



Leids Universitair
Medisch Centrum

Registries met NOACs – en dan?

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NATIONALE ANTISTOLLINGSDAG 04-10-2017



Relaties MV Huisman

Voor bijeenkomst mogelijk relevante relaties:	Bedrijfsnamen
Sponsoring of onderzoeksgeld	<ul style="list-style-type: none"> Boehringer Ingelheim, Pfizer-BMS, Bayer Health Care, Daiichi-Sankyo, Aspen
Honorarium of andere (financiële) vergoeding	<ul style="list-style-type: none">
Aandeelhouder	<ul style="list-style-type: none">
Andere relatie, namelijk ...	Chair Steering Committee Gloria-AF registry

Casus: Bloedingen onder dabigatran

NEJM 4 april 2013:

In the months following the approval of the oral anticoagulant dabigatran (Pradaxa, Boehringer Ingelheim) in October 2010, the Food and Drug Administration (FDA) received through the FDA Adverse Event Reporting System (FAERS) many reports of serious and fatal bleeding events associated with use of the drug

Was dit als gevolg van het nieuwe geneesmiddel?

Veel aandacht in de pers voor nieuwe middelen

RE-LY studie liet superioriteit van dabigatran zien bij de preventie van ischemisch herseninfarct en gelijk aantal ernstige bloedingen – met meer gastro-intestinale bloedingen en minder hersenbloedingen onder dabigatran 150 mg BID

Hoe nu verder?

Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

Insurance claim data

Geen controle op data

Geen inzage in patienten dossiers

Wat is de waarheid?

Randomised trials: goud standaard voor evaluatie geneesmiddelen en devices

‘They are designed to test a therapeutic hypothesis under optimal conditions in the absence of confounding factors: highly selected patients, optimal management conditions, and ideal settings; thus they provide information on “efficacy” under conditions very different from real life’

Interne validiteit is (heel) hoog

Externe validiteit is (heel) laag

Voor en nadelen van RCT en real life studies

Table 1

Advantages and disadvantages of RCTs and real life studies.

	RCTs	Real life studies
Advantages	<ul style="list-style-type: none"> • Rigorous experimental design • Randomization • Blinding • Control • Rigorous analysis methods 	<ul style="list-style-type: none"> • Non-selected population • Refer to the usual inhaler techniques • Realistic therapy adherence • Logistical and ethical feasibility • Able to evaluate complex therapies • Useful to detect rare or late side effect • Routine practice setting • Long duration
Disadvantages	<ul style="list-style-type: none"> • Selected patients • Setting and monitoring bias • Economical limitations • Logistical and ethical restrictions • Unsuitable for complex treatments studies • Inappropriate for thorough evaluation of side effects • Short duration 	<ul style="list-style-type: none"> • Lack of patient selection brings confounding factors • Lack of randomization • Absence of blinding • Residual monitoring bias • Confounding by indication • Economical limitations • Logistical problems • Immortality bias

German retrospective database analysis on bleeding risk with NOACs and phenprocoumon in routine care patients with NVAF

- For the enrolment period, 35,013 eligible patients were identified in the database

Non-interventional retrospective analysis based on an anonymised research database from the Health Risk Institute in Germany

- Enrolment period: 1 January 2013–31 December 2014
- Cox proportional hazard models were applied to adjust for baseline differences in the treatment populations
- Follow-up for up to 2 years
- Bleeding was defined as bleeding documented at hospital discharge during drug use or within 30 days after the end of the prescribed treatment
- Sensitivity analysis included only those patients treated with the highest approved dose of apixaban 5 mg BID, n=2,231 (61%); dabigatran 150 mg BID, n=1,496 (48%) and rivaroxaban 20 mg OD, n=8,379 (69%)
- Propensity score matching was used as an alternative to adjust for baseline characteristics

**Rivaroxaban vs
phenprocoumon
n=12,063**

**Dabigatran vs
phenprocoumon
n=3,138**

**Apixaban vs
phenprocoumon
n=3,633**

Study population

- Patients with a documented NVAF diagnosis in the same or the preceding quarter of the treatment initiation period
- Restricted to age ≥ 18
- Patients that had been newly prescribed OAC during the baseline period
- No use of heparin therapy at the start date
- No valvular heart disease/thrombosis/dialysis/gravidity

There are no head-to-head randomised clinical trials comparing the NOACs. This analysis compared individual NOACs with phenprocoumon. Comparisons cannot be made between individual NOACs based on these data

Edoxaban was not included in this research.

