Clinical trials with new direct oral anticoagulants

Additive value of indirect comparisons also named network meta-analyses

J. Harenberg[1]; C. Weiss[2]; S. Marx[1]; S. Zolfaghari[1]

[1]Department of Clinical Pharmacology, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany;
[2]Department of Biometry and Statistics, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

Keywords
Oral anticoagulants, Apixaban, Dabigatran, Rivaroxaban, Edoxaban, atrial fibrillation, total knee replacement, total hip replacement, prophylaxis of thromboembolism

Summary
To compare the efficacy and safety of the new direct oral anticoagulants (DOAC), ideally head-to-head clinical trials should be performed. Given the expense of such an undertaking, it is highly unlikely that such a comparison would be performed. Therefore, there is a need for an unbiased comparative assessment of the benefits and risks of the DOACs, based on the available trial data. Indirect or mixed treatment comparisons may be an useful tool to overcome these limitations also known as network meta-analysis (NMA).
The aim of this paper is to give an overview on published NMAs for dabigatran, rivaroxaban and apixaban, each assessed against warfarin in patients with atrial fibrillation, and against enoxaparin in patients undergoing total knee and total hip replacement surgery, in order to obtain insights into the comparability of the adopted methodological techniques.

Correspondence to:
Job Harenberg, MD, Professor of Medicine
Department of Clinical Pharmacology
Medical Faculty Mannheim, University of Heidelberg
Maybachstr. 14, 68169 Mannheim, Germany
Tel. +49-621/383 96–23, Fax –22
E-Mail: job.harenberg@medma.uni-heidelberg.de

Schlüsselwörter
Antikoagulanzien, Apixaban, Dabigatran, Rivaroxaban, Edoxaban, Vorhofflimmern, postoperative Thromboembolieprophylaxe

Zusammenfassung
Um die Wirksamkeit und Verträglichkeit neuer direkter oraler Antikoagulanzien (DOAK) zu vergleichen, müssten idealerweise direkte Vergleiche zwischen den Substanzen in klinischen Studien durchgeführt werden. Auf Grund des logistischen und finanziellen Aufwandes werden diese Projekte in absehbarer Zeit nicht durchgeführt werden. Indirekte Vergleiche, auch Netzwerkanalysen (NMA) genannt, lassen sich mit den vorliegenden Studien zwischen den DOAKs vornehmen, um die Frage der Vergleichbarkeit anzugehen. In der postoperativen Phase nach Knie- und Hüftgelenkersatz und bei Patienten mit Vorhofflimmern sind derzeit diese Vergleich möglich. Indirekte Vergleiche sind jedoch auch mit Einschränkungen behaftet.
Diese Arbeit gibt eine Übersicht der aktuell vorliegenden NMAs und versucht deren unterschiedliche Ergebnisse mit der Pharmakologie der DOAKs und den methodischen Problemen von NMAs zu beleuchten.

Klinische Studien mit neuen direkten oralen Antikoagulanzien
Mehrwert indirekter Vergleiche (Netzwerk-Meta-analysen)
Phlebologie 2013; 42: 143–152
DOI: 10.12687/phleb2146-3-2013

Updated, extended review from:
Hämostaseologie 2013;42: 62–70

Patients with non-valvular atrial fibrillation (NVAF) are exposed to an increased risk for ischaemic stroke and systemic embolism. Mortality and morbidity following stroke associated with NVAF are higher than in patients who suffer ischaemic strokes in the absence of NVAF (1). In these patients with NVAF (2) anticoagulation with vitamin K antagonists (VKA) reduces the incidence of

- ischaemic stroke,
- systemic embolism, and
- mortality.

However, severe bleeding complications including intracranial haemorrhage occur (3). VKA usage requires frequent dose adjustments to optimize the time in the therapeutic range (TTR) of international normalized ratio (INR) values between 2 and 3 (4). Due to these limitations, patients at risk for bleeding complications may be undertreated with VKA or receive less effective medications such as aspirin or even no prophylaxis (5).

Venous thromboembolism is one of the major complications following primary elective total hip (THR) and knee replacement (THR) surgery resulting in considerable preventable morbidity and mortality (6). Prophylaxis of thromboembolic events is currently performed by subcutaneous injection of low molecular weight heparins (LMWHs) or fondaparinux for 10 days in TKR or 35 days in THR (7). Limitations of the regimes include (8)

- heparin-induced thrombocytopenia type I and type II,
- local haematoma and allergy,
- transient increase of liver enzymes, and
- the systemic administration.

As new direct oral anticoagulants (DOACs) direct factor Xa and thrombin inhibitors have been developed to overcome the limitations of conventional anticoagulants (9).

- The direct oral factor Xa inhibitors rivaroxaban and apixaban specifically target factor Xa.
- The direct oral thrombin inhibitor dabigatran specifically inhibits the coagulation enzyme thrombin.

All new direct oral coagulation inhibitors are given at fixed doses without laboratory guided dose adjustment.

The three DOACs tested in clinical trials are dabigatran etexilate, which has anti-thrombin activity, and rivaroxaban and apixaban, which have anti-factor Xa activity (9). In NVAF, results for all three agents are now available from large prospective, randomized trials against standard VKA (warfarin) therapy for the prevention of ischaemic stroke and systemic embolism. The reported trials are the

- RE-LY trial using 110 mg bid and 150 mg bid dabigatran etexilate (10, 11),
- ROCKET-AF trial testing 20 mg od rivaroxaban (12),
- ARISTOTLE trial with 5 mg bid apixaban (13).

