Sessione Anticoagulanti

Trattamento Clinico

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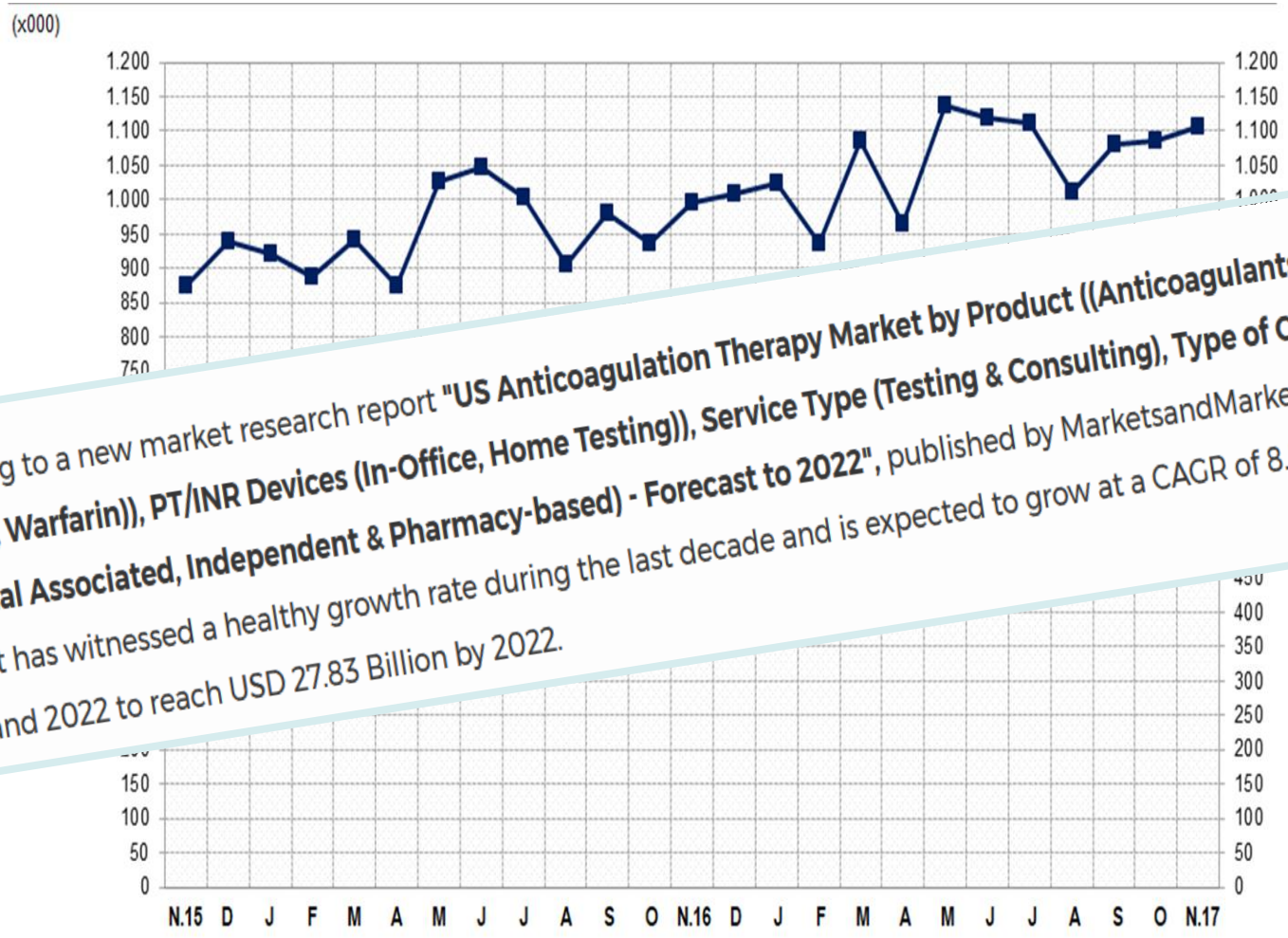
Conflitti di Interesse

Letture
Protocolli di Ricerca
Advisory Boards

- Bayer
- BMS/Pfizer
- Boehringer
- Daiichi Sankyo
- Sanofi
- Alfa Wasserman
- IL

ITALY_ OA Unfactored Market: VKA vs NOA
Pack EQ (RETAIL, HOSPITAL & DPC – MONTHLY Data)
Novembre 2017



According to a new market research report **"US Anticoagulation Therapy Market by Product ((Anticoagulants Drugs (NOACs, Warfarin)), PT/INR Devices (In-Office, Home Testing)), Service Type (Testing & Consulting), Type of Clinic (Hospital Associated, Independent & Pharmacy-based) - Forecast to 2022"**, published by MarketsandMarkets™, the market has witnessed a healthy growth rate during the last decade and is expected to grow at a CAGR of 8.5% between 2017 and 2022 to reach USD 27.83 Billion by 2022.

	N.15	D	J	F	M	A	M	J	J	A	S	O	N.16	D	J	F	M	A	M	J	J	A	S	O	N.17
VKA	594	628	614	571	597	532	650	659	592	540	565	522	554	564	551	485	561	497	575	561	550	499	502	496	511
NOA	283	310	307	317	344	342	377	389	410	365	416	414	440	446	473	452	525	467	562	559	562	513	578	590	597
TOT OA	876	939	921	888	942	874	1.027	1.048	1.003	905	981	936	995	1.010	1.024	937	1.086	965	1.137	1.119	1.112	1.012	1.080	1.086	1.107
±% L.Y.	+12,2	+12,2	+4,2	+17,0	+8,2	+2,5	+15,5	+12,5	+3,4	+16,8	+9,2	+6,0	+13,5	+7,5	+11,2	+5,5	+15,4	+10,3	+10,7	+6,8	+10,8	+11,8	+10,1	+16,0	+11,3

Source: IMS

(mini) Agenda

- Quale anticoagulante?
- Cosa devo fare in ambito clinico?
- Terapia antitrombotica nelle Popolazioni particolari ?
  - Anziano
  - Insuff Renale

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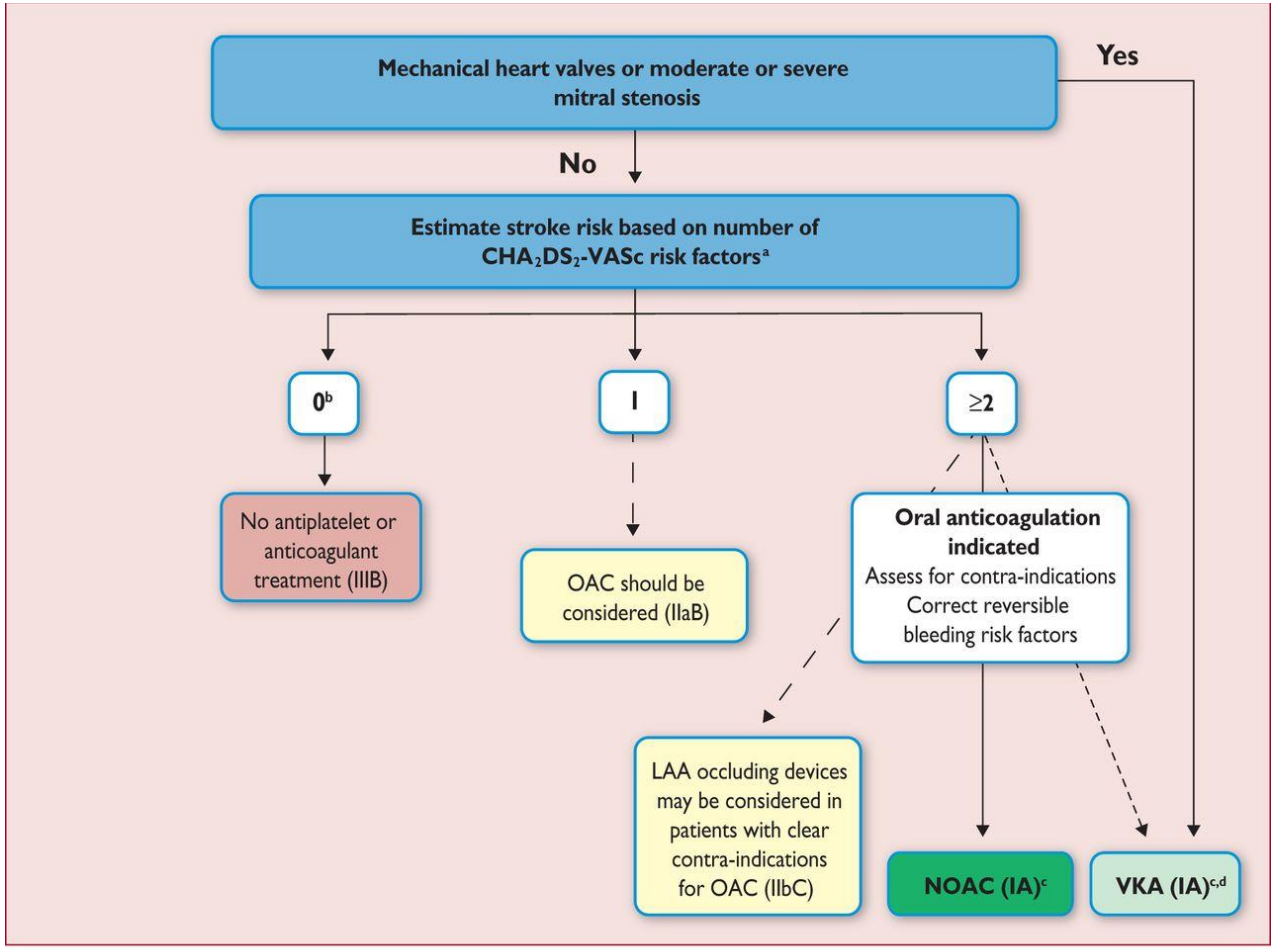
AF

ESC Guidelines

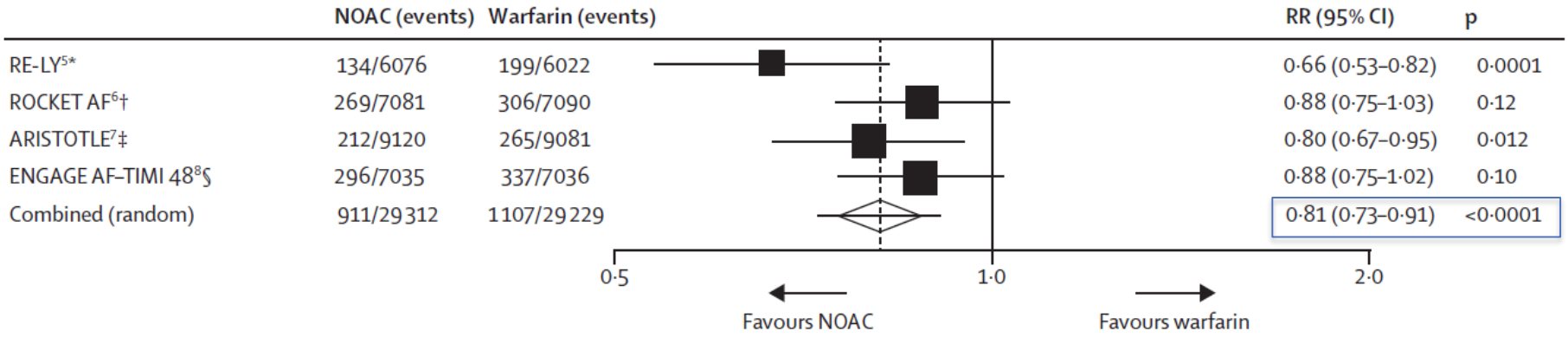


AF = atrial fibrillation; LAA = left atrial appendage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist.
[a]Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes, prior Stroke/TIA/embolus (2 points), Vascular disease, age 65–74 years, female Sex.
[b]Includes women without other stroke risk factors.
[c]IIaB for women with only one additional stroke risk factor.
[d]IB for patients with mechanical heart valves or mitral stenosis.