German retrospective database analysis: Endpoint definitions

- ▶ Major bleeding:
 - Bleeding consists of emergency admission to hospital and prespecified ICD10 GM hospital discharge diagnosis
- ▶ GI bleeding:
 - Bleeding at any time during exposure time with localisation in the GI tract and documented as hospital discharge diagnosis
- ▶ Any bleeding:
 - Prespecified primary or secondary ICD10 GM hospital discharge diagnoses at any time

German retrospective database analysis: Baseline characteristics after propensity score matching

Characteristic after propensity score matching	Phenprocoumon–apixaban cohort		Phenprocoumon–dabigatran cohort		Phenprocoumon–rivaroxaban cohort	
	Phenprocoumon (n=3,631)	Apixaban (n=3,631)	Phenprocoumon (n=3125)	Dabigatran (n=3125)	Phenprocoumon (n=11,275)	Rivaroxaban (n=11,275)
Age (mean ± SD)	75.4 (9.7)	75.5 (10.8)	72.8 (10.3)	72.6 (11.2)	74.6 (9.5)	74.2 (10.6)
Male (%)	49.4	49.2	51.9	51.9	50.3	50.9
CHA ₂ DS ₂ -VASc score (mean ± SD)	4.1 (1.7)	4.1 (1.8)	3.8 (1.7)	3.8 (1.8)	3.9 (1.6)	3.8 (1.7)
HAS-BLED score (mean ± SD)	2.9 (1.2)	2.9 (1.2)	2.7 (1.1)	2.6 (1.2)	2.7 (1.1)	2.7 (1.1)
Charlson comorbidity index (mean ± SD)	3.3 (2.6)	3.4 (2.7)	2.8 (2.6)	2.9 (2.5)	3.0 (2.6)	2.9 (2.5)

Mean follow-up was 218 days for apixaban, 261 days for dabigatran, 258 days for rivaroxaban and 280 days for phenprocoumon.

Reproduced from
Hohnloser et al. 2017¹

Use of the highest approved drug dose: 61% of apixaban-treated patients, 48% of dabigatran-treated patients and 69% of rivaroxaban-treated patients

There are no head-to-head randomised clinical trials comparing the NOACs. This analysis compared individual NOACs with warfarin. Comparisons cannot be made between individual NOACs based on these data

SD: standard deviation.

German retrospective database analysis: Event rates (per 100 person-years) and HRs for **NOACs vs phenprocoumon** – Cox proportional hazard adjusted

Event rate per 100 person-years (unadjusted)		Adjusted HR (95% CI)		P value
Apixaban n=3,633	Phenprocoumon n=16,179			
Major bleeding	2.4	3.2	0.68 (0.51–0.91)	0.008
GI bleeding	2.1	3.5	0.53 (0.39–0.72)	<0.001
Any bleeding	11.2	12.6	0.80 (0.70–0.92)	0.002

