[TIAB] OR NOAC[TIAB] OR DOAC[TIAB] OR "Dabigatran"[Mesh] OR "edoxaban" [Supplementary Concept] OR "Rivaroxaban"[Mesh] OR "apixaban" [Supplementary Concept] OR "Factor Xa Inhibitors" [Pharmacological Action] OR "Antithrombins" [Pharmacological Action]) OR (vitamin K antagonist*[TIAB] OR acenocoumarol[TIAB] OR phenprocoumon[TIAB] OR warfarin[TIAB] OR "4-Hydroxycoumarins"[Mesh])

AND
(Periprocedur* [TIAB] OR peri-procedur*[TIAB] OR perioperativ*[TIAB] OR peri-operativ* [TIAB] OR bridging[TIAB] OR "Perioperative Period"[Mesh])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB])
AND
("2014/06/01"[Date - Publication] : "2017/07/01"[Date - Publication])

23.7 DOAC vs DOAC cohort studies

(non vitamin K oral anticoagulant*[Title/Abstract] OR new oral anticoagulant*[Title/Abstract] OR direct oral anticoagulant*[Title/Abstract] OR indirect factor Xa inhibit*[TIAB] OR direct thrombin inhibitor*[TIAB] OR dabigatran[TIAB] OR apixaban[TIAB] OR rivaroxaban[TIAB] OR edoxaban[TIAB] OR NOAC[TIAB] OR DOAC[TIAB] OR "Dabigatran"[Mesh] OR "edoxaban" [Supplementary Concept] OR "Rivaroxaban"[Mesh] OR "apixaban" [Supplementary Concept] OR "Factor Xa Inhibitors" [Pharmacological Action] OR "Antithrombins" [Pharmacological Action]) AND
(atrial fibrillation[Title/Abstract] OR "Atrial Fibrillation"[Mesh] OR "Pulmonary Embolism"[Mesh] OR "Venous Thromboembolism"[Mesh] OR Thromboembolism[TIAB] OR Venous Thrombosis[TIAB] OR vein thrombosis[TIAB] OR dvt[TIAB] OR vte[TIAB] OR Pulmonary Emboli*[TIAB])
AND
(mortality[Title/Abstract] OR death[Title/Abstract] OR thromboembolism[Title/Abstract] OR stroke[Title/Abstract] OR bleeding[Title/Abstract] OR VTE[Title/Abstract] OR emboli*[Title/Abstract] OR hemorrhage[Title/Abstract])
AND
("Cohort Studies"[Mesh] OR Cohort*[Title/Abstract] OR longitudinal[Title/Abstract] OR prospective[Title/Abstract] OR retrospective[Title/Abstract])
AND
(new user*[Title/Abstract] OR naive*[Title/Abstract] OR initiat*[Title/Abstract] OR start*[Title/Abstract] OR first use*[Title/Abstract])

23.8 Adherence general

(“Patient Compliance"[Mesh] OR Complian*[TIAB] OR non-complian* OR non complian* OR noncomplian* [TIAB] OR adheren*[TIAB] OR non-adheren*[TIAB] OR nonadheren*[TIAB] OR non adheren*[TIAB] OR concordan*[TIAB] OR persistence[TIAB])
AND
((oral anticoagulant*[TIAB] OR indirect factor Xa inhibit*[TIAB] OR direct thrombin inhibitor*[TIAB] OR dabigatran[TIAB] OR apixaban[TIAB] OR rivaroxaban[TIAB] OR edoxaban[TIAB] OR NOAC[TIAB] OR DOAC[TIAB] OR "Dabigatran"[Mesh] OR "edoxaban" [Supplementary Concept] OR "Rivaroxaban"[Mesh] OR "apixaban" [Supplementary Concept] OR "Factor Xa Inhibitors" [Pharmacological Action] OR "Antithrombins" [Pharmacological Action])
OR
(vitamin K antagonist*[TIAB] OR acenocoumarol[TIAB] OR phenprocoumon[TIAB] OR warfarin[TIAB] OR "4-Hydroxycoumarins"[Mesh]))
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB] OR cohort[TIAB] OR prospective*[TIAB] OR retrospective*[TIAB] OR longitudinal[TIAB])
AND
("2016/01/01"[Date - Publication] : "2017/07/01"[Date - Publication])