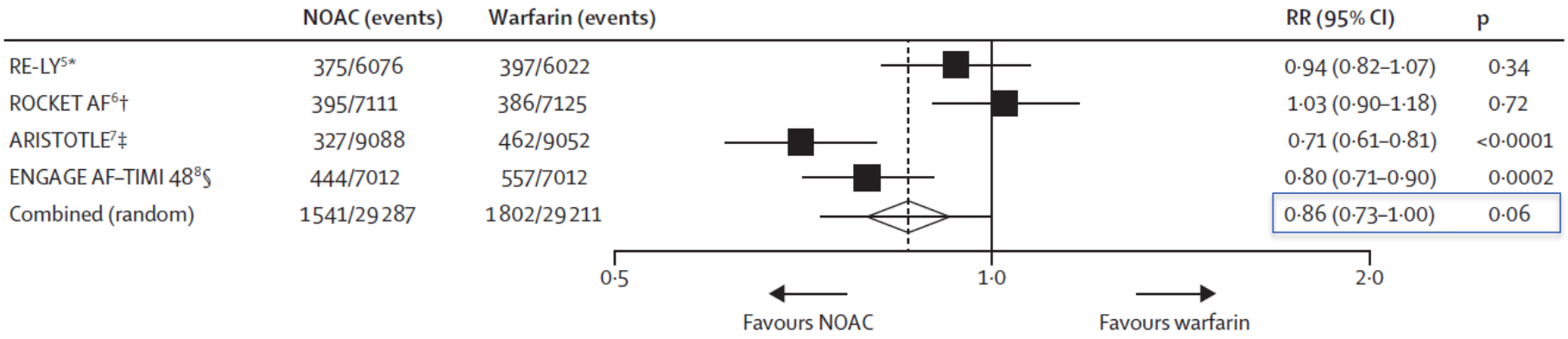
Kirchhof et al; EHJ 2016

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Stroke or SE



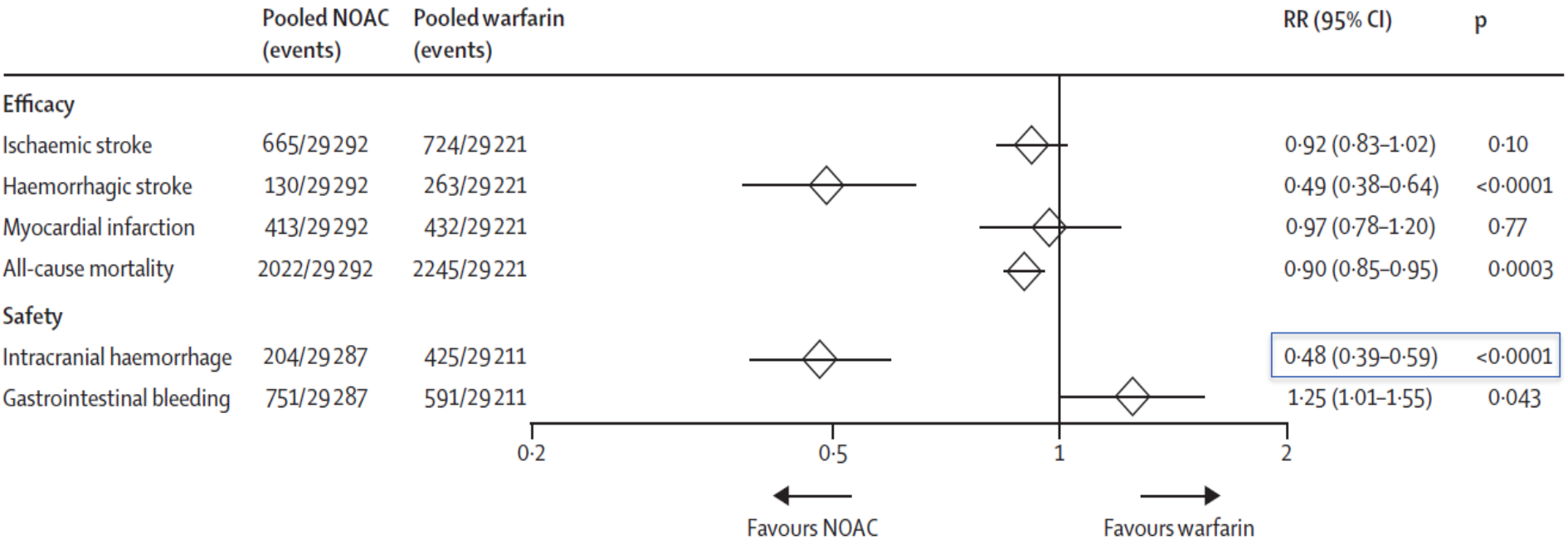
Major Bleeding



Ruff et al. Lancet 2013

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Other endpoints



Ruff et al. Lancet 2013

Differences Between Clinical Trials and Real-Life Settings

Clinical trial

- Strict inclusion and exclusion criteria
- Strict study protocol
- Objectively adjudicated event rates

Real life

- Unselected patient population
- Dose recommendations only
- Over- and under-reporting of events

Limitations of well conducted phase 3 RCTs

- Unintended adverse events (UAEs) are unlikely to be revealed during phase III trials because the usual sample sizes of such studies and even the entire new drug application may range from hundreds to only a few thousand patients.

- Phase III trials also are not useful for detecting UAEs that occur only after long-term therapy because of insufficient length of follow-up time

Rivaroxaban Versus Dabigatran or Warfarin in Real-World Studies of Stroke Prevention in Atrial Fibrillation

Systematic Review and Meta-Analysis

Ying Bai, PhD; Hai Deng, PhD; Alena Shantsila, PhD; Gregory Y.H. Lip, MD

Background and Purpose—This study was designed to evaluate the effectiveness and safety of rivaroxaban in real-world practice compared with effectiveness and safety of dabigatran or warfarin for stroke prevention in atrial fibrillation through meta-analyzing observational studies.

Methods—Seventeen studies were included after searching in PubMed for studies reporting the comparative effectiveness and safety of rivaroxaban versus dabigatran (n=3), rivaroxaban versus Warfarin (n=11), or both (n=3) for stroke prevention in atrial fibrillation.

Results—Overall, the risks of stroke/systematic thromboembolism with rivaroxaban were similar when compared with those with dabigatran (stroke/thromboembolism: hazard ratio, 1.02; 95% confidence interval, 0.91–1.13; I^2=70.2%, N=5), but were significantly reduced when compared with those with warfarin (hazard ratio, 0.75; 95% confidence interval, 0.64–0.85; I^2=45.1%, N=9). Major bleeding risk was significantly higher with rivaroxaban than with dabigatran (hazard ratio, 1.38; 95% confidence interval, 1.27–1.49; I^2=26.1%, N=5), but similar to that with warfarin (hazard ratio, 0.99; 95% confidence interval, 0.91–1.07; I^2=0.0%, N=6). Rivaroxaban was associated with increased all-cause mortality and gastrointestinal bleeding, but similar risk of acute myocardial infarction and intracranial hemorrhage when compared with dabigatran. When compared with warfarin, rivaroxaban was associated with similar risk of any bleeding, mortality, and acute myocardial infarction, but a higher risk of gastrointestinal bleeding and lower risk of intracranial hemorrhage.

Conclusions—In this systematic review and meta-analysis, rivaroxaban was as effective as dabigatran, but was more effective than warfarin for the prevention of stroke/thromboembolism in atrial fibrillation patients. Major bleeding risk was significantly higher with rivaroxaban than with dabigatran, as was all-cause mortality and gastrointestinal bleeding. Rivaroxaban was comparable to warfarin for major bleeding, with an increased risk in gastrointestinal bleeding and decreased risk of intracranial hemorrhage. **(*Stroke*. 2017;48:970-976. DOI: 10.1161/STROKEAHA.116.016275.)**

Key Words: atrial fibrillation ■ dabigatran ■ real-world data ■ rivaroxaban ■ warfarin

The use of oral anticoagulants (OACs), such as the vitamin K antagonists (eg, warfarin), in patients with atrial fibrillation (AF) results in a significant reduction in stroke, ischemic stroke (IS), and systematic thromboembolism (TE), as well as all-cause mortality, when compared with placebo or control.[1] However, warfarin has many limitations, including the necessity for regular anticoagulation monitoring, dietary and drug interactions, and the potential for serious bleeding if anticoagulation is poorly controlled, as reflected by a poor time in therapeutic range.[2]

The availability of the non-vitamin K antagonist oral anticoagulants (NOACs) has changed the landscape for stroke prevention in AF, and a meta-analysis of randomized clinical trials (RCTs) by Ruff et al[3] has shown that usual-dose NOACs result in a significant reduction in stroke/TE and mortality with NOACs compared with warfarin, with a trend toward less major bleeding and significantly lower intracranial hemorrhage (ICH). However, RCTs have specific inclusion/exclusion criteria, have set protocol-based follow-up, and perhaps represent a highly selected and controlled scenario, but still represent the gold standard of testing the effectiveness and safety of an intervention. Based on RCT data, indirect comparisons have been published showing how the different NOACs may perform relative to each other,[4,5] but only a head-to-head RCT can definitively assess the relative efficacy and safety of one NOAC against another.

When a drug is licensed and used in everyday clinical practice, these drugs are then prescribed to a broad spectrum of

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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.116.016275

OPEN

Comparison of the Short-Term Risk of Bleeding and Arteria Thromboembolic Events in Nonvalvular Atrial Fibrillation Patients Newly Treated With Dabigatran or Rivaroxaban Versus Vitamin K Antagonists

A French Nationwide Propensity-Matched Cohort Study

Géric Maura, PharmD*; Pierre-Olivier Blotière, MSc*; Kim Bouillon MD, PhD; Cécile Billionnet, MSc, PhD; Philippe Ricordeau, MD; François Alla, MD, PhD; Mahmoud Zureik, MD, PhD

Background—The safety and effectiveness of non–vitamin K antagonist (VKA) oral anticoagulants, dabigatran o rivaroxaban, were compared with VKA in anticoagulant-naive patients with nonvalvular atrial fibrillation during th early phase of anticoagulant therapy.

Methods and Results—With the use of the French medico-administrative databases (SNIIRAM and PMSI), this nationwid cohort study included patients with nonvalvular atrial fibrillation who initiated dabigatran or rivaroxaban between July an November 2012 or VKA between July and November 2011. Patients presenting a contraindication to oral anticoagulant were excluded. Dabigatran and rivaroxaban new users were matched to VKA new users by the use of 1:2 matching o the propensity score. Patients were followed for up to 90 days until outcome, death, loss to follow-up, or December 3 of the inclusion year. Hazard ratios of hospitalizations for bleeding and arterial thromboembolic events were estimated i an intent-to-treat analysis using Cox regression models. The population was composed of 19 713 VKA, 8443 dabigatrar and 4651 rivaroxaban new users. All dabigatran- and rivaroxaban-treated patients were matched to 16 014 and 9301 VKA treated patients, respectively. Among dabigatran-, rivaroxaban-, and their VKA-matched–treated patients, 55 and 122 an 31 and 68 bleeding events and 33 and 58 and 12 and 28 arterial thromboembolic events were observed during follow-uf respectively. After matching, no statistically significant difference in bleeding (hazard ratio, 0.88; 95% confidence interva 0.64–1.21) or thromboembolic (hazard ratio, 1.10; 95% confidence interval, 0.72–1.69) risk was observed betwee dabigatran and VKA new users. Bleeding (hazard ratio, 0.98; 95% confidence interval, 0.64–1.51) and ischemic (hazar ratio, 0.93; 95% confidence interval, 0.47–1.85) risks were comparable between rivaroxaban and VKA new users.

Conclusions—In this propensity-matched cohort study, our findings suggest that physicians should exercise cautio when initiating either non-VKA oral anticoagulants or VKA in patients with nonvalvular atrial fibrillation. **(*Circulation*. 2015;132:1252-1260. DOI: 10.1161/CIRCULATIONAHA.115.015710.)**

Key Words: atrial fibrillation ■ anticoagulants ■ comparative effectiveness research ■ databases, factual ■ France ■ hemorrhage ■ pharmacoepidemiology ■ stroke

Long-term prophylaxis with oral anticoagulants (OACs) is now widely recommended by international guidelines to prevent stroke in all patients with atrial fibrillation (AF) without contraindications presenting an independent risk factor for stroke.[1–3]

Clinical Perspective on p 1260

However, there are several important considerations in th management of patients taking OACs, starting with the ini tiation of therapy. The initial phase of anticoagulant therap especially in patients with newly diagnosed AF, is of concer early bleeding and thromboembolic risks have been observe to be significantly higher during the first 90 days of therapy i AF patients initiating warfarin.[4–6]

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Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIRCULATIONAHA.115.01571

ORIGINAL RESEARCH

Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation

Xiaoxi Yao, PhD; Neena S. Abraham, MD, MSCE; Lindsey R. Sangaralingham, MPH; M. Fernanda Bellolio, MD, MS; Robert D. McBane, MD; Nilay D. Shah, PhD; Peter A. Noseworthy, MD

Background—The introduction of non–vitamin K antagonist oral anticoagulants has been a major advance for stroke prevention in atrial fibrillation; however, outcomes achieved in clinical trials may not translate to routine practice. We aimed to evaluate the effectiveness and safety of dabigatran, rivaroxaban, and apixaban by comparing each agent with warfarin.

Methods and Results—Using a large US insurance database, we identified privately insured and Medicare Advantage patients with nonvalvular atrial fibrillation who were users of apixaban, dabigatran, rivaroxaban, or warfarin between October 1, 2010, and June 30, 2015. We created 3 matched cohorts using 1:1 propensity score matching: apixaban versus warfarin (n=15 390), dabigatran versus warfarin (n=28 614), and rivaroxaban versus warfarin (n=32 350). Using Cox proportional hazards regression, we found that for stroke or systemic embolism, apixaban was associated with lower risk (hazard ratio [HR] 0.67, 95% CI 0.46–0.98, *P*=0.04), but dabigatran and rivaroxaban were associated with a similar risk (dabigatran: HR 0.98, 95% CI 0.76–1.26, *P*=0.98; rivaroxaban: HR 0.93, 95% CI 0.72–1.19, *P*=0.56). For major bleeding, apixaban and dabigatran were associated with lower risk (apixaban: HR 0.45, 95% CI 0.34–0.59, *P*<0.001; dabigatran: HR 0.79, 95% CI 0.67–0.94, *P*<0.01), and rivaroxaban was associated with a similar risk (HR 1.04, 95% CI 0.90–1.20), *P*=0.60). All non–vitamin K antagonist oral anticoagulants were associated with a lower risk of intracranial bleeding.

Conclusions—In patients with nonvalvular atrial fibrillation, apixaban was associated with lower risks of both stroke and major bleeding, dabigatran was associated with similar risk of stroke but lower risk of major bleeding, and rivaroxaban was associated with similar risks of both stroke and major bleeding in comparison to warfarin. **(*J Am Heart Assoc*. 2016;5:e003725 doi: 10.1161/JAHA.116.003725)**

Key Words: atrial fibrillation • bleeding • non–vitamin K antagonist oral anticoagulants • stroke • warfarin

Atrial fibrillation (AF) is common, with a 1-in-4 lifetime risk after age 40 years,[1] and is associated with a 3- to 5-fold increased risk of stroke.[2,3] Treatment with warfarin can reduce the risk of stroke by 60% to 70%,[4] but its use can be cumbersome because of numerous food and drug interactions and the need for ongoing laboratory testing and dose adjustment.[5] Non–vitamin K antagonist oral anticoagulants (NOACs) provide more convenient therapeutic options and have demonstrated at least equivalent efficacy in comparison to warfarin in large phase III clinical trials.[6–9]

The efficacy and safety achieved in the idealized clinical trial settings may not necessarily translate to routine practice because of the differences in the patient populations, the intensity of follow-up, and the variations in care that patients receive. Extrapolating findings from trials to general practice is especially challenging for anticoagulation therapies. Because anticoagulants are long-term preventive medications that address no ongoing symptoms, adherence is substantially lower in observational studies than in clinical trials.[10–13] Furthermore, appropriate dosing may be hard to achieve in clinical practice because of the complexity of real-world settings.[14]

As these medications are more broadly adopted,[15,16] ongoing evaluation of their effectiveness and safety is important. Until observational studies confirm the generalizability of the clinical trials, some clinicians may remain skeptical and withhold NOACs from patients who stand to

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OPEN ACCESS

Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study

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ABSTRACT

OBJECTIVE

To study the effectiveness and safety of the non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) dabigatran, rivaroxaban, and apixaban compared with warfarin in anticoagulant naïve patients with atrial fibrillation.