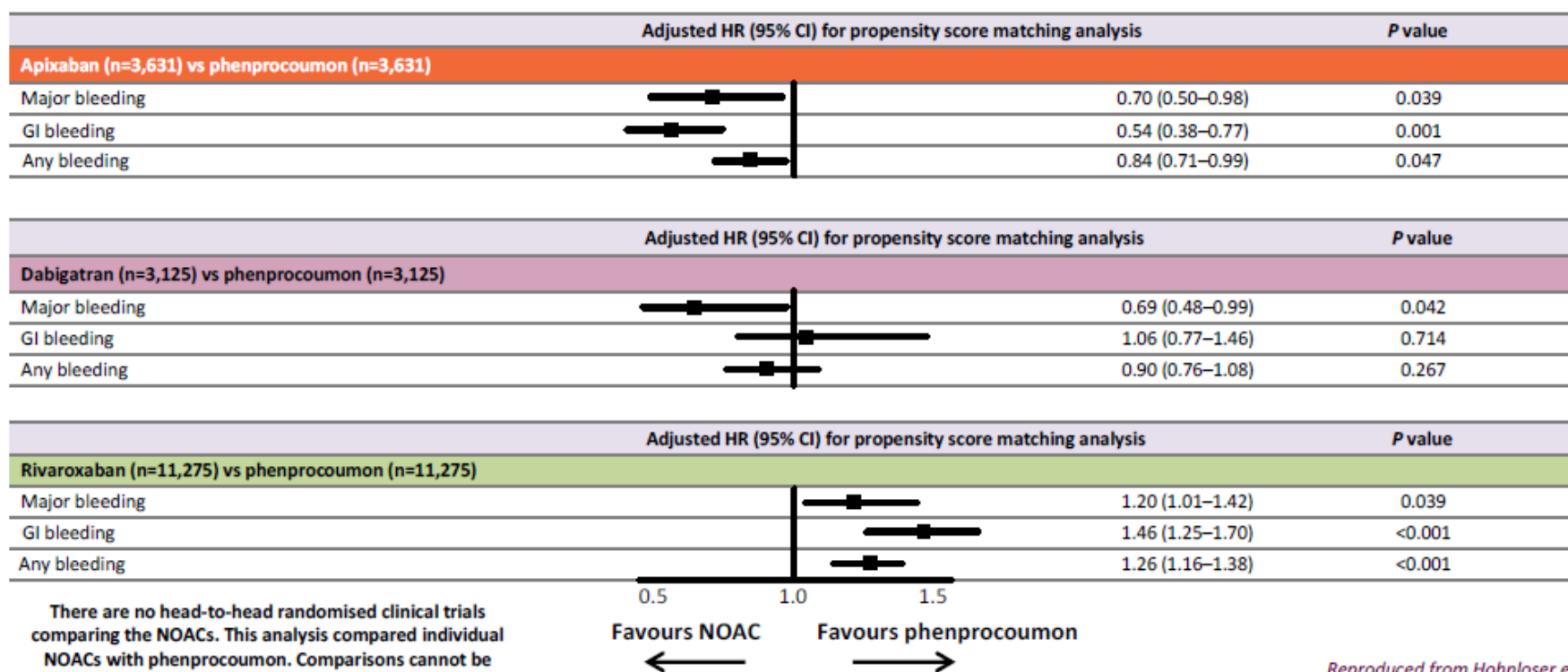
Event rate per 100 person-years (unadjusted)		Adjusted HR (95% CI)		P value
Dabigatran n=3,138	Phenprocoumon n=16,179			
Major bleeding	2.2	3.2	0.76 (0.57–1.03)	0.080
GI bleeding	3.4	3.5	1.11 (0.87–1.42)	0.414
Any bleeding	10.0	12.6	0.88 (0.76–1.01)	0.078

Event rate per 100 person-years (unadjusted)		Adjusted HR (95% CI)		P value
Rivaroxaban n=12,063	Phenprocoumon n=16,179			
Major bleeding	3.3	3.2	1.10 (0.94–1.28)	0.233
GI bleeding	4.5	3.5	1.39 (1.20–1.59)	<0.001
Any bleeding	14.1	12.6	1.19 (1.10–1.28)	<0.001

There are no head-to-head randomised clinical trials comparing the NOACs. This analysis compared individual NOACs with phenprocoumon. Comparisons cannot be made between individual NOACs based on these data

0.5 1.0 1.5
Favours NOAC ← → Favours phenprocoumon

German retrospective database analysis: Adjusted HRs for NOACs vs phenprocoumon – propensity score matching