All three studies used dose-adjusted warfarin as standard of care control, using a prospective open label blinded endpoint evaluation (RE-LY) or double blind, double-dummy study design (ROCKET AF, ARISTOTLE). These trials showed non-inferiority or superiority for the efficacy outcome of combined ischaemic stroke and systemic embolism. Further, the rates of major bleeding complications were similar or even reduced in comparison with warfarin for all three DOACs.

To compare the efficacy and safety of the DOACs, ideally head-to-head clinical trials should be performed. Given the expense of such an undertaking, it is highly unlikely that such a comparison would be performed. Therefore, there is a need for an unbiased comparative assessment of the benefits and risks of the DOACs, based on the available trial data. Indirect or mixed treatment comparisons may be an useful tool to overcome these limitations also known as network meta-analysis (NMA) (14, 15). This approach allows for indirect comparisons of the three compounds for efficacy and safety outcomes, using information obtained from the connected network of published NVAF trial data (16).

Direct comparisons between two or more treatment regimens are performed in regular clinical trials. Indirect comparisons (also named NMAs) can be performed between the published direct comparisons if the direct comparisons include the same comparator such as enoxaparin or warfarin (▶Fig. 1).

- The advantages of NMAs are to gain information of treatment regimes, which are highly unlikely to become available due to organizational or economic reasons in near future. They may also generate information about the comparison of efficacy and safety of treatment options which otherwise would be unlikely to be obtained. This may help the medical society to improve patient care.
- The limitations of NMAs include differences in
  - biographic patient's data,
  - inclusion and exclusion criteria,
  - definition and documentation of efficacy or safety endpoints.

The aim of this paper is to give an overview on published NMAs for dabigatran, rivaroxaban and apixaban, each assessed against warfarin in patients with NVAF, and against enoxaparin in patients undergoing TKR and THR surgery, in order to obtain insights into the comparability of the adopted techniques. The high number of NMAs of DOACs in the different indications prompted us to analyse the methodologies using published guidelines (19, 20).

Methodological considerations

The methodological techniques of NMAs are not generally applicable and may be subject to biases and other limitations. Assumptions of similarity and consistency are particularly sensitive to error thereby rendering results questionable (17, 18).

The international society for pharmacoeconomics and outcome research (ISPOR) provided guidelines for the interpretation of indirect treatment comparisons and network metaanalyses for health-care decision making (19, 20). When these techniques are applied adherence to the ISPOR checklist, diligence and transparency should be employed. The standardization of methods as facilitated by this checklist should enhance the overall credibility, transparency and applicability of ITC (indirect treatment comparisons) and NMA (19).

The major points are summarized as follows:

- The studies included into our indirect comparison of new oral anticoagulants clearly stated the same
  - rationale to prevent embolic diseases in patients with NVAF or VTE in TKR and THR surgery,
  - eligibility criteria based on the definition of NVAF and additional risk factors based on the CHADS2 score (C cardiac failure, H hypertension, A age ≥ 75 years, D Diabetes mellitus, S stroke, 2 two points for stroke)
  - as well as for VTE prophylaxis in orthopaedic surgery.
- The studies were prospective, randomized, multicentric, adequately powered and controlled to adjusted warfarin therapy.
- The search strategy was based on Medline and Embase search strategies to identify the relevant publications according the PRISMA (Preferred Reporting Items for Systematic reviews and Metaanalyses) strategy (21).
- Only studies reporting the incidence of predefined primary outcome-events; the secondary outcome measures included
  - major bleeding complications,
  - intracranial haemorrhage,
  - myocardial infarction and -mortality and using dose adjusted warfarin as comparator or major bleeding and mortality in TKR and THR surgery.
- Figures with results for the paired comparisons were included as point estimates and 95% confidence intervals.
- Possible biases and inconsistencies between the studies caused by gender could be excluded.