DESIGN

Observational nationwide cohort study.

SETTING

Three Danish nationwide databases, August 2011 to October 2015.

PARTICIPANTS

61678 patients with non-valvular atrial fibrillation who were naïve to oral anticoagulants and had no previous indication for valvular atrial fibrillation or venous thromboembolism. The study population was distributed according to treatment type: warfarin (n=35 436, 57%), dabigatran 150 mg (n=12 701, 21%), rivaroxaban 20 mg (n=7192, 12%), and apixaban 5 mg (n=6349, 10%).

MAIN OUTCOME MEASURES

Effectiveness outcomes defined a priori were ischaemic stroke; a composite of ischaemic stroke or systemic embolism; death; and a composite of ischaemic stroke, systemic embolism, or death. Safety outcomes were any bleeding, intracranial bleeding, and major bleeding.

RESULTS

When the analysis was restricted to ischaemic stroke, NOACs were not significantly different from warfarin. During one year follow-up, rivaroxaban was associated with lower annual rates of ischaemic stroke or systemic embolism (3.0% *v* 3.3%, respectively) compared with warfarin: hazard ratio 0.83 (95% confidence interval 0.69 to 0.99). The hazard ratios for dabigatran and apixaban (2.8% and 4.9% annually, respectively) were non-significant compared with warfarin. The annual risk of death was significantly lower with apixaban (5.2%) and dabigatran (2.7%) (0.65, 0.56 to 0.75 and 0.63, 0.48 to 0.82, respectively) compared with warfarin (8.5%), but not with rivaroxaban (7.7%). For the combined endpoint of any bleeding, annual rates for apixaban (3.3%) and dabigatran (2.4%) were significantly lower than for warfarin (5.0%) (0.62, 0.51 to 0.74). Warfarin and rivaroxaban had comparable annual bleeding rates (5.3%).

CONCLUSION

All NOACs seem to be safe and effective alternatives to warfarin in a routine care setting. No significant difference was found between NOACs and warfarin for ischaemic stroke. The risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran compared with warfarin.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The use of non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) has been increasing since their introduction

Based on data from clinical practice, however, limited evidence exists on effectiveness and safety of NOACs compared with warfarin

WHAT THIS STUDY ADDS

No significant difference in risk of ischaemic stroke was evident between NOACs and warfarin

Rivaroxaban was associated with a lower risk of ischaemic stroke or systemic embolism than warfarin, but with comparable major bleeding rates

Dabigatran and apixaban had non-significant hazard ratios compared with warfarin for ischaemic stroke or systemic embolism, whereas major bleeding rates were significantly lower with reference to warfarin

Introduction

Oral anticoagulant treatment with either vitamin K antagonists or non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) is essential for the prevention of stroke or systemic embolism and all cause mortality in patients with atrial fibrillation and one or more risk factors for stroke. The four currently available NOACs are dabigatran, rivaroxaban, apixaban, and edoxaban.[1-4] In clinical studies these drugs show similar efficacy and safety to warfarin, but with more convenience such as no requirement of meticulous dose adjustment to achieve optimal treatment. NOACs are therefore the preferred treatment option in some guidelines, especially where anticoagulation control with warfarin is suboptimal.[5]

A meta-analysis showed that NOACs at standard dose have a favourable risk-benefit profile compared with warfarin, with significant reductions in stroke or systemic embolism, intracranial haemorrhage, and mortality, but a similar major bleeding profile to warfarin, apart from increased gastrointestinal bleeding.[6] The relative efficacy and safety of NOACs were consistent across a wide range of patients.

Thus the use of NOACs in daily clinical practice has been increasing since their introduction.[7] Only large scale real world comparisons of a single NOAC versus warfarin have been published or presented. Evidence relating to the comparative effectiveness and safety of all oral anticoagulant drugs used in clinical practice is currently lacking.

Dabigatran Versus Warfarin for Atrial Fibrillation in Real-World Clinical Practice

A Systematic Review and Meta-Analysis

Robert J. Romanelli, PhD, MPH; Laura Nolting, BS; Marina Dolginsky, BS; Eunice Kym, PharmD; Kathleen B. Orrico, PharmD

ground—Trial data for the benefits and risks of dabigatran versus warfarin in the treatment of nonvalvular atrial rillation are lacking. We sought to review real-world observational evidence for the comparative effectiveness and fety of these agents.

ods and Results—A systematic search of multiple databases was conducted from first available date to March 10, 015 for longitudinal, observational studies comparing dabigatran with warfarin. Two reviewers evaluated studies for igibility and extracted hazard ratios for ischemic stroke and gastrointestinal and intracranial bleeding. hazard ratios were ooled using random-effects meta-analysis. Metaregression was performed to assess treatment-effect heterogeneity. We entified 232 unique citations. Seven retrospective cohort studies met study eligibility criteria, with 348 750 patients and mean follow-up of 2.2 years. In pooled analyses, dabigatran-150 mg was not superior to warfarin in preventing stroke azard ratio, 0.92; 95% confidence interval, 0.84–1.01; *P*=0.066), but had a significantly lower hazard of intracranial eeding (0.44; 0.34–0.59; *P*<0.001). Dabigatran-150 mg had a significantly greater hazard of gastrointestinal bleeding an warfarin (1.23; 1.01–1.50; *P*=0.041), which was potentiated in studies of older (elderly) versus younger populations edian/mean age, ≥75 versus <75 years; β=1.53; 95% confidence interval, 1.10–2.14; *P*=0.020).

lusions—In real-world clinical practice, dabigatran is comparable with warfarin in preventing ischemic stroke among tients with nonvalvular atrial fibrillation. However, dabigatran is associated with a lower risk for intracranial bleeding lative to warfarin, but—particularly among the elderly—a greater risk for gastrointestinal bleeding. Bleeding outcomes om observational studies are consistent with those from the pivotal Randomized Evaluation of Long-Term Anticoagulation herapy trial. **(*Circ Cardiovasc Qual Outcomes*. 2016;9:126-134. DOI: 10.1161/CIRCOUTCOMES.115.002369.)**

Key Words: atrial fibrillation ■ dabigatran ■ evidence-based medicine ■ meta-analysis ■ stroke

trial fibrillation (AF) is associated with a 5-fold increase in the risk of stroke.[1] For more than a half century, the in K antagonist warfarin has been used for stroke preven- n patients with nonvalvular AF (NVAF). The safe use of rin requires frequent blood testing and dose adjustments intain therapeutic anticoagulation and prevent bleeding s, as well as dietary and other lifestyle restrictions.[2] In the first novel oral anticoagulant (NOAC), dabigatran, a thrombin inhibitor, became available for the treatment VAF. Dabigatran challenged the mainstay of treatment, as f this agent is a more convenient treatment option, which not require frequent blood testing or lifestyle restrictions. he Randomized Evaluation of Long-Term Anti- lation Therapy (RE-LY) was a large-scale multicenter mized clinical trial (RCT), evaluating 2 fixed doses of atran (110 mg or 150 mg, twice daily) versus adjusted- warfarin for >2 years. The study was conducted in 44 ries and included 18 113 patients with NVAF.[3] The trial showed that dabigatran-150 mg was superior to warfarin in preventing ischemic stroke, and had a lower rate of intracranial bleeding, but a higher rate of gastrointestinal bleeding. Dabigatran-110 mg was noninferior to warfarin in preventing ischemic stroke and had a similar rate of gastrointestinal bleeding, but a lower rate of intracranial bleeding. On the basis of the findings from this trial, dabigatran-110 mg and dabigatran-150 mg both became available for the treatment of NVAF in most countries, except in the United States, where the 150 mg, but not the 110 mg, dose was approved.

RCTs provide the strongest evidence for drug safety and efficacy. The synthesis of data from multiple and similarly designed RCTs, for a given drug and particular condition, is an important tool in comparative effectiveness research.[4] Such techniques add to the extant body of knowledge by overcoming some of the limitations of individual trials, namely by increasing sample size and improving the precision of effect estimates. Moreover, these techniques allow for the evaluation

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ORIGINAL RESEARCH

Efficacy and Safety of Apixaban, Dabigatran, Rivaroxaban, and Warfarin in Asians With Nonvalvular Atrial Fibrillation

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Background—Whether non–vitamin K antagonist oral anticoagulants (NOACs) are superior to warfarin among Asians with nonvalvular atrial fibrillation remains unclear.

Methods and Results—In this nationwide retrospective cohort study collected from Taiwan National Health Insurance Research Database, there were 5843, 20 079, 27 777, and 19 375 nonvalvular atrial fibrillation patients taking apixaban, dabigatran, rivaroxaban and warfarin, respectively, from June 1, 2012 to December 31, 2016. Propensity-score weighting was used to balance covariates across study groups. Patients were followed until the first occurrence of any efficacy or safety outcome or the end date of study. Hazard ratios (95% confidence intervals) comparing apixaban, dabigatran, and rivaroxaban with warfarin were: ischemic stroke/systemic embolism (IS/SE), 0.55 (0.43–0.69), 0.82 (0.68–0.98), and 0.81 (0.67–0.97); major bleeding, 0.41 (0.31–0.53), 0.65 (0.53–0.80), and 0.58 (0.46–0.72); and all-cause mortality, 0.58 (0.51–0.66), 0.61 (0.54–0.68), and 0.57 (0.51–0.65). A total of 3623 (62%), 17 760 (88%), and 26 000 (94%) patients were taking low-dose apixaban (2.5 mg twice daily), dabigatran (110 mg twice daily), and rivaroxaban (10–15 mg once daily), respectively. Similar to all-dose NOACs, all low-dose NOACs had lower risk of IS/SE, major bleeding, and mortality when compared with warfarin. In contrast to other standard-dose NOACs, apixaban was associated with lower risks of IS/SE (0.45 [0.31–0.65]), major bleeding (0.29 [0.18–0.46]), and mortality (0.23 [0.17–0.31]) than warfarin.

Conclusions—All NOACs were associated with lower risk of IS/SE, major bleeding, and mortality compared with warfarin in the largest real-world practice among Asians with nonvalvular atrial fibrillation. All low-dose NOACs had lower risk of IS/SE, major bleeding, and mortality when compared with warfarin. Standard-dose apixaban caused a lower risk of IS/SE, major bleeding, and mortality compared with warfarin. **(*J Am Heart Assoc*. 2018;7:e008150. DOI: 10.1161/JAHA.117.008150.)**

Key Words: atrial fibrillation • direct thrombin inhibitor • factor Xa inhibitor • hemorrhage • ischemic stroke • mortality • warfarin

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a global prevalence of 2% to 3%. AF significantly increases the risk of thromboembolic events and death.[1] Oral anticoagulants like vitamin K antagonists (eg, warfarin) or non–vitamin K antagonist oral anticoagulants (NOACs; eg, dabigatran, rivaroxaban, apixaban, and edoxaban) are indicated for stroke/systemic embolism prevention in AF patients with 1 or more risk factors for stroke. Several large trials have suggested that NOACs have similar or improved efficacy compared with warfarin and are more convenient and safer alternatives to warfarin.[2–5] The safety profiles showed that all NOACs caused a lower risk of intracranial hemorrhage, but an increased risk of gastrointestinal bleeding with rivaroxaban, edoxaban, and dabigatran (150 mg twice daily) compared with warfarin. Of particular note, Asians may receive greater benefit from NOACs compared with non-Asians, as they carry a higher risk of intracranial hemorrhage and have a greater difficulty maintaining the therapeutic range of international normalized ratio of 2 to 3 when taking warfarin.[6,7] The subgroup analyses from 4 pivotal NOAC trials indicated that NOACs may be more effective and safer in Asians than in non-Asians.[8,9] Also, a recent real-world study showed that dabigatran and rivaroxaban have favorable efficacy and safety profiles compared with warfarin in a large nationwide Asian cohort with nonvalvular AF (NVAF).[10] However, the follow-up periods and patient numbers in those

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CLINICAL RESEARCH
Thrombosis and antithrombotic therapy

Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study

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Background	Non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) are widely used as stroke prophylaxis in non-valvular atrial fibrillation (AF), but comparative data are sparse.
Purpose	To compare dabigatran, rivaroxaban, and apixaban vs. VKA and the risk of stroke/thromboembolism (TE) and intracranial bleeding in AF.
Methods	Using Danish nationwide registries (2011–15), anticoagulant-naïve AF patients were identified when initiating VKA or an NOAC. Outcomes were stroke/TE and intracranial bleeding. Multiple outcome-specific Cox regression was performed to calculate average treatment effects as standardized differences in 1-year absolute risks.
Results	Overall, 43 299 AF patients initiated VKA (42%), dabigatran (29%), rivaroxaban (13%), and apixaban (16%). Mean CHA_2DS_2-VASc (SD) score was: VKA 2.9 (1.6), dabigatran 2.7 (1.6), rivaroxaban 3.0 (1.6), and apixaban 3.1 (1.6). Within patient-specific follow-up limited to the first 2 years, 1054 stroke/TE occurred and 261 intracranial bleedings. Standardized absolute risk (95% CI) of stroke/TE at 1 year after initiation of VKA was 2.01% (1.80% to 2.21%). In relation to VKA, the absolute risk differences were for dabigatran 0.11% (−0.16% to 0.42%), rivaroxaban 0.05% (−0.33% to 0.48%), and apixaban 0.45% (−0.001% to 0.93%). For the intracranial bleeding outcome, the standardized absolute risk at 1 year was for VKA 0.60% (0.49% to 0.72%); the corresponding absolute risk differences were for dabigatran −0.34% (−0.47% to −0.21%), rivaroxaban −0.13% (−0.33% to 0.08%), and apixaban −0.20% (−0.38% to −0.01%).
Conclusions	Among anticoagulant-naïve AF patients, treatment with NOACs was not associated with significantly lower risk of stroke/TE compared with VKA, but intracranial bleeding risk was significantly lower with dabigatran and apixaban.
Keywords	Atrial fibrillation • Stroke • NOACs • Dabigatran • Rivaroxaban • Apixaban

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CLINICAL RESEARCH

Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naïve atrial fibrillation patients: Danish nationwide descriptive data 2011–2013