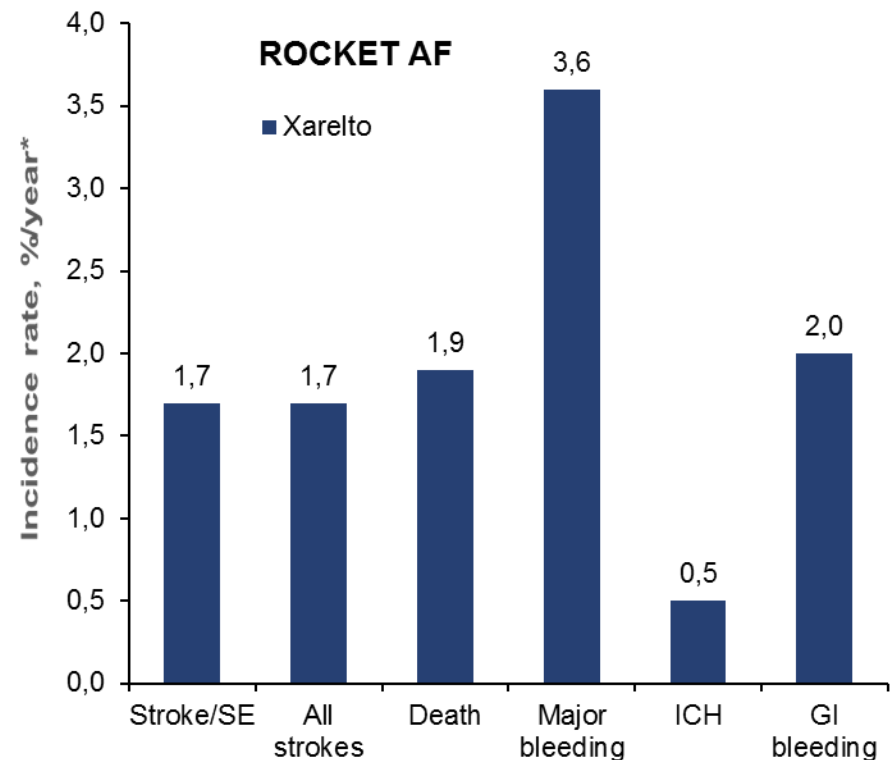
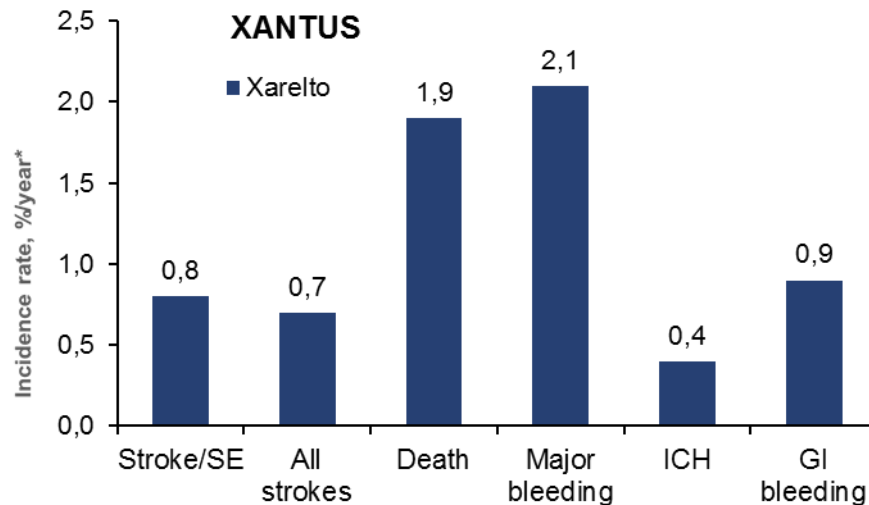
Reproduced from Hohnloser et al. 2017¹

Comparison of Main Outcomes: XANTUS versus ROCKET AF

	CHADS ₂	Prior stroke [#]
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ROCKET AF¹ 3.5 55%