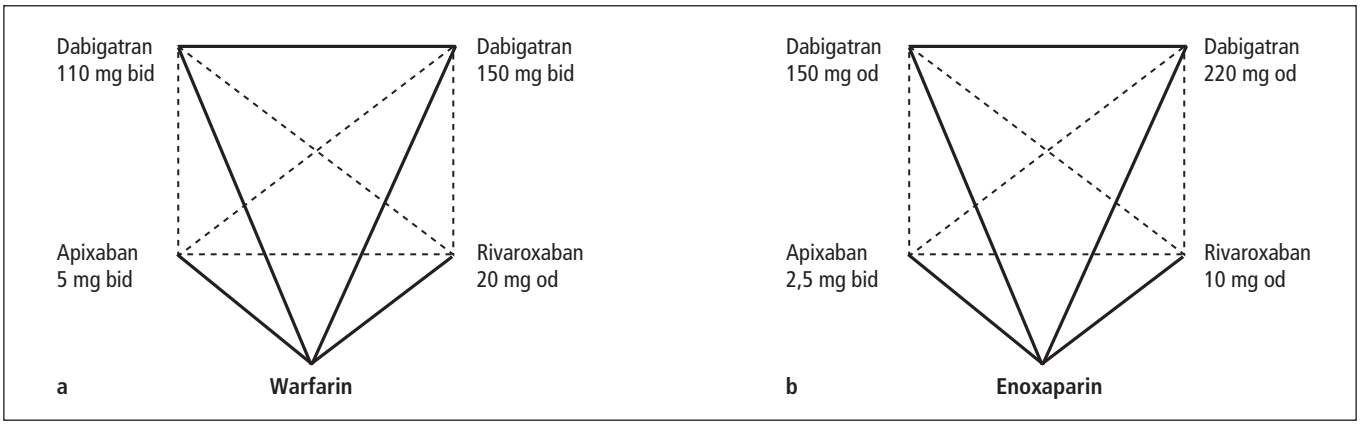

Fig. 1 Direct (solid line) and indirect (dotted) comparisons of trials; adapted from (26, 43)
a) DOACs or warfarin including patients with NVAF
b) DOAC or enoxaparin in patients undergoing primary elective TKR and THR and on prophylaxis of VTE (indirect comparison also called network meta-analysis

Age, creatinine, CHADS2 score and INR ranges were reported differently and therefore could not be analysed statistically for the AF-trials.

Heterogeneity is another relevant aspect when several studies were performed for one indication. For each clinical endpoint (such as thromboembolism, major bleeding or mortality) homogeneity has to be demonstrated between studies before inclusion into the metaanalysis. This may not always be respected (22); at least at the level of studies on the these DOACs this did not apply here as only one study was available for each DOAC in NVAF.

Indirect comparisons

DOACs in NVAF

Within a time frame of only three months four NMAs were published. Four NMAs were published on this topic (22–25). All NMAs employed near identical statistical methods and conclude that some differences exist regarding the occurrence of embolic events, intracranial haemorrhage, major bleeding, myocardial infarction, but not on mortality between the DOACs. These studies were compared recently and some minor differences were identified (26) (▶Fig. 1).

The NMAs reporting on the efficacy and safety of DOACs in NVAF differ in the statistical approach in that three authors used the odds ratio (OR) for endpoint calculations (22), (24), (25) and one used the hazard ratio (HR) (23) (▶Tab. 1). The advantage of the OR is its independence from the time point at which an event occurs in the study. In contrast, the exact date of an event has to be known for all trials to calculate the HR. The detailed event dates are not available from the DOAC publications, and thus, the majority of authors elected to use the OR (26).

Another indirect comparison of the DOACs was published for a subgroup of patients at increased risk for embolism (CHADS2 score ≥3) 'to address a lack of comparability between trial populations caused by the restriction of ROCKET-AF to high-risk patients' (27) (▶Tab. 1). In this context, some confusion may arise by this publication because patients at risk for embolic events (and hence, eligible for anticoagulation) are defined at a CHADS2 score of ≥3 in their study, in contrast to those with ≥1 stroke risk factors, as recommended in guidelines (28, 29). Also, the studies may not be adequately powered for sub-analysis (only a third of the RE-LY and ARISTOTLE populations were CHADS2 score ≥3, in contrast to ROCKET-AF) (30). The RE-LY reported major bleed and ICH was reported separately. In addition, ROCKET-AF had 101 patients with CHADS2 score not reported for the rivaroxaban group versus only 4 in the warfarin group. The NMA did not include dabigatran 110 mg bid. This dose was suggested by the EMA for those patients included. Accordingly, analysis of homogeneity between the selected subgroups of patients would have been relevant. These considerations limit the interpretation of this NMA (30).

A recently published NMA performed an indirect comparison of these anticoagulants in those patients by pooling the results of the control groups of the three studies treated with warfarin (31, 32). In addition, they also pooled the results of the DOACs and compared them to the results they calculated for the pooled data of the warfarin groups of the three studies. The authors concluded that an "*overall superiority of DOAC over warfarin is largely influenced by the reduction of haemorrhagic stroke*". They further conclude „*dabigatran 150 mg bid seems to have the best risk/benefit profile*" (▶Tab. 1). In this context, some confusion may arise by the publication because the authors have added another limitation to the problematic analysis of indirect comparisons of the DOACs. The variance of their results is increased if the outcome data of the control groups of the RE-LY, ROCKET AF, and ARISTOTLE trials were pooled. This limits the interpretation of these data.

One NMA of DOACs in NVAF included also phase II studies of smaller sizes and of shorter treatment periods and not reporting all secondary endpoints (33) (▶Tab. 1). The authors also pooled the results the efficacy and safety endpoints of the DOACs despite the known pharmacological variations between them. They also included results of unpublished trials making the interpretation of the data even