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Aims	Non-vitamin K antagonist oral anticoagulation (NOAC) agents have been approved for stroke prophylaxis in atrial fibrillation (AF). We investigated 'real-world' information on how these drugs are being adopted.
Methods and results	Using Danish nationwide administrative registers, we identified all oral anticoagulation-naïve AF patients initiating oral anticoagulation from 22 August 2011 through 31 October 2013. Using logistic regression analysis, baseline characteristics and temporal utilization trends were compared between initiators of warfarin vs. one of the N OACs: dabigatran, rivaroxaban, or apixaban. We identified 18 611 oral anticoagulation-naïve AF patients of which 9902 (53%) initiated warfarin treatment, 7128 (38%) dabigatran, 1303 (7%) rivaroxaban, and 278 (1%) apixaban. Overall, 40% of newly initiated patients were started on dabigatran within the first 4 months of when the drug came on market. By October, 2013, 40% were being started on warfarin and dabigatran, respectively, and another 20% were started on either rivaroxaban or apixaban. Rivaroxaban and apixaban users generally had a higher predicted risk of stroke and bleeding compared with warfarin and dabigatran users. Older age, female gender, and prior stroke were some of the factors associated with NOAC use vs. warfarin, whereas chronic kidney disease, myocardial infarction, and heart failure showed the opposite association.
Conclusion	Among oral anticoagulation-naïve AF patients initiated on oral anticoagulation in Denmark, warfarin initiation has declined since the introduction of dabigatran in August 2011. Dabigatran is the most frequently used alternative option to warfarin; however, use of rivaroxaban and apixaban is increasing. Patients initiated with rivaroxaban or apixaban in general have a higher predicted stroke and bleeding risks compared with warfarin or dabigatran initiators.
Keywords	Atrial fibrillation • Oral anticoagulation • Warfarin • Dabigatran • Rivaroxaban • Apixaban

Introduction

Warfarin has long been the treatment of choice for stroke prophylaxis in atrial fibrillation (AF)—the most common cardiac dysrhythmia with a lifetime prevalence of ∼25% for subjects >40 years.[1] While warfarin is effective for preventing thromboembolic complications, it is associated with several treatment-related drawbacks (e.g. continuous monitoring and interactions with other drugs and food) which has encouraged the development of non-vitamin K antagonist oral anticoagulation (NOAC) agents.[2] Albeit the increased risk of stroke and systemic thromboembolism associated with AF, oral anticoagulation (OAC) therapy has shown efficacy for preventing these disabling outcomes,[3] yet at the expense of increased risk of bleeding.[4–6] Dabigatran, apixaban, and rivaroxaban are all examples

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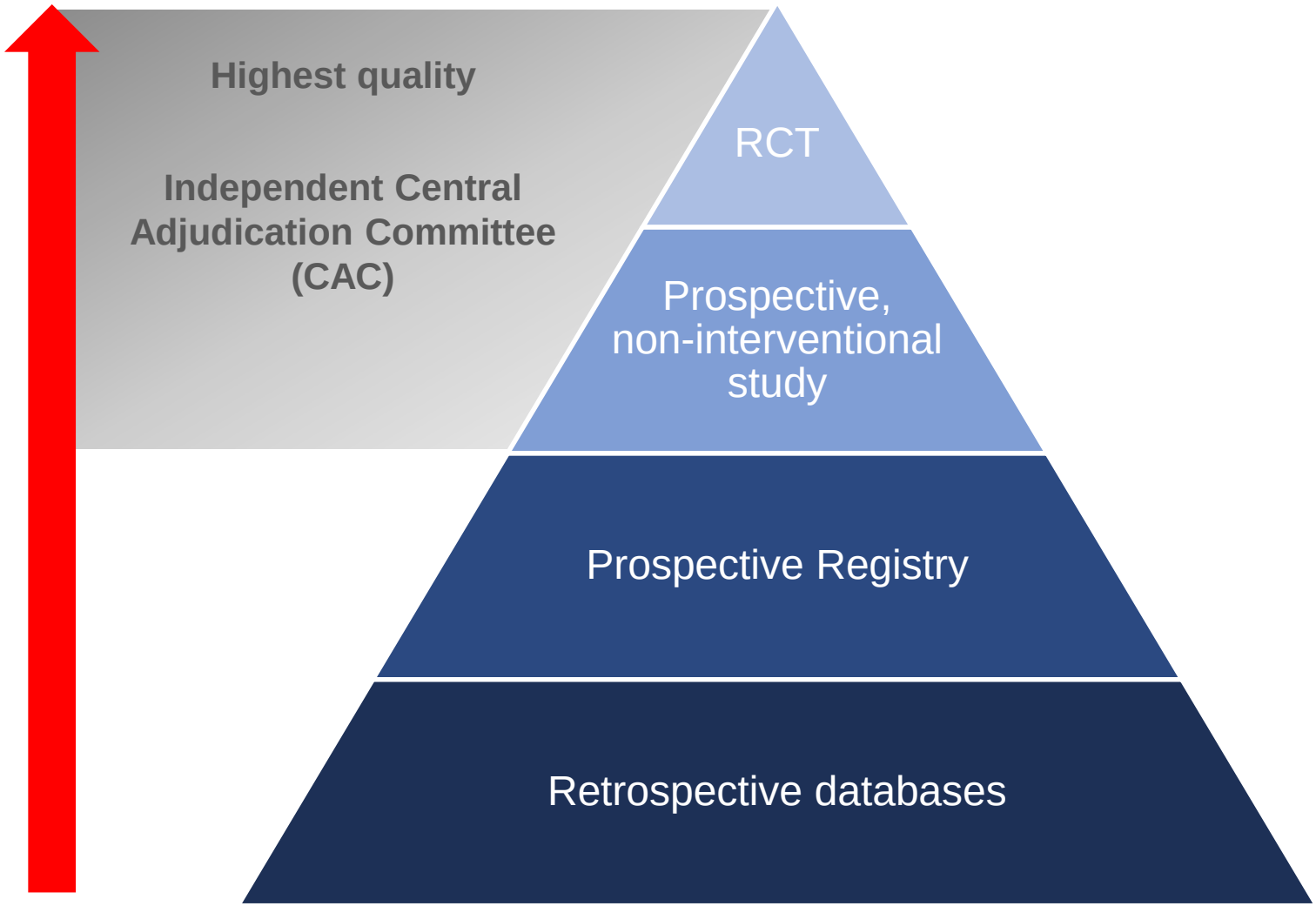
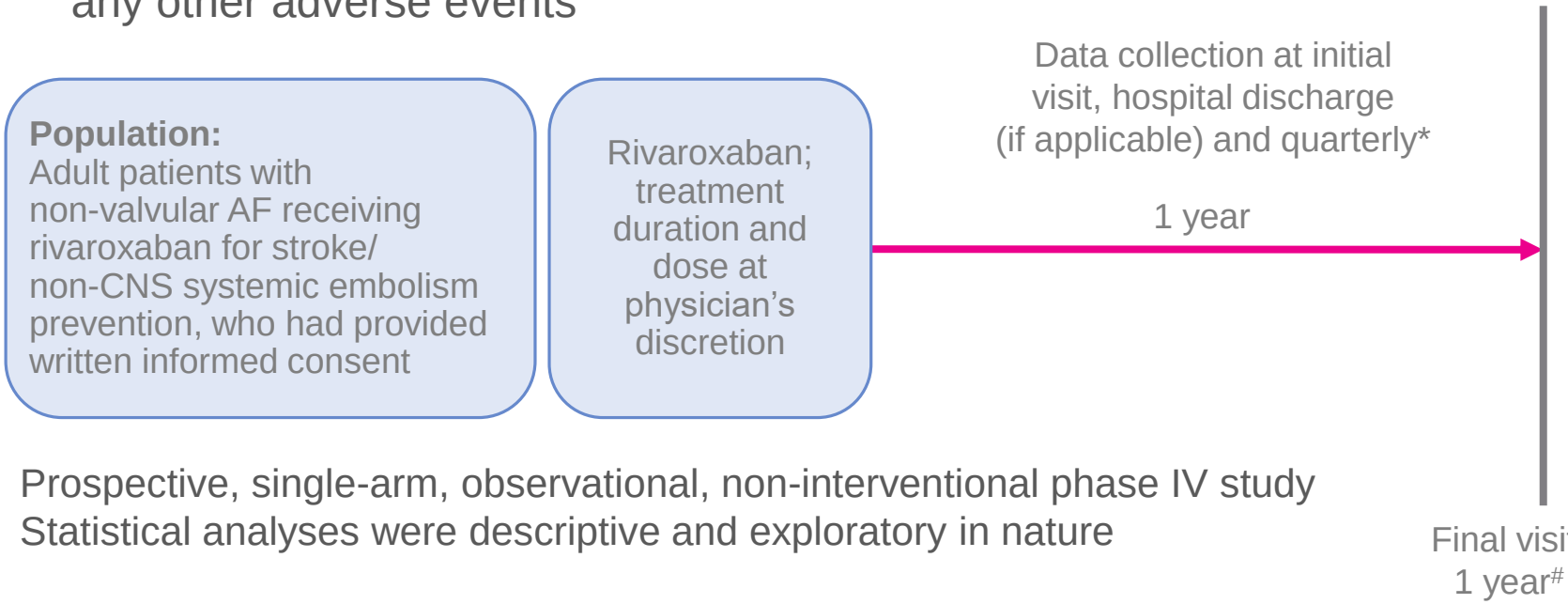

Highest quality
Independent Central Adjudication Committee (CAC)
RCT
Prospective, non-interventional study
Prospective Registry
Retrospective databases

XANTUS: Study Objective and Design

- To collect real-life data on adverse events in patients with non-valvular AF treated with rivaroxaban to determine the safety profile of rivaroxaban across the broad range of patient risk profiles encountered in routine clinical practice
  - Primary outcomes: major bleeding (ISTH definition), all-cause mortality, any other adverse events



Prospective, single-arm, observational, non-interventional phase IV study
Statistical analyses were descriptive and exploratory in nature

*Exact referral dates for follow-up visits not defined (every 3 months recommended); #for rivaroxaban discontinuation ≤1 year, observation period ends 30 days after last dose. Observational design means no interference with clinical practice was allowed

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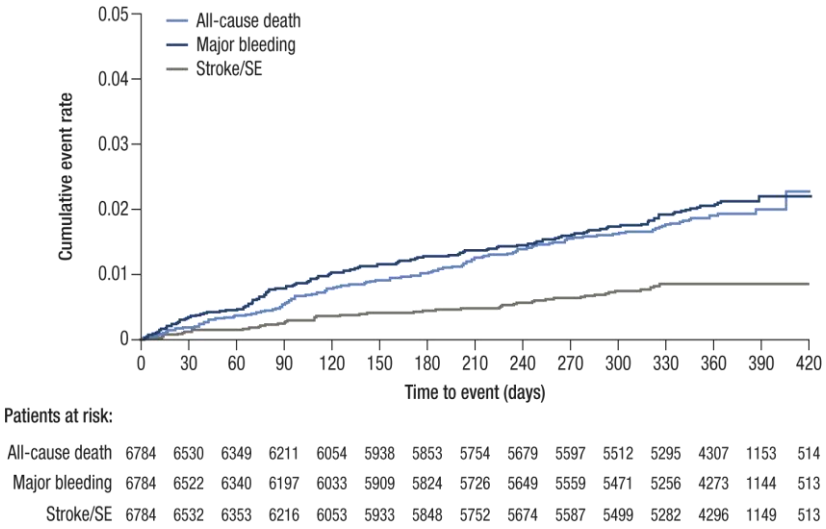
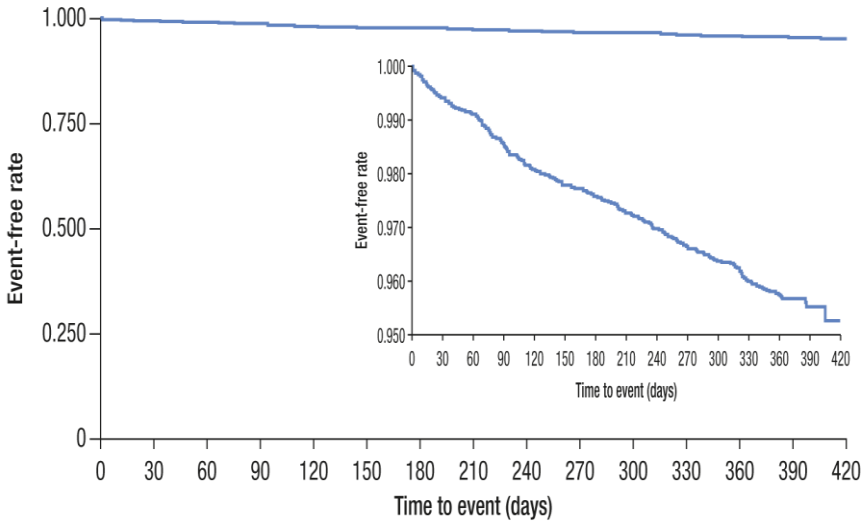
Cumulative Rates (Kaplan–Meier) for Treatment-Emergent Primary Outcomes



Patients at risk:

All-cause death	6784	6530	6349	6211	6054	5938	5853	5754	5679	5597	5512	5295	4307	1153	514
Major bleeding	6784	6522	6340	6197	6033	5909	5824	5726	5649	5559	5471	5256	4273	1144	513
Stroke/SE	6784	6532	6353	6216	6053	5933	5848	5752	5674	5587	5499	5282	4296	1149	513



Patients at risk: 6784 6515 6332 6181 6016 5896 5812 5713 5633 5549 5458 5237 4258 1139 510

- In total, 6522 (96.1%) patients did not experience any of the outcomes of treatment-emergent all-cause death, major bleeding or stroke/SE

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(mini) Agenda

- Quale anticoagulante?
- Cosa devo fare in ambito clinico?
- Terapia antitrombotica nelle Popolazioni particolari ?
  - Anziano
  - Insuff Renale