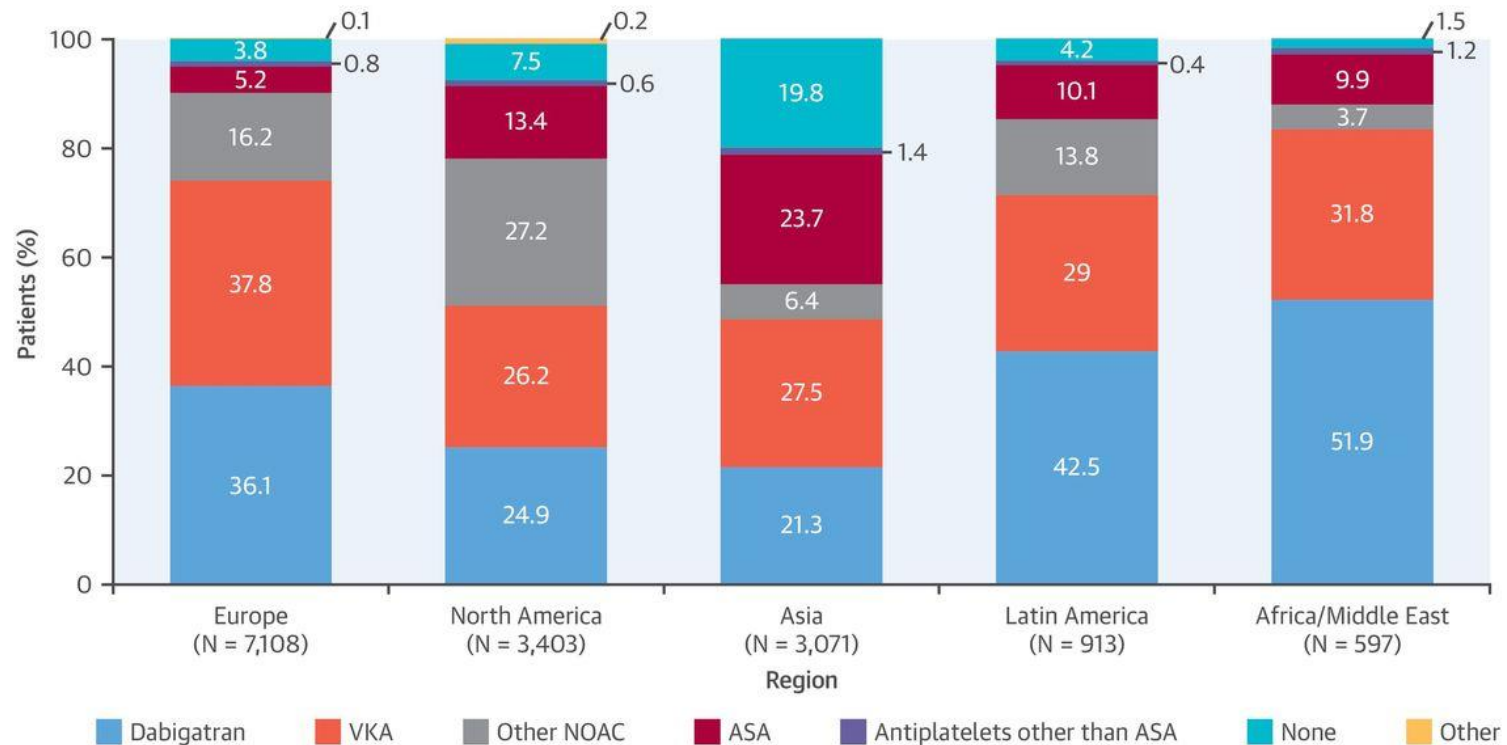
XANTUS² 2.0 19%



[#]Includes prior stroke, SE or TIA;

Gloria-AF registry

CENTRAL ILLUSTRATION: Stroke Prevention in AF: Antithrombotic Treatment per Region



Huisman, M.V. et al. J Am Coll Cardiol. 2017;69(7):777-85.

Persistentie van DOACs –Lijfering abstract ISTH '17

Stichting Farmaceutische Kengetallen

Cohort patiënten met AF en cohort met veneuze tromboembolie

43% van de patienten na 1 jaar met DOAC gestopt – 1/5 naar andere DOAC,
VKA of aspirine

34 % gestopt na 1 jaar – 22% bij VKA gebruikers

66% gestopt na 4 jaar – 36% bij VKA gebruikers

Table 3
Strategies for overcoming the limitations of real life studies.

Problem or limitation	Solution purposes	Complementarities by RCTs
<ul style="list-style-type: none"> • Lack of patient selection brings confounding factors • Lack of randomization 	A priori strict critical design.	<ul style="list-style-type: none"> • Rigorous experimental design • Randomization • Blinding
<ul style="list-style-type: none"> • Absence of blinding • Residual monitoring bias • Immortality bias 	<p>Report the results in a correct, accurate and reliable way following appropriate statements.</p> <p>Time-dependent analysis.</p>	<ul style="list-style-type: none"> • Rigorous analytical method
<ul style="list-style-type: none"> • Confounding by indication 	Propensity score.	<ul style="list-style-type: none"> • Rigorous experimental design • Rigorous analytical method • Randomization • Blinding

Wat kunnen we wel en wat niet concluderen?