Tab. 1 Overview of results of indirect comparisons – also named network meta-analyses – using new direct oral anticoagulants (DOACs) versus warfarin in non valvular atrial fibrillation (NVAF) for prophylaxis of stroke and systemic embolism

		citation									
		Wells	Harenberg	Lip	Mantha	Schneeweis	Testa	Miller	Dentali	Rasmussen	Alonso
stroke or systemic embolism							+	+	+	+	
	D 150 vs R	+	+	+	+	-	na	na	na	-	na
	D 110 vs R	-	-	-	-	-	na	na	na	-	na
	D 150 vs A	-	-	-	-	-	na	na	na	-	na
	D 110 vs A	-	-	-	-	-	na	na	na	-	na
	R vs A	-	-	-	-	-	na	na	na	-	na
	D 110 vs 150	+	+	na	na	na	na	na	na	-	na
	D 150 vs HM										-
major bleeding							+	+	+	+	
	D 150 vs R		-			--	+	na	na	-	na
	D 110 vs R	+	+	+	+	-	-	na	na	-	na
	D 150 vs A	+	+	+	+	+	-	na	na	-	na
	D 110 vs A	-	-	-	-	-	-	na	na	-	na
	R vs A	+	+	+	+	+	+	na	na	-	na
	D 110 vs 150	+	-	na	na	-	na	na	na	-	na
	D 150 vs HM										-
intracranial haemorrhage							+	+	+	+	
	D 150 vs R	-	-	-	-	na	na	na	na	-	na
	D 110 vs R	+	+	+	+	na	na	na	na	-	na
	D 150 vs A	-	-	-	-	na	na	na	na	-	na
	D 110 vs A	-	-	-	-	na	na	na	na	-	na
	R vs A	-	-	na	-	na	na	na	na	-	na
	D 110 vs D 150				na	na	na	na	na	-	na
mortality							+	-	+		
	D 150 vs R	-	-	-	-	na	na	na	na	-	na
	D 110 vs R	-	-	-	-	na	na	na	na	-	na
	D 150 vs A	-	-	-	-	na	na	na	na	-	na
	D 110 vs A	-	-	-	-	na	na	na	na	-	na
	R vs A	-	-	-	-	na	na	na	na	-	na
	D 110 vs D 150	-	-	na	-	na	na	na	na	-	na
	D 150 vs HM										-
myocardial infarction							-	-	-	-	
	D 150 vs R	+	+	+	na	na	na	na	na	-	na
	D 110 vs R	+	+	+	na	na	na	na	na	-	na
	D 150 vs A		+	-	na	na	na	na	na	+	na
	D 110 vs A		+	-	na	na	na	na	na	-	na
	R vs A		-	-	na	na	na	na	na	-	na
	D 110 vs D 150		-	na	na	na	na	na	na	-	na

Tab. 1 Continued

	citation									
	Wells	Harenberg	Lip	Mantha	Schneeweis	Testa	Miller	Dentali	Rasmussen	Alonso
p-values	√	√	√	√	√	√	√	√	v	√
PRISMA criteria	√	√	√	√	√	√	√	√	√	√
ISPOR criteria	√	√	√	√						
hazard ratio			√		√		√	√	√	
odds ratio	√	√		√		√				√
DOAC pooling						√	√	√		
subgroups					√					
phase II trials								√		
other bleedings							+		√	

DOAC: new direct oral anticoagulant; na: not analysed; D: dabigatran; A: apixaban; R: rivaroxaban; + significant, – not significant,
PRISMA and ISPOR: see main document; √ applied; if information (+ or -) is given in the line of the outcome event; Data of the DOACs were pooled.

more difficult. Asymmetrical funnel plots for systemic embolism and myocardial infarction may indicate a bias of the studies included into their analysis (33).

Another NMA analysed several subgroups of bleeding complications without finding differences between the DOACs in NVAF. However, ISTH (international society of thrombosis and haemostasis) definition of bleeding was significantly less frequent in patients receiving apixaban compared to rivaroxaban. In addition, this analysis published data on a combination of the results of all DOACs on the primary efficacy and secondary safety endpoints (34). Such analyses remain difficult to interpret because the DOACs were initially developed separately as individual drugs due to their distinct pharmacological properties. Despite the pharmacological differences the results of the clinical trial are nonetheless pooled and compared to INR-adjusted warfarin, data that were also pooled from the studies included into the analysis.

Self-monitoring and self-management improves the efficacy and safety of INR-adjusted VKA therapy compared to usual management. An indirect comparison with the data of dabigatran's RE-LY trial suggested that the treatments have similar impact on thrombosis, bleeding and death (35) (▶Tab. 1). The authors stated as limitation that the incidence of endpoint in the self-management group is too low to draw a definite conclusion (34). It is well known that younger patients perform self-management of warfarin therapy. Patients suffer mainly from artificial heart valve replacement and have few concomitant diseases and medication. In contrast patients of the RE-LY study displayed an age of 75 years or older, were multimorbid and most probably took more concomitant medications. These differences add substantial limitations for the comparability of the patient groups included into this NMA. A comparison of the NMAs performed with DOACs in NVAF to date is given (▶Tab. 1).

DOACs in elective TKR and THR surgery

Several network meta-analyses were carried out including studies of DOACs versus LMWHs in elective TKR and THR surgery. The direct comparison of an DOAC used a LMWH as comparator. Homogeneity within the study programs for dabigatran (two doses), rivaroxaban, and apixaban were achieved only if enoxaparin 40 mg od was used as comparator (43). Therefore, the indirect comparison between the DOACs could be performed only with this set of homogenous data of the study programs (▶Fig. 1b).

Initially, some NMAs were performed using only some of the four treatment regimens of the DOACs in this indication. Trkulja et al. did not find differences in the efficacy and safety between rivaroxaban and dabigatran in this indication (36). Le-Reun et al. described a superior efficacy of rivaroxaban over dabigatran 220 mg for prevention of VTE and VTE related death as well as major VTE in THR and TKR surgery. There were no differences for major bleeding complications (37). Loke et al. confirmed these data and added that rivaroxaban was superior also to dabigatran 150 mg daily and that the results were independent of the dose of enoxaparin used as comparator (38).