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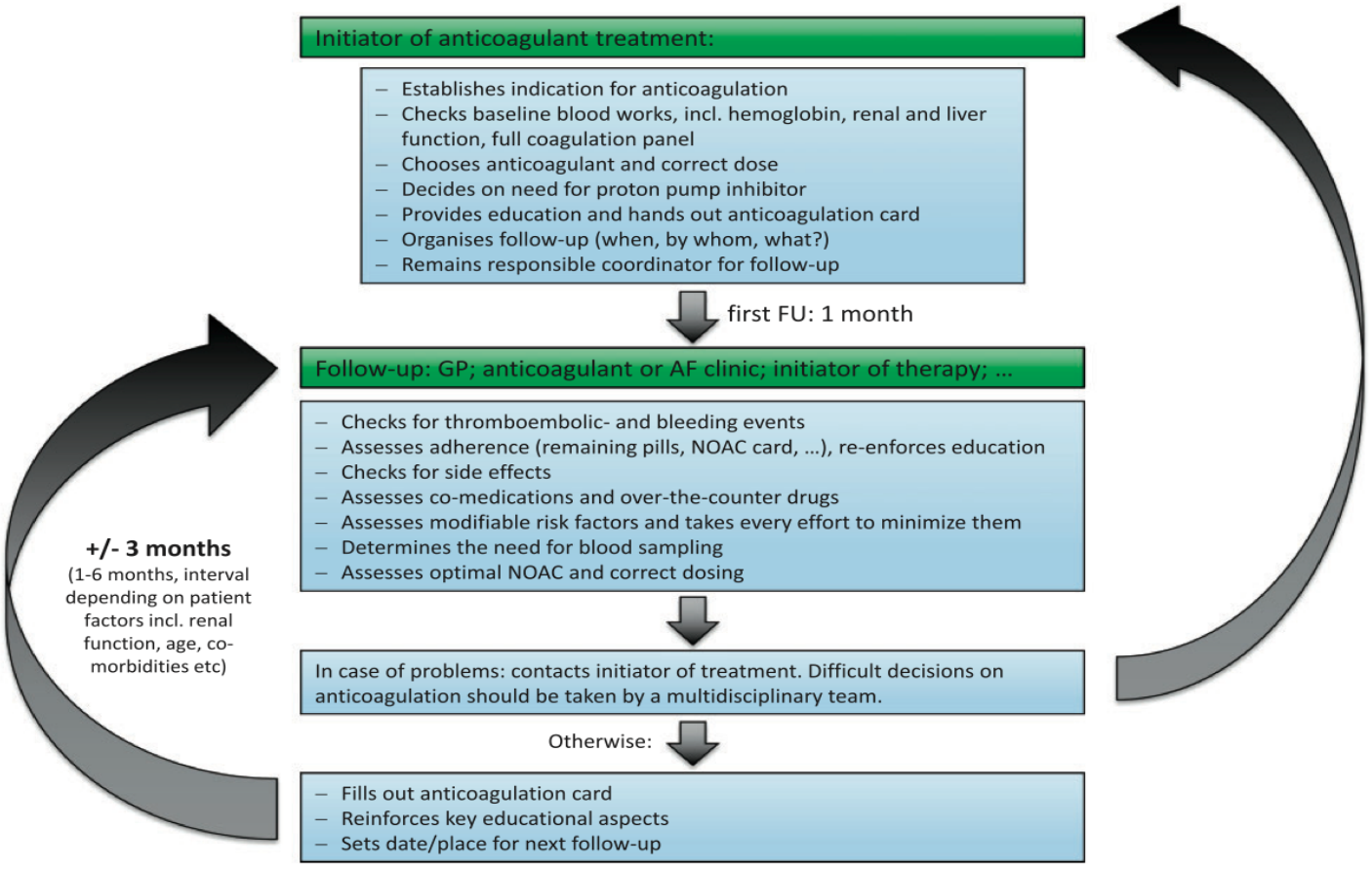

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Contraindications in AF patients (VHD)

Condition	Eligibility for NOAC therapy
Mechanical prosthetic valve	Contraindicated
Moderate to severe mitral stenosis (usually of rheumatic origin)	Contraindicated
Mild to moderate other native valvular disease (e.g., mild-moderate aortic stenosis or regurgitation, degenerative mitral regurgitation etc.)	Included in NOAC trials
Severe aortic stenosis	Limited data (excluded in RE-LY) Most will undergo intervention
Bioprosthetic valve (after > 3 months post operatively)	Not advised if for rheumatic mitral stenosis
	Acceptable if for degenerative mitral regurgitation or in the aortic position
Mitral valve repair (after > 3 months post operatively)	Some patients included in some NOAC trials
PTAV and TAVI	No prospective data yet May require combination with single or dual antiplatelet therapy
Hypertrophic cardiomyopathy	Few data, but patients may be eligible for NOACs

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Phase III Trials - Patient Characteristics

		ROCKET AF[1] (n=14,264)	ARISTOTLE[2] (n=18,201)	ENGAGE AF[3] (n=21,105)	RE-LY[4,5] (n=18,113)
Mean $CHADS_2$-Score		3.5	2.1	2.8	2.1
C	CHF*	64%	35%	57%	32%
H	Hypertension	91%	87%	94%	79%
A	Age ≥75 years	44%	31%	40%	40%
D	Diabetes mellitus	40%	25%	36%	23%
S2	Prior stroke or TIA#	55%	19%	28%	20%

* LVEF <40%; #Data include patients with systemic embolism

Not intended for direct comparison of studies results

[1] Van Diepen S et al. Circ Heart Fail. 2013;6(4):740–47.;
[2] Granger CB et al. N Engl J Med. 2011;365(11):981-992;
[3] Giugliano RP et al. N Engl J Med. 2013;369(22):2093-2104;
[4] Connolly SJ et al. N Engl J Med. 2009;361(12):1139-1151; 5. Eikelboom JW et al. Circulation 2011;123(21):2363-2372

Absorption and metabolism of different DOACs

	Dabigatran[158,182]	Apixaban[183]	Edoxaban[184]	Rivaroxaban[185,186]
Bioavailability	3–7%	50%	62%	15 mg/20 mg: 66% without food, 80–100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose	20%/80%	73%/27%	50%/50%	65%/35%
Plasma protein binding	35%	87%	55%	95%
Dialysability	50–60% (in part dialysable)	14% (in part dialysable)	n.a. (in part dialysable)	n.a. (in part dialysable)
Liver metabolism: CYP3A4 involved	No	Yes [elimination, moderate contribution (≈25%)[a]]	Minimal (<4% of elimination)	Yes (hepatic elimination ≈18%)[131]
Absorption with food	No effect	No effect	6-22% more; minimal effect on exposure	+39% more (see above)
Absorption with H2B/PPI	-12% to 30% (not clinically relevant)	No effect	No effect	No effect
Asian ethnicity	+25%[166]	No effect	No effect	No effect
Elimination half-life	12–17 h	12 h	10–14 h	5–9 h (young)
				11–13 h (elderly)
Other	Dyspepsia (5–10%)			Intake of 15 mg/20 mg with food mandatory

[a]Hepatic metabolism in total of ≈25%, mostly via CYP3A4, with minor contributions of CYP1A2, 2J2, 2C8, 2C9, and 2C19.

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Approved Dose

Stroke prevention in atrial fibrillation (SPAF)		
	Standard dose	**Comments/dose reduction**
Apixaban[30]	2 × 5 mg	2 × 2.5 mg if two out of three: weight ≤60 kg, age ≥80 years, serum creatinine ≥133 µmol/(1.5 mg/dL) [*or* if CrCl 15–29 mL/min]
Dabigatran[28]	2 × 150 mg / 2 × 110 mg	No pre-specified dose-reduction criteria[a]
Edoxaban[31]	1 × 60 mg	1 × 30 mg if: weight ≤60 kg, CrCl ≤50 mL/min, concomitant therapy with strong P-Gp inhibitor (see **chapter 5**)
Rivaroxaban[29]	1 × 20 mg	1 × 15 mg if CrCl ≤50 mL/min
Treatment of DVT/PE		
	Initial therapy	**Remainder of treatment phase**
Apixaban[330]	2 × 10 mg, 7 days	2 × 5 mg, no dose reduction
Dabigatran[331]	Heparin/LMWH	No pre-specified dose-reduction criteria[b]
Edoxaban[332]	Heparin/LMWH	1 × 60 mg, same dose reduction as for SPAF (see above)
Rivaroxaban[333,334]	2 × 15 mg, 21 days	1 × 20 mg, no dose reduction[c]

Renal function estimation and categories of renal dysfunction

Decreased GFR[a]	GFR <60 mL/min/1.73 m^2		
Markers of kidney damage (≥1)	• Excessive albuminuria (AER ≥30 mg/24 h; ACR ≥30 mg/g or ≥3 mg/mmol) • Urine sediment abnormalities • Electrolyte or other abnormality caused by tubular disorders • Abnormal histology • Structural abnormalities detected by kidney imaging • History of kidney transplantation		
GFR category	CKD stage	GFR[a]	Descriptions
G1	1	≥90	Normal or high
G2	2	60–89	Mildly decreased
G3a	3	45–59	Mildly to moderately decreased
G3b		30–44	Moderately to severely decreased
G4	4	15–29	Severely decreased
G5	5	<15	Kidney failure (requires renal replacement therapy – dialysis or kidney transplantation)

Estimation of renal function in NOAC patients best by Creatinine Clearance (Cockroft–Gault):

$$\text{CrCl [mg/dl]} = \frac{(140 - \text{age}) \times \text{weight (in kg)} \times [0.85 \text{ if female}]}{72 \times \text{serum creatinine (in mg/dL)}]}$$

Online calculators available at (e.g.): www.kidney.org/professionals/kdoqi/gfr_calculator; www.nephron.com/cgi-bin/CGSI.cgi; www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation; https://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault.
Popular Apps are NephroCalc, MedMath, MedCalc, Calculate by QxMD, and Archimedes.
CKD, chronic kidney disease; GFR, glomerular filtration rate; AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CrCl, creatinine clearance.
[a]mL/min/1.73 m^2.

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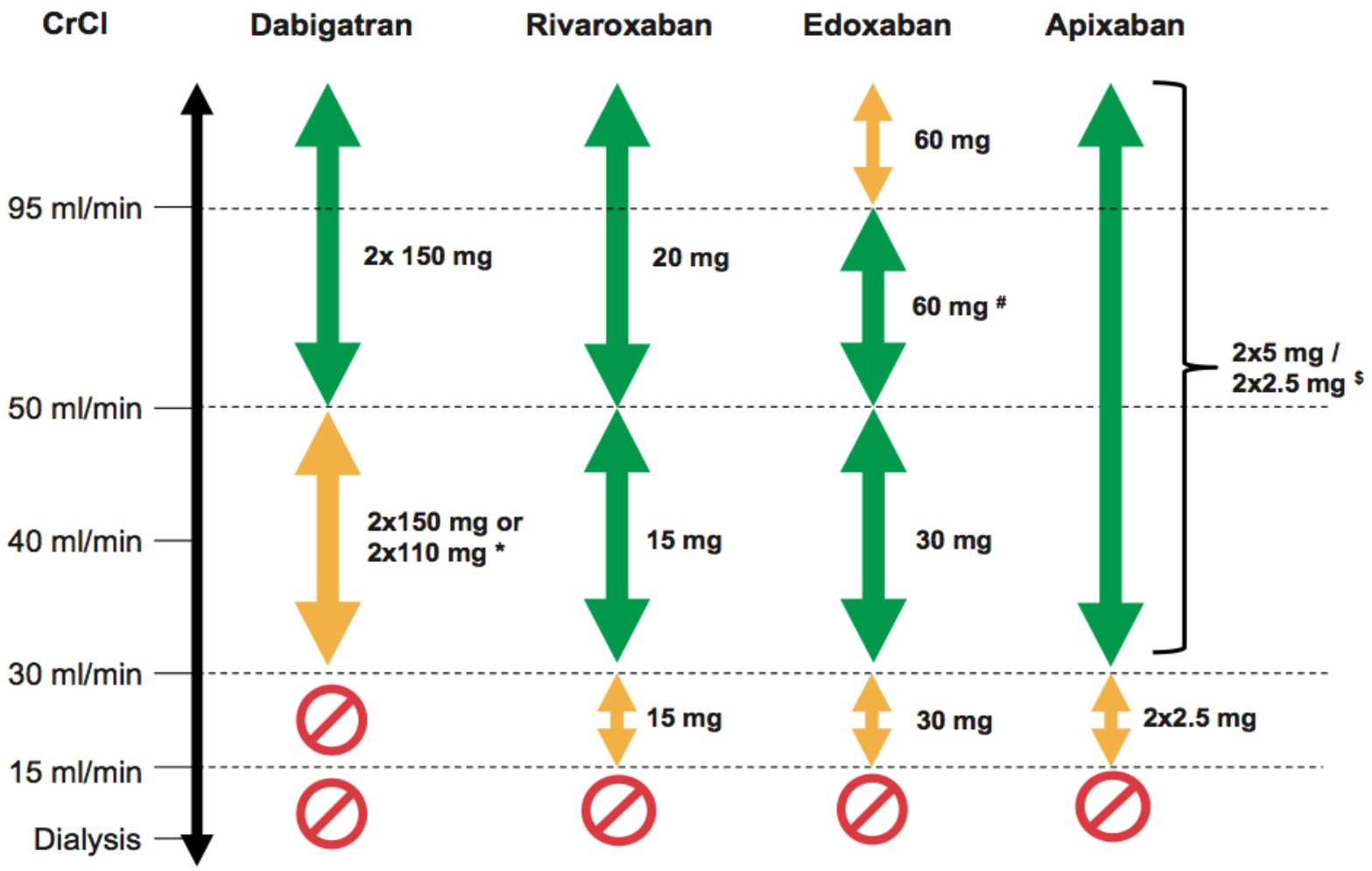
DOAC dose according to renal function in AF patients



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Child-Turcotte-Pugh score and DOACs use in hepatic insufficiency

Parameters	1 point	2 points	3 points
Encephalopathy	No	Grade 1–2 (suppressed with medication)	Grade 3–4 (refractory/chronic)
Ascites	No	Mild (diuretic-responsive)	Moderate–severe (diuretic-refractory)
Bilirubin	<2 mg/dL	2–3 mg/dL	>3 mg/dL
	<34 µmol/L	34–50 µmol/L	>50 µmol/L
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
	>35 g/L	28–35 g/L	<28 g/dL
INR	<1.7	1.71–2.30	>2.30