WEL: studies bevestigen de veiligheid van de DOACs

Er lijken verschillen tussen de DOACs te zijn

Adherentie/persistentie en dosering van DOACs vormt een – grote – uitdaging

NIET: We kunnen op grond van deze studies niet concluderen dat de ene of de andere NOAC beter of veiliger is dan de andere

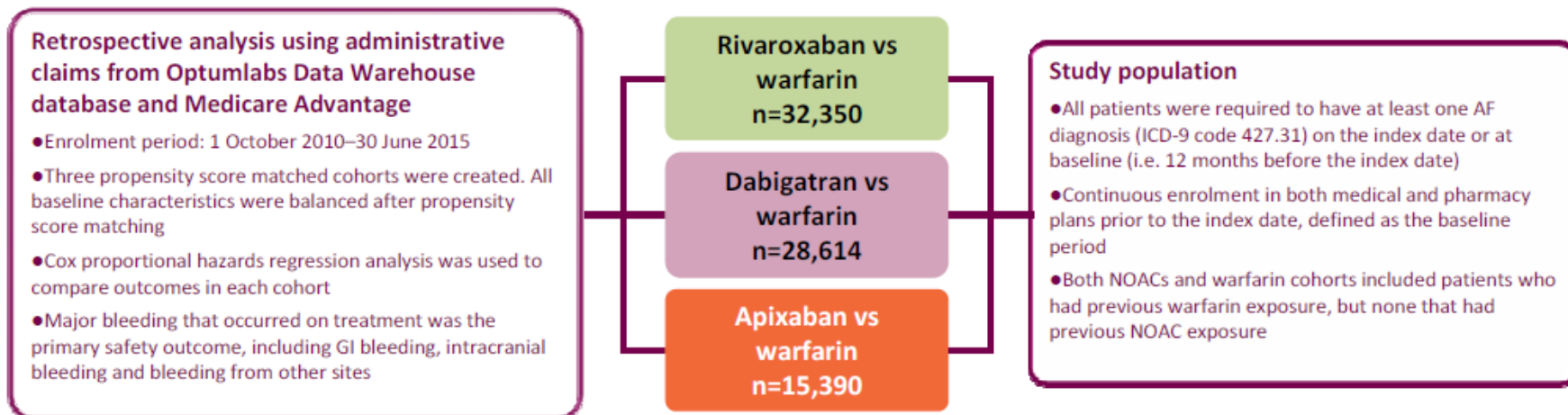
We moeten streven naar optimalisatie van ‘real life’ PROSPECTIEVE studies

DUTCH-AF registry – we zoeken nog leden voor de adjudicatiecommissie

DUTCH- VTE registry - dromen worden werkelijkheid

US retrospective real-world database research assessing the effectiveness and safety of NOACs vs warfarin for stroke prevention in patients with NVAF

► Three matched cohorts using 1:1 propensity score matching vs warfarin



There are no head-to-head randomised clinical trials comparing the NOACs. This analysis compared individual NOACs with warfarin. Comparisons cannot be made between individual NOACs based on these data

Edoxaban was not included in this research.

Endpoint definitions

- ▶ Primary effectiveness outcome:
 - Stroke or SE, including ischaemic stroke, haemorrhagic stroke and systolic embolism
- ▶ Primary safety outcome:
 - Major bleeding, including GI bleeding, intracranial bleeding and bleeding from other sites, as identified by ICD-9 codes in primary or secondary diagnosis of inpatient claims

US retrospective real-world database research: Baseline characteristics after propensity score matching*

Characteristic	Warfarin–apixaban cohort		Warfarin–dabigatran cohort		Warfarin–rivaroxaban cohort	
	Warfarin (n=7,695)	Apixaban (n=7,695)	Warfarin (n=14,307)	Dabigatran (n=14,307)	Warfarin (n=16,175)	Rivaroxaban (n=16,175)
Age, median (IQR)	73 (66–81)	73 (66–81)	70 (61–78)	70 (62–78)	72 (64–80)	72 (64–79)
Female, %	46.8	46.9	40.4	39.7	43.7	43.2
CHA ₂ DS ₂ -VASc score, median (IQR)	4 (3–5)	4 (3–5)	3 (2–5)	3 (2–5)	4 (2–5)	4 (2–5)
HAS-BLED score, median (IQR)	2 (2–3)	2 (2–3)	2 (1–3)	2 (1–3)	2 (2–3)	2 (2–3)
Charlson comorbidity index, median (IQR)	2 (1–4)	2 (1–4)	2 (1–3)	2 (1–3)	2 (1–4)	2 (1–4)

Mean follow-up was 0.5 years for the apixaban-matched cohort, 0.7 years for the dabigatran-matched cohort and 0.6 years for the rivaroxaban-matched cohort.