Cohen et al. included apixaban as well as several LMWHs and fondaparinux for prophylaxis of VTE after TKR and THR. They pooled the results of the control groups of all studies for the comparison to the other anticoagulants including the DOACs (39). Studies of control groups cannot be pooled across study programs because of differences in definitions of VTE and major bleeding (40). Maratea et al. reported on the efficacy of all DOACs following total TKR and THR orthopaedic surgery (▶Tab. 2). They did not include safety parameters into their NMA. This adds a substantial limitation to their study since major bleeding complication and mortality are relevant aspects for patients undergoing VTE prophylaxis postoperatively (41). Another limitation of NMA becomes evident if the end points are pooled to a net clinical benefit from studies for prevention of VTE in patients under-

going elective TKR and THR surgery. Accordingly, the main conclusion of this paper of a higher efficacy of new anticoagulants were generally associated with a higher bleeding tendency and that the DOACs did not differ significantly for efficacy and safety reflect the contradictory statements based on such pooling of data (42).

One NMA compared all four treatment regimens against each other without pooling of data, but by using the data of the individual control groups for every study (43). A cluster analysis preceded the meta-analysis and the following NMA to identify homogenous groups within a study program. Clustering algorithms are developed for datasets that are too large and complex for manual analysis. Briefly, clustering partitions objects into clusters, such that objects with similar characteristics are clustered together and dissimilar objects are in different clusters. It is anticipated that no prior knowledge exists on any object classifications (44–46). Only the separation for treatment durations of 10 ± 5 days and 34 ± 5 days led to homogenous groups, whereas other variables such as type and dose of LMWH, gender, age and other

Tab. 2 Overview of results of indirect comparisons – also named network meta-analyses – using new direct oral anticoagulants (DOACs) versus enoxaparin in total knee and hip replacement (TKR and THR) surgery for postoperative prophylaxis of venous thromboembolism

citation		Trkulja	LeReun		Loke	Cohen		Marateka	Harenberg		Gomez
			TKR	THR		TKR	THR		10 ± 5 days	34 ± 5 days	
venous thrombo-embolism	D 150 vs D 220	na	na	na	na	na	na	na	-	-	na
	D 150 vs R	+ +	na	na	+	na	na	+	+	+	- major VTE
	D 220 vs R		+	+	+	na	na	+	+	+	
	D 150 vs A	na	na	na	na	+	+	+	na	+	- major VTE
	D 220 vs A	na	na	na	na	+	+	+	na	+	
	R vs A	na	na	na	na	-	-		na	-	- major VTE
major bleeding	D 150 vs D 220	na	na	na	na	na	na	na	-	-	na
	D 150 vs R	- -	na	na	-	na	na	na	-	-	-
	D 220 vs R		-	-	-	na	na	na	-	-	
	D 150 vs A	na	na	na	na	-	-	na	-	-	+ A, CRMB
	D 220 vs A	na	na	na	na	-	-	na	-	-	
	R vs A	na	na	na	na	-	-	na	-	-	-
mortality	D 150 vs D 220	na	na	na	na	na	na	na	-	-	na
	D 150 vs R	na	na	na	na	na	na	na	-	-	na
	D 220 vs R	na	na	na	na	na	na	na	-	-	na
	D 150 vs A	na	na	na	na	na	na	na	-	-	na
	D 220 vs A	na	na	na	na	na	na	na	-	-	na
	R vs A	na	na	na	na	na	na	na	-	-	na
p-values		√	√	√	√			√	√	√	√
PRISMA criteria		√	√	√	√	√	√	√	√	√	√
ISPOR criteria									√	√	
cluster analysis									√	√	
odds ratio		√	√	√	√	√	√		√	√	√
DOAC pooling											
enoxaparin pooling						√	√				

DOAC: new direct oral anticoagulant; TK(H)R: total knee (hip) replacement; VTE: venous thromboembolism; CRMB: clinical relevant major bleeding; D: dabigatran; A: apixaban; R: rivaroxaban; PRISMA and ISPOR: see main document; na: not analysed; + significant; – not significant; √ applied

variables did not lead to homogeneous groups. The relevant additional findings were that

1. rivaroxaban performed better than both doses of dabigatran for 10 ± 5 days and 34 ± 5 days of prophylaxis on the incidence of the composite of VTE events,
2. apixaban and rivaroxaban did not differ for this outcome for both treatment periods at 35 days.
3. There were no differences in major bleeding events between all DOAC treatment regimens.

Whether the trend for a lower incidence of major bleeding with apixaban compared to rivaroxaban during 34 ± 5 days of prophylaxis is relevant remains to be confirmed in additional trials (43) (▶Tab. 2). NMAs without proving for heterogeneity between trails, without using OR and 95% CI of each trial program, and without comparison for statistical significant differences between the DOACs for their efficacy and safety (47) may be easier to perform but do not follow the ISPOR guidelines described.