Child–Pugh category	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
A (5–6 points)	No dose reduction	No dose reduction	No dose reduction	No dose reduction
B (7–9 points)	Use with caution	Use cautiously	Use cautiously	Do not use
C (10–15 points)	Do not use	Do not use	Do not use	Do not use

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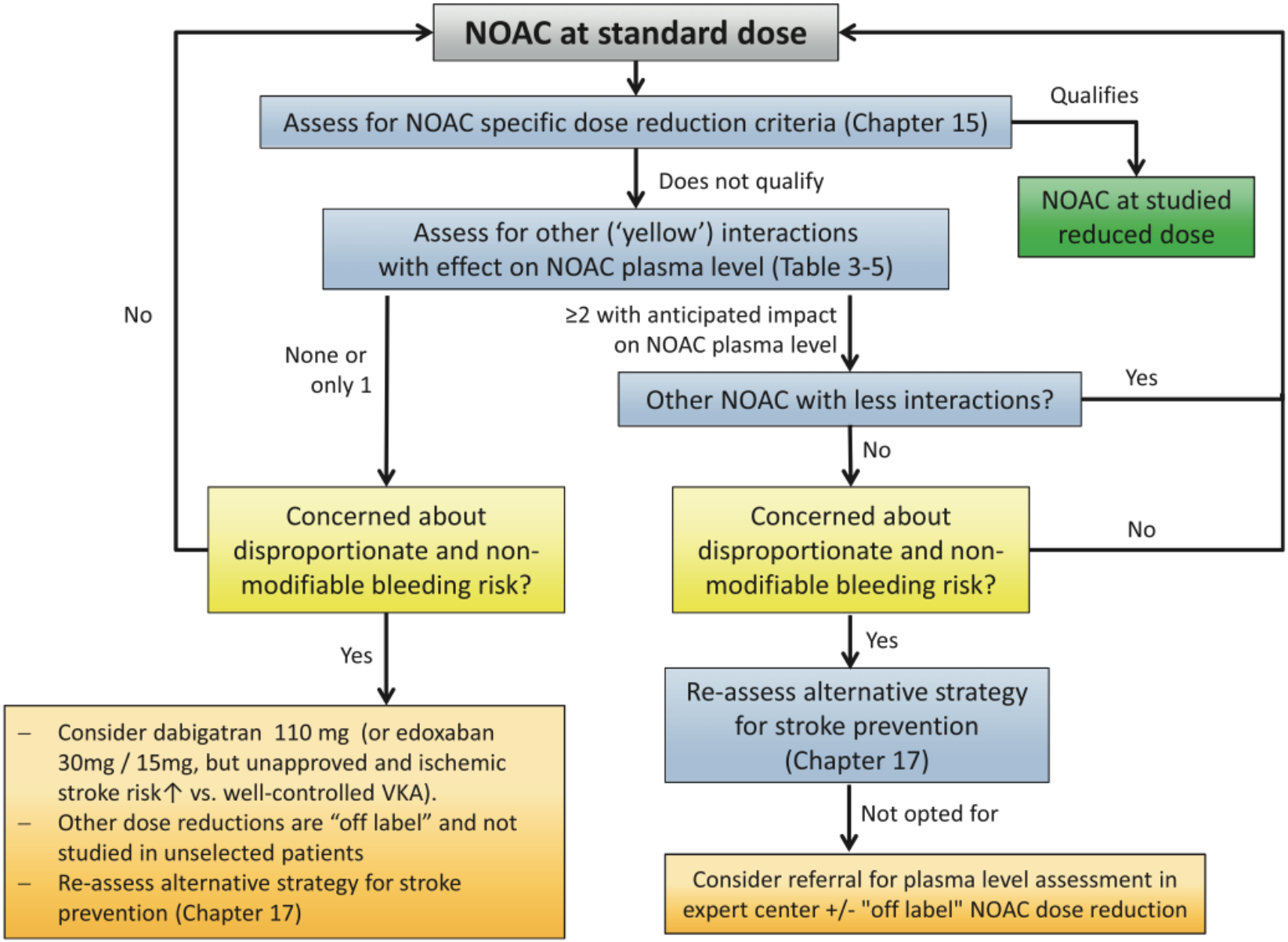

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Checklist during follow-up contacts of AF patients on anticoagulation

	Interval	Comments
1. Adherence	Each visit	• Instruct patient to bring NOAC card and complete list of medication: make note and assess average adherence • Re-educate on importance of strict intake schedule • Inform about adherence aids (special boxes; smartphone applications; . . .). Consider specific adherence measuring interventions (review of pharmacy refill data; electronic monitoring[51]; special education session; . . .)
2. Thromboembolism	Each visit	• Systemic circulation (TIA, stroke, peripheral) • Pulmonary circulation
3. Bleeding	Each visit	• 'Nuisance' bleeding: preventive measures possible? Motivate patient to diligently continue anticoagulation • Bleeding with impact on quality-of-life or with risk: prevention possible? Need for revision of anticoagulation indication, dose or timing?
4. Other side effects	Each visit	Carefully assess relation with NOAC: decide for continuation (and motivate), temporary cessation, or change of anticoagulant drug
5. Co-medications	Each visit	• Prescription drugs; over-the-counter drugs (Pharmacokinetics and drug–drug interactions of non-vitamin K antagonist oral anticoagulants section). • Careful interval history: also temporary use can be risky
6. Blood sampling (incl. hemoglobin, renal and liver function)	Yearly	Patients other than those specified below
	6-monthly	≥75 years (especially if on dabigatran) or frail (see **chapter 2**)
	x-monthly	If renal function CrCl ≤60 mL/min: recheck interval = CrCl/10
	If needed	If intercurrent condition that may impact renal or hepatic function
7. Assessing and minimizing modifiable risk factors for bleeding	Each visit	• As recommended by current guidelines[3] • Particularly: uncontrolled hypertension (systolic >160 mmHg), medication predisposing for bleeding (e.g. aspirin, NSAIDs), labile INR (if on VKA), excessive alcohol intake)
8. Assess for optimal NOAC and correct dosing	Each visit	Especially based on the above, re-assess whether a. The chosen NOAC is the best for the patient b. The chosen dose is correct

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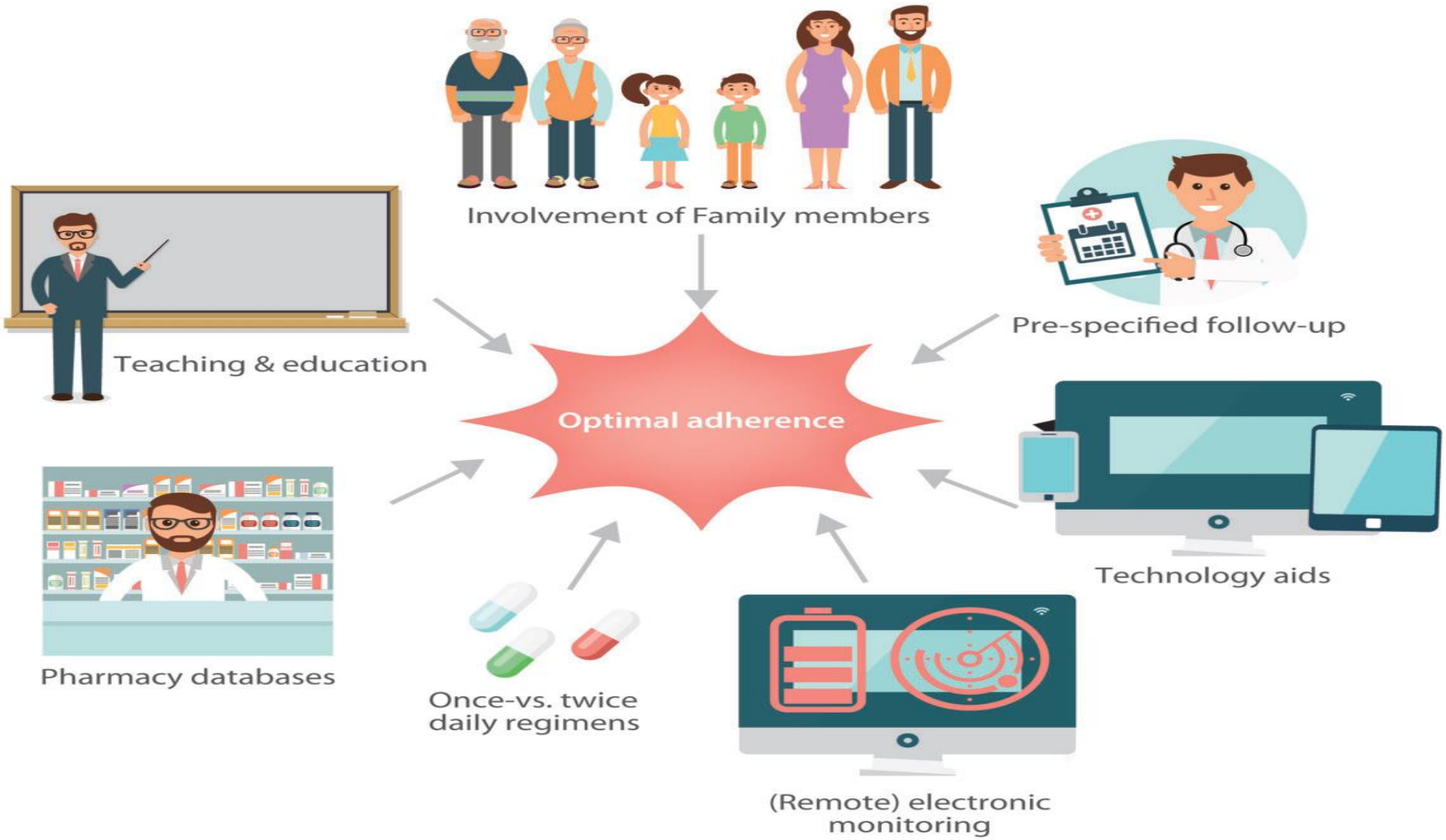
Adherence


Involvement of Family members
Teaching & education
Pre-specified follow-up
Optimal adherence
Technology aids
Pharmacy databases
Once-vs. twice daily regimens
(Remote) electronic monitoring

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Plasma levels and coagulation assays in patients treated with NOACs

	Dabigatran[229,230]	Apixaban[231], SmPc	Edoxaban[184,232]	Rivaroxaban[131,186]
Expected plasma levels of NOACs in patients treated for AF (based on dTT/ECA for dabigatran and anti-FXa activity for Xa inhibitors)				
Expected range of plasma levels *at peak* for standard dose (ng/mL)[a]	64–443	69–321	91–321	184–343
Expected range of plasma levels *at trough* for standard dose (ng/mL)[a]	31–225	34–230	31–230	12–137
Expected impact of NOACs on routine coagulation tests				
PT	↑	(↑)	↑(↑)	↑↑ (↑)
aPTT	↑↑(↑)	(↑)	↑	↑
ACT	↑(↑)	↑	↑	↑
TT	↑↑↑↑	—	—	—

Steffel et al. EHJ 2018

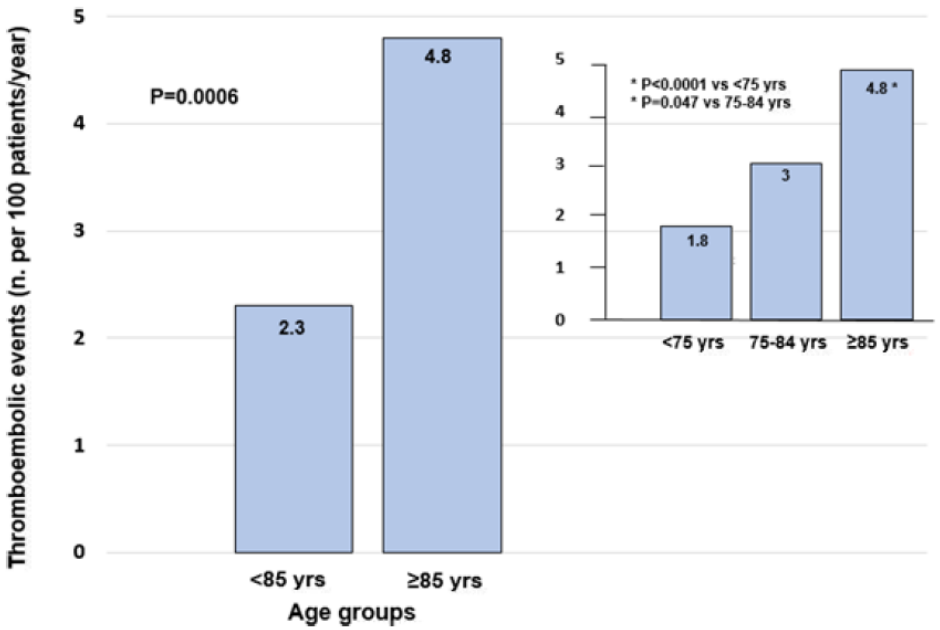
(mini) Agenda

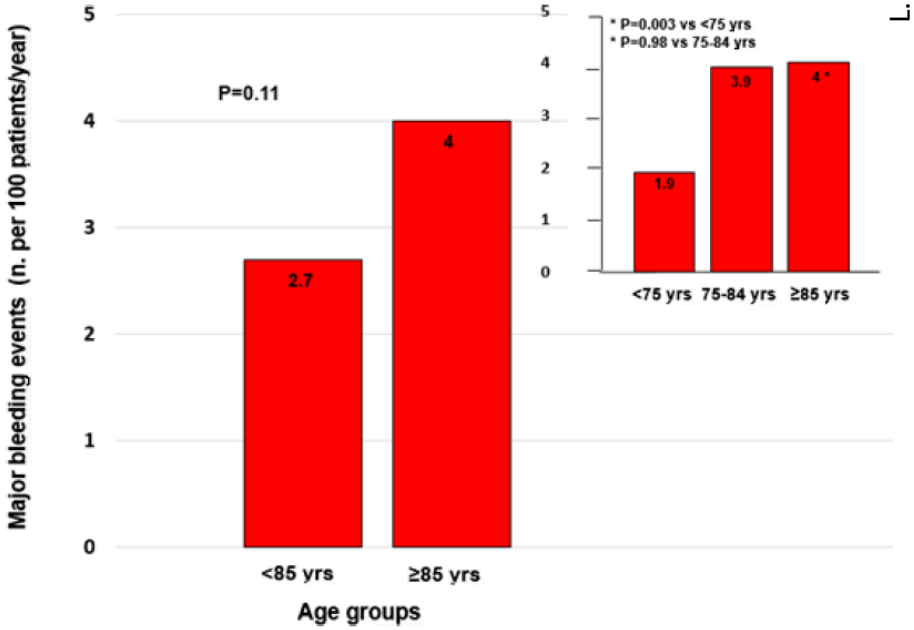
- Quale anticoagulante?
- Cosa devo fare in ambito clinico?
- Terapia antitrombotica nelle Popolazioni particolari ?
  - Anziano
  - Insuff Renale

Old/very Old?