Reproduced from Yao et al. 2016¹

**18% of apixaban-treated patients, 9% of dabigatran-treated patients and
22% of rivaroxaban-treated patients received the reduced drug dose[†]**

There are no head-to-head randomised clinical trials comparing the NOACs. This analysis compared individual NOACs with warfarin.
Comparisons cannot be made between individual NOACs based on these data

*Propensity score-matched NOAC or warfarin users. [†]In the US, the approved doses of dabigatran for stroke prevention in NVAF are 150 mg BID and 75 mg BID.²
In Europe, the approved doses of dabigatran for stroke prevention in NVAF are 150 mg BID and 110 mg BID.³ IQR: interquartile range.


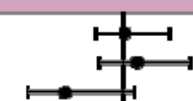
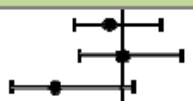
US retrospective real-world database research: Bleeding outcomes

Event rate per 100 person-years			HR (95% CI)	P value
Apixaban n=7,695	Warfarin n=7,695			
Major bleeding	2.33	4.46	0.45 (0.34–0.59)	<0.001
Intracranial bleeding	0.29	1.06	0.24 (0.12–0.50)	<0.001
GI bleeding	1.78	3.04	0.51 (0.37–0.70)	<0.001
Event rate per 100 person-years			HR (95% CI)	P value
Dabigatran n=14,307	Warfarin n=14,307			
Major bleeding	2.37	3.03	0.79 (0.67–0.94)	<0.01
Intracranial bleeding	0.28	0.79	0.36 (0.23–0.56)	<0.001
GI bleeding	1.97	1.95	1.03 (0.84–1.26)	0.78
Event rate per 100 person-years			HR (95% CI)	P value
Rivaroxaban n=16,175	Warfarin n=16,175			
Major bleeding	4.04	3.64	1.04 (0.90–1.20)	0.60
Intracranial bleeding	0.44	0.79	0.51 (0.35–0.75)	<0.001
GI bleeding	3.26	2.53	1.21 (1.02–1.43)	0.03

Favours NOAC ← 1.0 → Favours warfarin *Reproduced from Yao et al. 2016¹*

There are no head-to-head randomised clinical trials comparing the NOACs. This analysis compared individual NOACs with warfarin.
Comparisons cannot be made between individual NOACs based on these data

US retrospective real-world database research: Effectiveness outcomes

Event rate per 100 person-years			HR (95% CI)	P value
	Apixaban n=7,695	Warfarin n=7,695		
Stroke/SE	1.33	1.66	0.67 (0.46–0.98)	0.04
Ischaemic stroke	1.03	1.05	0.83 (0.53–1.29)	0.40
Haemorrhagic stroke	0.19	0.46	0.35 (0.14–0.88)	0.03
				
Event rate per 100 person-years			HR (95% CI)	P value
	Dabigatran n=14,307	Warfarin n=14,307		
Stroke/SE	1.18	1.22	0.98 (0.76–1.26)	0.88
Ischaemic stroke	0.92	0.88	1.06 (0.79–1.42)	0.70
Haemorrhagic stroke	0.16	0.29	0.56 (0.30–1.04)	0.07
				
Event rate per 100 person-years			HR (95% CI)	P value
	Rivaroxaban n=16,175	Warfarin n=16,175		
Stroke/SE	1.26	1.29	0.93 (0.72–1.19)	0.56
Ischaemic stroke	0.95	0.88	1.01 (0.75–1.36)	0.95
Haemorrhagic stroke	0.21	0.32	0.61 (0.35–1.07)	0.08
				

Favours NOAC ← 1.0 → Favours warfarin *Reproduced from Yao et al. 2016¹*

There are no head-to-head randomised clinical trials comparing the NOACs. This analysis compared individual NOACs with warfarin.
Comparisons cannot be made between individual NOACs based on these data