An indirect comparison between the DOAC trial-programs was published to overcome problems of direct comparisons between these new compounds. However reporting of the defined endpoints may differ markedly between the study programs and in particular, for the bleeding events (40). Pooling data with divergent endpoint criteria will introduce a bias that may influence the result of the meta-analysis (43). The original approach for an indirect comparison intended to minimize bias by using the OR and 95% CI of endpoints of homogeneous trials included into network meta-analysis (14, 15). Therefore, we decided to use this approach to indirectly compare the DOACs from the respective trial programs. However, due to the lack of standardized definitions for VTE and bleeding, we adopted cluster analysis to identify groups of those studies within the trial programs leading to homogeneity for these endpoints as well as mortality before performing meta-analysis for each DOAC followed by NMA. A comparison of the results of the NMAs using DOACs compared to enoxaparin following TKR and THR surgery is summarized (▶Tab. 2).

Treatment with DOACs

DOACs are currently investigated in clinical trials for treatment of acute deep vein thrombosis and stable pulmonary embolism. Rivaroxaban was approved by the FDA and EMA for both indications. Dabigatran and apixaban are at different stages of the clinical development. A NMA was published including the data of abstracts (48). This is not in agreement with the PRISMA and ISPOR guidelines for performing metaanalysis or NMAs. Further NMAs will be available in this field as soon as the corresponding studies are published in peer reviewed journals.

Discussion

In the absence of a direct comparison of treatments of interest, an indirect comparison can provide useful information about differences in efficacy and safety aspects between competing interventions. DOACs represent an important example as they have never been compared in head-to-head trials. In trials on DOACs, low molecular weight heparins or warfarin have been used as common comparators. Therefore, an indirect treatment comparison (ITC) can utilize the relative effects of the treatments versus the common comparator. NMA is an emerging tool for ITC. The international society for pharmacoeconomics and outcome research (ISPOR) provided a checklist of good research practices for reporting network meta-analyses (19, 20).

Limitations of NMA of DOAC in patients with NAVF include that warfarin treatment open in the RE-LY study versus double dummy in the two other studies; differences in time in therapeutic range of the international nationalized ratio between the studies; differences in biographic data of the patients across the studies such as gender, CHADS2 score, creatinine clearance, and concomitant use of aspirin (26).

> These limitations are neglected by several authors pooling the data of the control groups for the direct comparison as well as of treatment groups for a indirect comparison of the DOACs.

Although the methodological issues regarding ITC and NMA are recognized, these methods are increasingly applied to trials on DOACs, as it is assumed that compiling and analysing information from all available sources as an evolving process may improve health-care decision making. For that reason, the goal of the Task Force is to inform and educate policymakers and health care professionals about the studies and identify areas of future research such as NMAs and to sort out methodological weaknesses (19, 20).

NMAs typically encounter a number of statistical problems. Heterogeneity is one relevant aspect when several studies were performed for one indication.

> For each clinical endpoint (such as thromboembolism, major bleeding or mortality) homogeneity has to be demonstrated between studies before performing the metaanalysis. This may not always be respected.

If only one but large study (more than 6000 patients per group) is available for each DOACs in NVAF this did not apply. It has also to be taken into consideration, that the pharmacology of DOACs differs substantially and clinical data on DOACs may thus not necessarily be pooled versus the comparator. Therefore, pooling of data of the DOACs or of the control groups may be problematic.

Several NMAs have been conducted after the publication of the RE-LY and ROCKET AF, and ARISTOTLE trials for prevention of embolism in atrial fibrillation (22–25, 27, 30–34) and of many studies for prevention of thromboembolism following total hip and knee replacement surgery (35–41). Sub-analyses mainly reflect the interest of experts and health communities to optimize treatment for patients. This motivation and the opportunities inherent to NMAs may not always be fully appreciated when related publications are criticised. Even small progresses in science may improve patient care, and NMAs appear as a useful tool in the decision making process of doctors and patients to change or not to change from conventional anticoagulation to a DOAC. However, the complex methodology of ITC

and NMA render the interpretation of these specific re-analyses difficult.

The three DOACs dabigatran, rivaroxaban, and apixaban differ (9) in

- mode of action (factor IIa and factor Xa inhibition),
- pharmacology (prodrug, association and dissociation constants),
- pharmacokinetic and pharmacodynamic parameters (absorption and elimination half lives, metabolism),
- drug interactions and
- side effects.

For this reason the DOACs are regarded as different drugs and therefore their data obtained from clinical studies cannot be pooled. The analyses which pooled the data of the DOACs lead to a substantial confusion in the new area of anticoagulation where substantial sets of data are now available leading to an improvement patient care suffering from non-valvular atrial fibrillation after over 50 years of using vitamin-K antagonists as the only available blood thinner.

Which oral anticoagulant does the patient prefer?

Now that direct oral anticoagulant drugs (DOAC) have been licensed for various indications, not only doctors but also patients now have the chance to choose between conventional vitamin K antagonists (VKA) and DOACs (9, 2). The patient's preference in this new setting has been emphasised in the guidelines on anticoagulation in atrial fibrillation of both the ACCP and the ESC (55, 56).

From the patients' point of view, the reasons for switching from a VKA to a DOAC, or the decision on which of these anticoagulants should be used for the first time, have not been investigated adequately. Personal experience and expectations of anticoagulation probably have a major impact on patients when switching or starting anticoagulants. Previous studies with patients being treated with VKAs or DOACs used three validated questionnaires (STAI = Anxiety Inventory), the Freiburg Personality Inventory (FPI), an SF12 Health Survey, and one of our own questionnaires that concentrates on the personal interests of patients on anticoagulation. Regression analysis was applied to identify 7 items that predict with more than 90% probability whether a patient will prefer a VKA or a DOAC.