Incidence of **thromboembolic events** (stroke/TIA/systemic embolism) and **major bleeding** at 1 year in patients aged <85 and ≥85 years.

A Sub-Analysis From the PREFER in AF
(PREvention oF Thromboembolic Events–European Registry in Atrial Fibrillation)



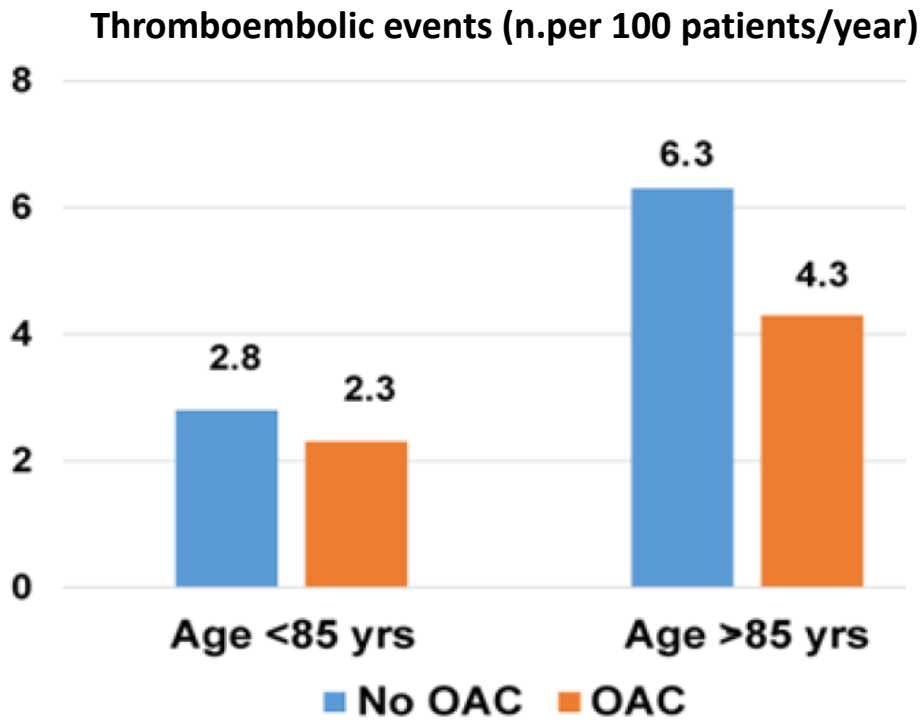


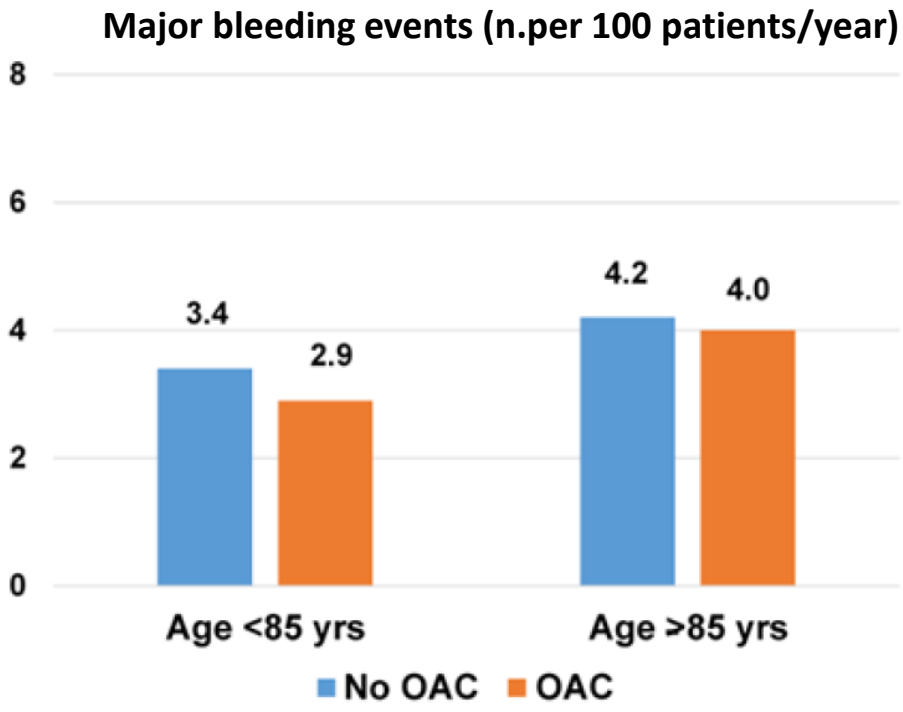
Rates of events according to 3 age strata (<75, 75–84, and ≥85 years) are also depicted.

G.Patti et al. J Am Heart Assoc. 2017;6:e005657. DOI:10.1161/JAHA.117.005657

Incidence of **thromboembolic events** (stroke/TIA/systemic embolism) and **major bleeding** at 1 year in patients aged <85 and ≥85 years receiving OAC or no OAC (antiplatelet therapy only or no antithrombotic drug).

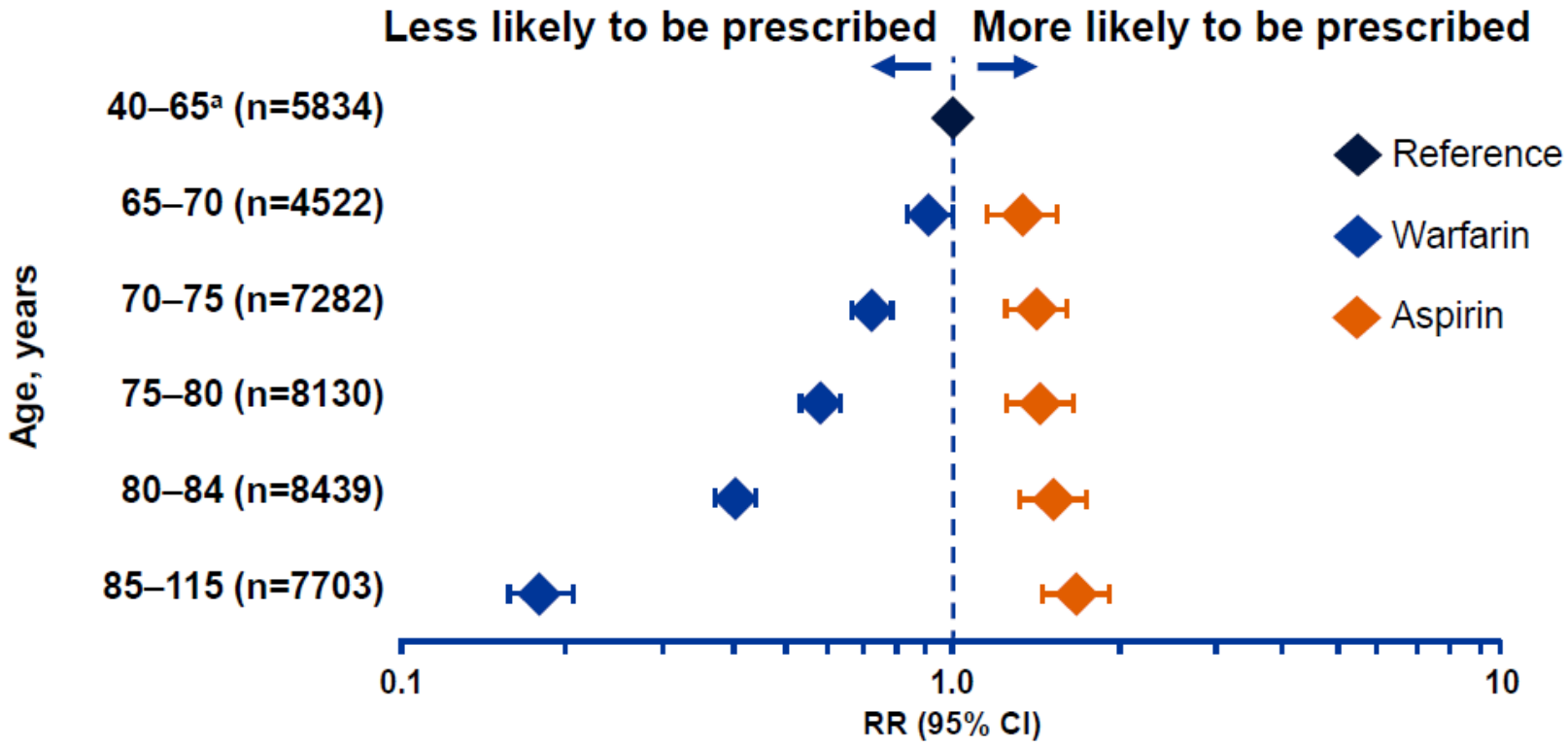
A Sub-Analysis From the PREFER in AF
(PREvention oF Thromboembolic Events–European Registry in Atrial Fibrillation)





G.Patti et al. J Am Heart Assoc. 2017;6:e005657. DOI:10.1161/JAHA.117.005657

Probability of Prescription



An analysis of computerised medical records from general practitioners in the United Kingdom; [a]reference population.
Gallagher AM, et al. *J Thromb Haemost* 2008; 6:1500–1506.

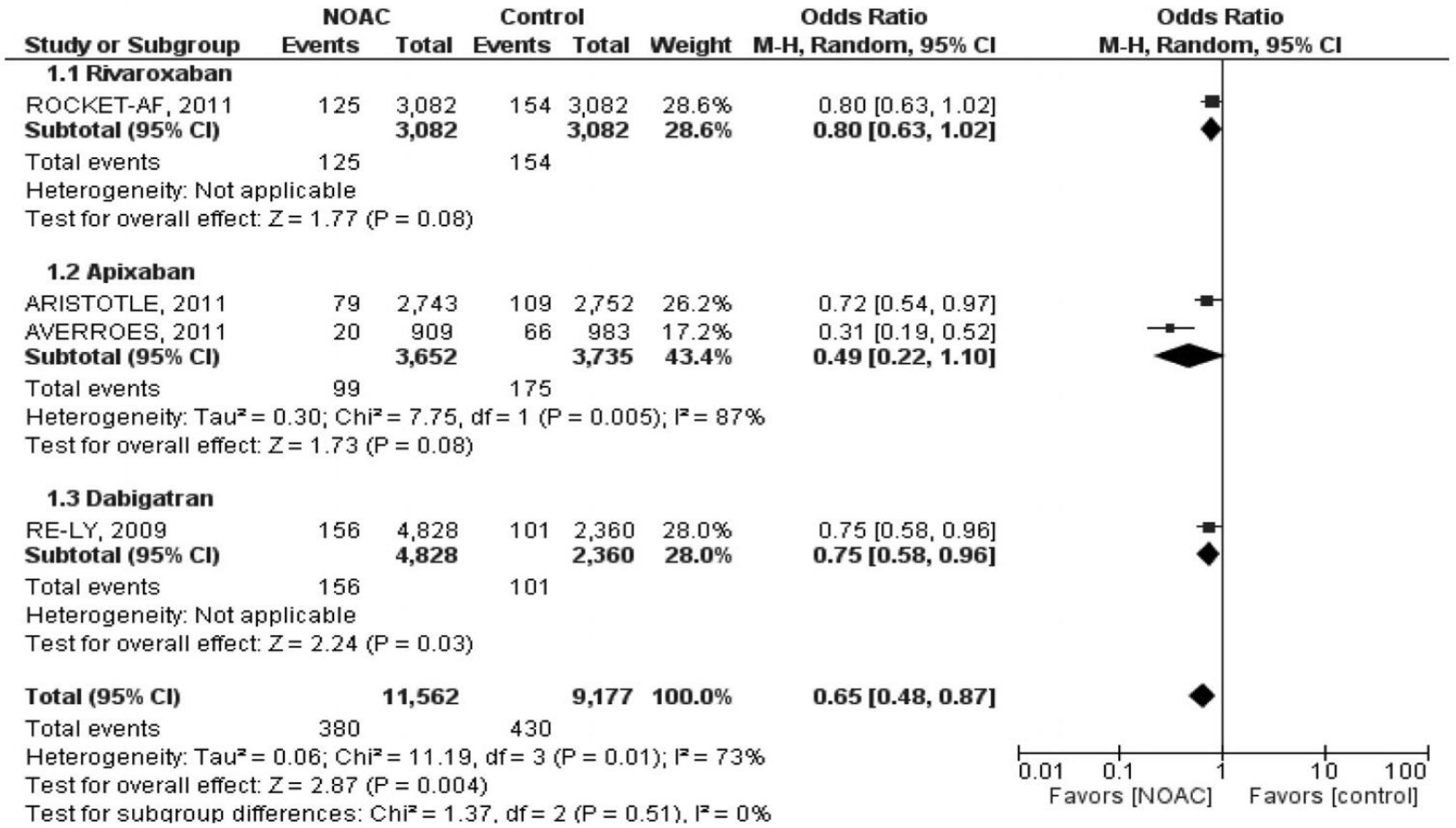
Clinical Features Associated with OACs Nonuse on Discharge After Ischemic Stroke