23.9 Interventions to improve adherence

(“Patient Compliance"[Mesh] OR Complian*[TIAB] OR non-complian* OR non complian* OR noncomplian* [TIAB] OR adheren*[TIAB] OR non-adheren*[TIAB] OR nonadheren*[TIAB] OR non adheren*[TIAB] OR concordan*[TIAB] OR persistence[TIAB] OR TTR[TIAB] OR time in therapeutic range[TIAB])
AND
(anticoagulant*[TIAB] OR indirect factor Xa inhibit*[TIAB] OR direct thrombin inhibitor*[TIAB] OR dabigatran[TIAB] OR apixaban[TIAB] OR rivaroxaban[TIAB] OR edoxaban[TIAB] OR NOAC[TIAB] OR DOAC[TIAB] OR "Dabigatran"[Mesh] OR "edoxaban" [Supplementary Concept] OR "Rivaroxaban"[Mesh] OR "apixaban" [Supplementary Concept] OR "Factor Xa Inhibitors" [Pharmacological Action] OR "Antithrombins" [Pharmacological Action] OR vitamin K antagonist*[TIAB] OR acenocoumarol[TIAB] OR phenprocoumon[TIAB] OR warfarin[TIAB] OR "4-Hydroxycoumarins"[Mesh])
AND
(systematic[sb] OR medline[TIAB])
AND
(improve[Title/Abstract] OR improving[Title/Abstract] OR intervention*[Title/Abstract] OR impact[Title/Abstract])

24 List of excluded publications

- *Abed HS, Chen V, Kilborn MJ, et al. Periprocedural Management of Novel Oral Anticoagulants During Atrial Fibrillation Ablation: Controversies and Review of the Current Evidence. Heart Lung Circ 2016;25:1164-76.**n. not a research question***
- *2. Abraham NS, Singh S, Alexander GC, et al. Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. Bmj 2015;350:h1857.**n. no comparison of DOAC vs DOAC***
- *Ageno W, Turpie AG. Spotlight on real-world evidence for the treatment of DVT: XALIA. Thromb Haemost 2016;116:S41-s9.**n. doac vs vka observational***
- *Alamneh EA, Chalmers L, Bereznicki LR. Suboptimal Use of Oral Anticoagulants in Atrial Fibrillation: Has the Introduction of Direct Oral Anticoagulants Improved Prescribing Practices? American Journal of Cardiovascular Drugs 2016;16:183-200.**n. no information on patient adherence as such***
- *Albaladejo P, Bonhomme F, Blais N, et al. Management of direct oral anticoagulants in patients undergoing elective surgeries and invasive procedures: Updated guidelines from the French Working Group on Perioperative Hemostasis (GIHP) - September 2015. Anaesth Crit Care Pain Med 2017;36:73-6.**n. guideline not selected***
- *Almutairi AR, Zhou L, Gellad WF, et al. Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants for Atrial Fibrillation and Venous Thromboembolism: A Systematic Review and Meta-Analyses. Clin Ther 2017.**n. no real MA done. seperate analysis for each doac. no added value to the results from the individual trials, that we already present.***
- *Ando G, Capranzano P. Non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with chronic kidney disease: A systematic review and network meta-analysis. Int J Cardiol 2017;231:162-9.**n. network meta-analysis***
- *Anonymous. Point-of-Care International Normalized Ratio (INR) Monitoring Devices for Patients on Long-term Oral Anticoagulation Therapy: An Evidence-Based Analysis. Ont Health Technol Assess Ser 2009;9:1-114.**n. we have more recent SRs***
- *Anonymous. Deep venous thrombosis and pulmonary embolism. Part 2--Prevention of recurrences: warfarin or low-molecular-weight heparin for at least 3 months. Prescrire Int 2013;22:129-33.**n. no SR, old publication***
- *Anonymous. [Long-term oral anticoagulation. Self monitoring optimizes vitamin K antagonist therapy]. MMW Fortschr Med 2014;156:79.**n. we have a more recent source***
- *Anonymous. Apixaban (Eliquis) in deep vein thrombosis and pulmonary embolism. Warfarin remains the standard therapy. Prescrire Int 2015;24:206.**n. not SR***
- *Antoniou S. Rivaroxaban for the treatment and prevention of thromboembolic disease. J Pharm Pharmacol 2015;67:1119-32.**n. not sr***
- *Aryal MR, Ukaigwe A, Pandit A, et al. Meta-analysis of efficacy and safety of rivaroxaban compared with warfarin or dabigatran in patients undergoing catheter ablation for atrial fibrillation. Am J Cardiol 2014;114:577-82.**n. not a research question***
- *Ayoub K, Nairooz R, Almomani A, et al. Perioperative Heparin Bridging in Atrial Fibrillation Patients Requiring Temporary Interruption of Anticoagulation: Evidence from Meta-analysis. J Stroke Cerebrovasc Dis 2016;25:2215-21.**n. observational***
- *Bach M, Bauersachs R. Spotlight on advances in VTE management: CALLISTO and EINSTEIN CHOICE. Thromb Haemost 2016;116:S24-s32.**n.not the original studies***
- *Bahit MC, Lopes RD, Wojdyla DM, et al. Non-major bleeding with apixaban versus warfarin in patients with atrial fibrillation. Heart 2017;103:623-8.**n. secondary publication. we have the original article.***