The score resulting from this questionnaire (0 to 3: VKA, 4 to 6: undecided, 7 to 10: DOAC) is intended to help doctors predict which anticoagulant a particular patient is likely to prefer. This also applies to patients already on VKA treatment.

The questions are now available at www.blutverduennung.uni-hd.de (▶ QR-Code), and can be answered there by patients before and during oral anticoagulation.

Conclusion

The additive value of indirect treatment comparisons becomes difficult to substantiate due to the manifold methodological problems. Comparing the literature of NMAs on DOACs in NVAF and in TKR/THR surgery the most frequent methodological issues refer to:

- use of hazard ratio instead of odds ratio,
- analysing not all treatment regimens performed,
- not analysing safety endpoints,
- analysis of subgroup of patients,
- pooling of data of the DOACs as well as of the comparator, and
- not respecting heterogeneity within a trial program.

Standardization of methods is required including search of approaches to identify homogenous groups such as hierarchical clustering. The large number of NMAs makes it more difficult for practitioners and patients to identify those following published guidelines. Despite all these limitations all NMAs identify a non-inferiority versus INR-adjusted warfarin in atrial fibrillation and NMH-prophylaxis of VTE following elective TKR/THR surgery regarding efficacy and frequently also of safety. In addition to the results of the NMAs the cost-effectiveness evaluations (49–53) may facilitate patients and health care professionals to improve patient care by DOAC in NVAF and elective TKR/THR surgery in favour of DOACs.

Conflict of interest

The authors declare that they do not have to declare any conflicts of interest.

References

1. Roskell NS, Lip GY, DOACk H et al. Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparisons versus dabigatran etexilate. Thromb Haemost 2010; 104: 1106–1115.
2. Hart RG, Pearce LA, Aguilar MI. Adjusted-dose warfarin versus aspirin for preventing stroke in patients with atrial fibrillation. Ann Intern Med 2007; 147: 590–592.
3. Lip GY, Andreotti F, Fauchier L et al. Bleeding risk assessment and management in atrial fibrillation patients. Thromb Haemost 2011; 106: 997–1011.
4. Ansell J, Hirsh J, Hylek E et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed). Chest 2008; 133(6 Suppl): 160S-198S.
5. Ogilvie IM, Newton N, Welner SA et al. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med 2010; 123: 638–645
6. Tasker A, Harbord R, Bannister GC. Meta-analysis of low molecular weight heparin versus placebo in patients undergoing total hip replacement and post-operative morbidity and mortality since their introduction. Hip Int 2010; 20: 64–74.
7. Falck-Ytter Y, Francis CW, Johanson NA et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl): e278S-325S.
8. Linkins LA, Dans AL, Moores LK et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl): e495S-530S.
9. Harenberg J, Wehling M. Current and future prospects for anticoagulant therapy: inhibitors of factor Xa and factor IIa. Semin Thromb Hemost 2008; 34: 39–57.
10. Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139–1151.
11. Connolly SJ, Ezekowitz MD, Yusuf S et al. Newly identified events in the RE-LY trial. N Engl J Med 2010; 363: 1875–1876.

12. Patel MR, Mahaffey KW, Garg J et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883–891.
13. Granger CB, Alexander JH, McMurray JJ et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981–992.
14. Glenny AM, Altman DG, Song F et al. Indirect comparisons of competing interventions. Health Technol Assess 2005; 9: 1–134.
15. Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med 2002; 21: 2313–2324.
16. Ades AE, Madan J, Welton NJ. Indirect and mixed treatment comparisons in arthritis research. Rheumatology 2011; 50 (Suppl 4): iv5–9.
17. Cooper NJ, Sutton AJ, Morris D et al. Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: application to stroke prevention treatments in individuals with nonrheumatic atrial fibrillation. Stat Med 2009; 28: 1861–1881.
18. Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. Stat Methods Med Res 2008; 17: 279–301.
19. Jansen JP, Fleurence R, Devine B et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 2011; 14: 417–428.
20. Hoaglin DC, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value Health 2011; 14: 429–437.
21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151: 264–269.
22. Harenberg J, et al. Comparison of efficacy and safety of dabigatran, rivaroxaban and apixaban in patients with atrial fibrillation using network meta-analysis. Int Angiol 2012; 31: 330–339.
23. Lip GY, et al. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. J Am Coll Cardiol 2012; 60: 738–746.
24. Mantha S, Ansell J. An indirect comparison of dabigatran, rivaroxaban and apixaban for atrial fibrillation. Thromb Haemost 2012; 108: 476–484.
25. Wells GA, Coyle D, Cameron C et al. Safety, effectiveness, and cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation. www.cadth.ca/media/pdf/DOAC_Therapeutic_Review_final_report.pdf (assessed Dec 22, 2012).
26. Harenberg J, Marx S, Wehling M. Head-to-head or indirect comparisons of the novel oral anticoagulants in atrial fibrillation: what's next? Thromb Haemost 2012; 108: 407–409.
27. Schneeweiss S, Gagne JJ, Patrick AR et al. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes 2012; 5: 480–486.
28. Camm AJ, Kirchhof P, Lip GY et al. Guidelines for the management of atrial fibrillation: The task force for the management of atrial fibrillation of the European Society of Cardiology. Europace 2010; 12: 1360–1420.
29. You JJ, Singer DE, Howard PA et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 2012; 141: e531S-575S.
30. Harenberg J, Lip GY. Differences between indirect comparison studies of the oral anticoagulants for stroke prevention in atrial fibrillation: where do we go next? QJM 2013; 106: 95–96.
31. Testa L, Agnifili M, Latini RA et al. Adjusted indirect comparison of new oral anticoagulants for stroke prevention in atrial fibrillation. QJM 2012; 105: 949–957.
32. Miller CS, Grandi SM, Shimony A et al. Meta-analysis ofefficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. Am J Cardiol 2012; 110: 453–460.
33. Dentali F, Riva N, Crowther M et al. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation 2012; 126: 2381–2391.
34. Rasmussen LH, Larsen TB, Graungaard T et al. Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis. BMJ 2012; 345: e7097.
35. Alonso-Coello P, Zhou Q, Guyatt G. Home-monitoring of oral anticoagulation vs. dabigatran. An indirect comparison. Thromb Haemost 2012; 108: 647–653.
36. Trkulja V, Kolundzic R. Rivaroxaban vs dabigatran for thromboprophylaxis after joint-replacement surgery: exploratory indirect comparison based on meta-analysis of pivotal clinical trials. Croat Med J 2010; 51: 113–123.
37. Lereun C, Wells P, Diamantopoulos A et al. An indirect comparison, via enoxaparin, of rivaroxaban with dabigatran in the prevention of venous thromboembolism after hip or knee replacement. J Med Econ 2011; 14: 238–244.
38. Loke YK, Kwok CS. Dabigatran and rivaroxaban for prevention of venous thromboembolism--systematic review and adjusted indirect comparison. J Clin Pharm Ther 2011; 36: 111–124.
39. Cohen A, Drost P, Marchant N et al. The Efficacy and Safety of Pharmacological Prophylaxis of Venous Thromboembolism Following Elective Knee or Hip Replacement: Systematic Review and Network Meta-Analysis. Clin Appl Thromb Hemost 2012; 18: 611–627.
40. Dahl OE, Quinlan DJ, Bergqvist D et al. A critical appraisal of bleeding events reported in venous thromboembolism prevention trials of patients undergoing hip and knee arthroplasty. J Thromb Haemost 2010; 8: 1966–1975.
41. Maratea D, Fadda V, Trippoli S, Messori A. Prevention of venous thromboembolism after major orthopedic surgery: indirect comparison of three new oral anticoagulants. J Thromb Haemost 2011; 9: 1868–1870.
42. Gómez-Outes A, et al. . Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. BMJ 2012; 344: e3675.
43. Harenberg J, Marx S, Dahl OE, et al. Interpretation of endpoints in a network meta-analysis of new oral anticoagulants following total hip or total knee replacement surgery. Thromb Haemost 2012; 108: 903–912.
44. Hamid JS, Meaney C, Crowcroft NS, et al. ; UK Etiology of Encephalitis Study Group. Cluster analysis for identifying sub-groups and selecting potential discriminatory variables in human encephalitis. BMC Infect Dis 2010; 10: 364–374.
45. Song EK, Moser DK, Rayens MK, Lennie TA. Symptom clusters predict event-free survival in patients with heart failure. J Cardiovasc Nurs 2010; 25: 284–291.
46. McLachlan GJ. Cluster analysis and related techniques in medical research. Stat Methods Med Res 1992; 1: 27–48.
47. Schulman S. Is the network meta-analysis (NETMA) bringing us closer to the truth? Insights from recent antithrombotic drug data. Thromb Haemost 2012; 108: 872–875.
48. Fox BD, Kahn SR, Langleben D et al. Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-analysis of randomised controlled trials. BMJ 2012 ; 345: e7498.
49. Freeman JV, Zhu RP, Owens DK et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Ann Int Med 2011; 154: 1–11.
50. Kansal AR, Sorensen SV, Gani R et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation. Heart 2012; 98: 573–578.
51. Lee S, Anglade MW, Pham D et al. Cost-effectiveness of rivaroxaban compared to warfarin for stroke prevention in atrial fibrillation. Am J Cardiol 2012; 110: 845–851.
52. Deitelzweig S, Amin A, Jing Y et al. Medical cost reductions associated with the usage of novel oral anticoagulants vs warfarin among atrial fibrillation patients, based on the RE-LY, ROCKET-AF, and ARISTOTLE trials. J Med Econ 2012; 15: 776–785.
53. Krejczy M, Harenberg J, Marx S et al. Comparison of cost-effectiveness of anticoagulation with dabigatran, rivaroxaban and apixaban in patients with non-valvular atrial fibrillation across countries. Blood 2012; 120 (Suppl): P1164.
54. Harenberg J, Weiss C. Clinical trials with new oral anticoagulants. Additive value of indirect comparisons also named network meta-analyses. Hamostaseologie. 2013; 33: 62–70.
55. MacLean S, Mulla S, Akl EA, et al.; American College of Chest Physicians. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: Am College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012, 141(2 Suppl): e1S-23S
56. Camm AJ, Lip GY, De Caterina R, et al.; ESC Committee for Practice Guidelines-CPG; Document Reviewers. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the Eur Heart Rhythm Assoc 2012; 14(10): 1385–1413.