- *Bai Y, Chen H, Yang Y, et al. Safety of antithrombotic drugs in patients with atrial fibrillation and non-end-stage chronic kidney disease: Meta-analysis and systematic review. Thromb Res 2016;137:46-52.**n. comparison is not a research question***
- *Bancroft T, Lim J, Wang C, et al. Health Care Resource Utilization, Costs, and Persistence in Patients Newly Diagnosed as Having Nonvalvular Atrial Fibrillation and Newly Treated With Dabigatran versus Warfarin in the United States. Clin Ther 2016;38:545-56.e1-6.**n. USA persistence study; DOAC vs VKA***
- *Baron-Esquivias G, Marin F, Sanmartin Fernandez M. Rivaroxaban in patients with atrial fibrillation: from ROCKET AF to everyday practice. Expert Rev Cardiovasc Ther 2017;15:403-13.**n. vka vs doac for observational studies not a research question***
- *Becattini C, Agnelli G. Treatment of Venous Thromboembolism With New Anticoagulant Agents. J Am Coll Cardiol 2016;67:1941-55.**n. not SR***
- *Bell BR, Spyropoulos AC, Douketis JD. Perioperative Management of the Direct Oral Anticoagulants: A Case-Based Review. Hematol Oncol Clin North Am 2016;30:1073-84.**n. study type***
- *Beyer-Westendorf J, Camm AJ, Coleman CI, et al. Rivaroxaban real-world evidence: Validating safety and effectiveness in clinical practice. Thromb Haemost 2016;116:S13-s23.**n. not SR***
- *Beyer-Westendorf J, Forster K, Ebertz F, et al. Drug persistence with rivaroxaban therapy in atrial fibrillation patients-results from the Dresden non-interventional oral anticoagulation registry. Europace 2015;17:530-8.**n. 40% not OAC naïve. no seperate info on OAC naïve subgroup (and n<1000)***
- *Blandino A, Bianchi F, Biondi-Zoccai G, et al. Apixaban for periprocedural anticoagulation during catheter ablation of atrial fibrillation: a systematic review and meta-analysis of 1691 patients. J Interv Card Electrophysiol 2016;46:225-36.**n. ablation not a specific research question***
- *Bloom BJ, Filion KB, Atallah R, et al. Meta-analysis of randomized controlled trials on the risk of bleeding with dabigatran. Am J Cardiol 2014;113:1066-74.**n. 1. pooling of VTE and AF. 2. analysis per indication: no added value for our review.***
- *Bo M, Grisoglio E, Brunetti E, et al. Oral anticoagulant therapy for older patients with atrial fibrillation: a review of current evidence. Eur J Intern Med 2017;41:18-27.**n. incomplete SR***
- *Boey JP, Gallus A. Drug Treatment of Venous Thromboembolism in the Elderly. Drugs Aging 2016;33:475-90.**n. no access. but no SR, apparently***
- *Borg Xuereb C, Shaw RL, Lane DA. Patients' and health professionals' views and experiences of atrial fibrillation and oral-anticoagulant therapy: a qualitative meta-synthesis. Patient Educ Couns 2012;88:330-7.**n. study type, topic***
- *Boutitie F, Pinede L, Schulman S, et al. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. Bmj 2011;342:d3036.**n. no systematic search***
- *Brancaccio D, Neri L, Bellocchio F, et al. Atrial fibrillation in dialysis patients: time to abandon warfarin? Int J Artif Organs 2016;39:99-105.**n. no dialysis***
- *Brown JD, Shewale AR, Talbert JC. Adherence to Rivaroxaban, Dabigatran, and Apixaban for Stroke Prevention in Incident, Treatment-Naive Nonvalvular Atrial Fibrillation. J Manag Care Spec Pharm 2016;22:1319-29.**n. USA cohort for adherence***
- *Brunetti L, Chen C, White J. Dabigatran for stroke prevention in nonvalvular atrial fibrillation: focus in the geriatric population. Consult Pharm 2014;29:169-78.**n. included only RE-LY rct. we have the original publication.***
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