Variable	Not Discharged with OAC, %	Univariate	Multivariable
		Odds Ratio (95% Confidence Interval)	
Age			
<65	17.4	Reference	
65–74	33.6	2.40 (1.43–4.03)	3.25 (1.79–5.89)
75–84	37.8	2.88 (1.79–4.65)	3.43 (1.98–5.94)
≥85	68.8	10.46 (6.36–17.18)	8.96 (5.01–16.04)
Sex			
Male	40.9	Reference	
Female	46.8	1.27 (1.03–1.57)	0.79 (0.60–1.05)
Renal impairment			
No	41.8	Reference	
Yes	51.5	1.48 (1.16–1.90)	1.38 (1.00–1.90)
Diagnosed dementia			
No	40.6	Reference	
Yes	65.6	2.80 (2.04–3.84)	1.69 (1.12–2.57)
Prior gastrointestinal hemorrhage			
No	42.0	Reference	
Yes	63.2	2.38 (1.65–3.42)	1.95 (1.25–3.04)
Prior intracranial hemorrhage			
No	42.9	Reference	
Yes	72.2	3.45 (1.89–6.33)	3.76 (1.74–8.12)
No OAC at time of admission for ischemic stroke			
No	59.6	Reference	
Yes	11.6	11.24 (8.21–15.39)	11.25 (7.95–15.92)
Disability at discharge[a]			
No disability	27.2	Reference	
Minor	32.2	1.27 (0.76–2.14)	1.39 (0.77–2.51)
Major	49.6	2.64 (1.57–4.42)	2.78 (1.53–5.05)
Severe	82.4	12.55 (6.53–24.11)	12.58 (5.82–27.21)

McGrath et al; JAGS 2016

Patients ≥ 75 years

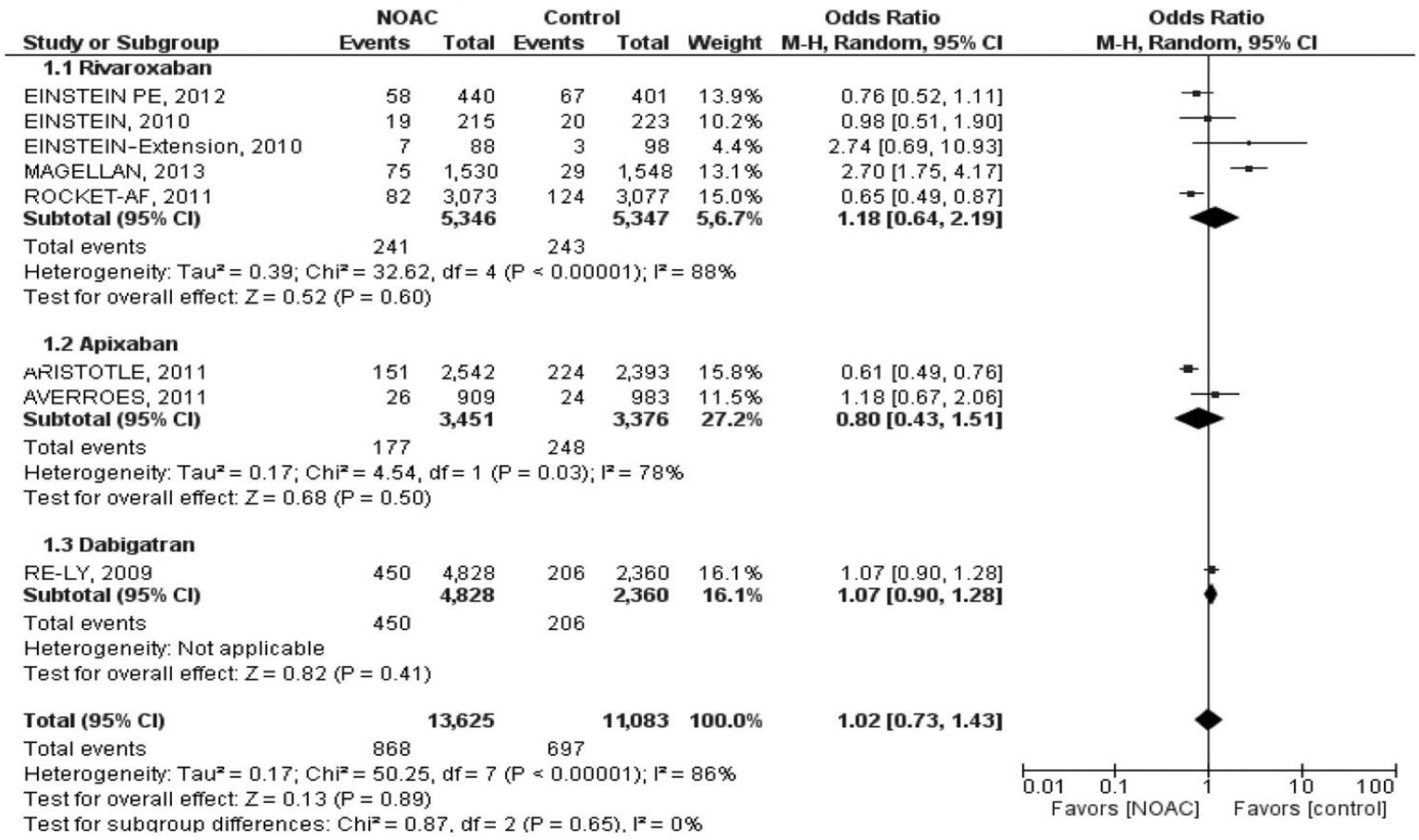
Stroke or SE



Sardar et al; JAGS 2014

Patients ≥ 75 years

Major or Clinically Relevant Bleeding



Study or Subgroup	NOAC Events	NOAC Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1 Rivaroxaban						
EINSTEIN PE, 2012	58	440	67	401	13.9%	0.76 [0.52, 1.11]
EINSTEIN, 2010	19	215	20	223	10.2%	0.98 [0.51, 1.90]
EINSTEIN-Extension, 2010	7	88	3	98	4.4%	2.74 [0.69, 10.93]
MAGELLAN, 2013	75	1,530	29	1,548	13.1%	2.70 [1.75, 4.17]
ROCKET-AF, 2011	82	3,073	124	3,077	15.0%	0.65 [0.49, 0.87]
Subtotal (95% CI)		**5,346**		**5,347**	**5,6.7%**	**1.18 [0.64, 2.19]**
Total events	241		243			
Heterogeneity: Tau² = 0.39; Chi² = 32.62, df = 4 (P < 0.00001); I² = 88%						
Test for overall effect: Z = 0.52 (P = 0.60)						
1.2 Apixaban						
ARISTOTLE, 2011	151	2,542	224	2,393	15.8%	0.61 [0.49, 0.76]
AVERROES, 2011	26	909	24	983	11.5%	1.18 [0.67, 2.06]
Subtotal (95% CI)		**3,451**		**3,376**	**27.2%**	**0.80 [0.43, 1.51]**
Total events	177		248			
Heterogeneity: Tau² = 0.17; Chi² = 4.54, df = 1 (P = 0.03); I² = 78%						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.3 Dabigatran						
RE-LY, 2009	450	4,828	206	2,360	16.1%	1.07 [0.90, 1.28]
Subtotal (95% CI)		**4,828**		**2,360**	**16.1%**	**1.07 [0.90, 1.28]**
Total events	450		206			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
Total (95% CI)		**13,625**		**11,083**	**100.0%**	**1.02 [0.73, 1.43]**
Total events	868		697			
Heterogeneity: Tau² = 0.17; Chi² = 50.25, df = 7 (P < 0.00001); I² = 86%						
Test for overall effect: Z = 0.13 (P = 0.89)						
Test for subgroup differences: Chi² = 0.87, df = 2 (P = 0.65), I² = 0%						

Sardar et al; JAGS 2014

(mini) Agenda

- Quale anticoagulante?

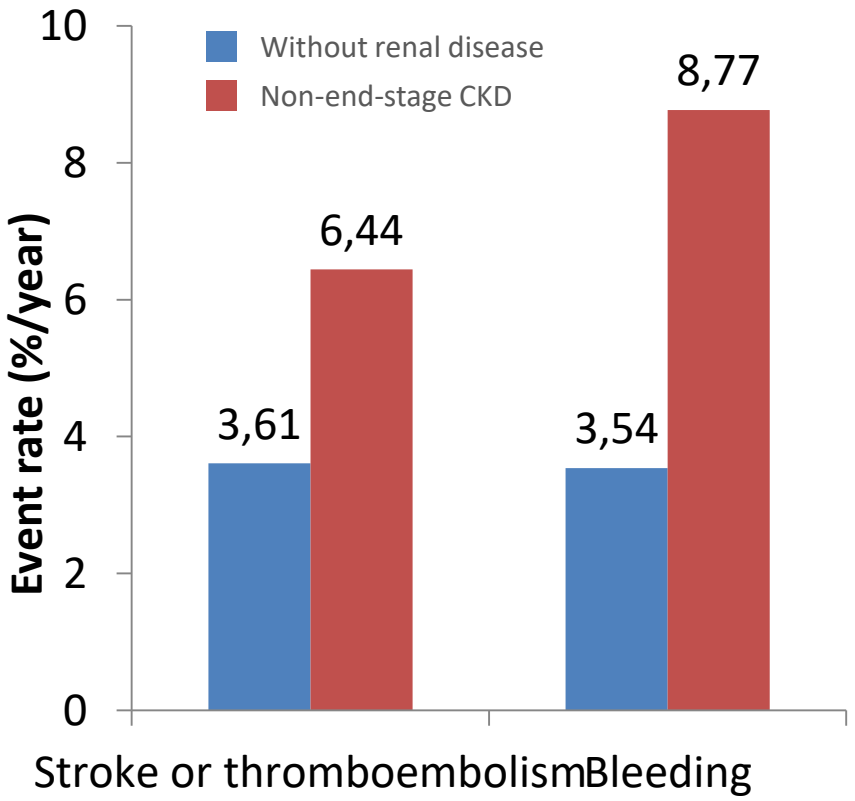
- Cosa devo fare in ambito clinico?

- Terapia antitrombotica nelle Popolazioni particolari ?
  - Anziano
  - Insuff Renale

Renal Impairment Increases the Risk of Stroke and Bleeding in Patients with AF

- Every third patient with AF has CKD[1]
- Patients with AF and renal impairment are at higher risk for bleeding and stroke[2]
- Patients with AF and renal impairment were more often undertreated with warfarin than those with normal renal function[3]

Danish registry[2] (N=132,372)
(~28% of patients received warfarin)

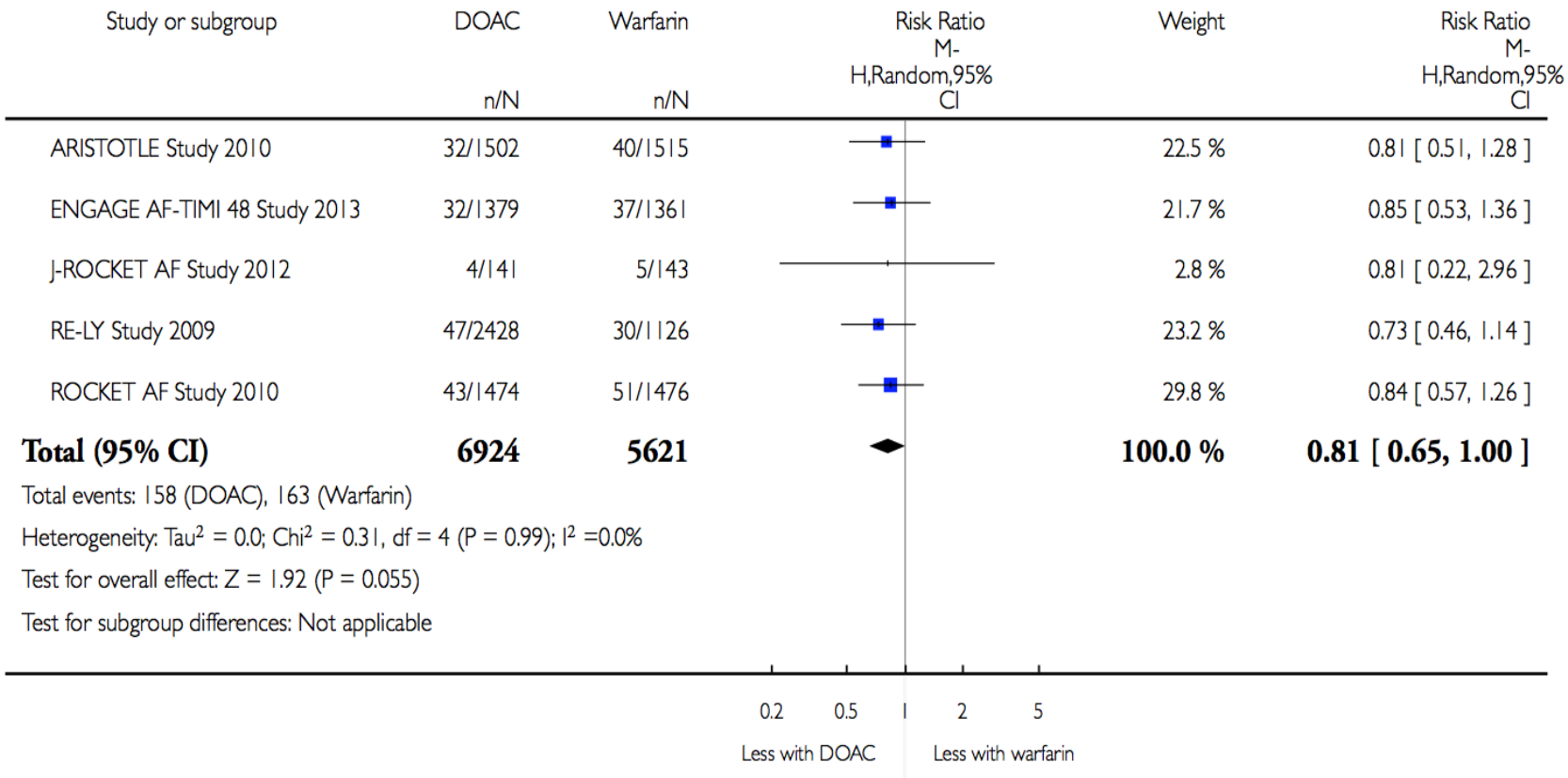


1. Hart RG *et al*, *Can J Cardiol* 2013;23:S71–S78; 2. Olesen JB *et al*, *N Engl J Med* 2012;367:625–635;
3. Capodanno D *et al*, *Circulation* 2012;125:2649–2661

Patients with Chronic Renal Failure

Stroke or SE

Cochrane Library

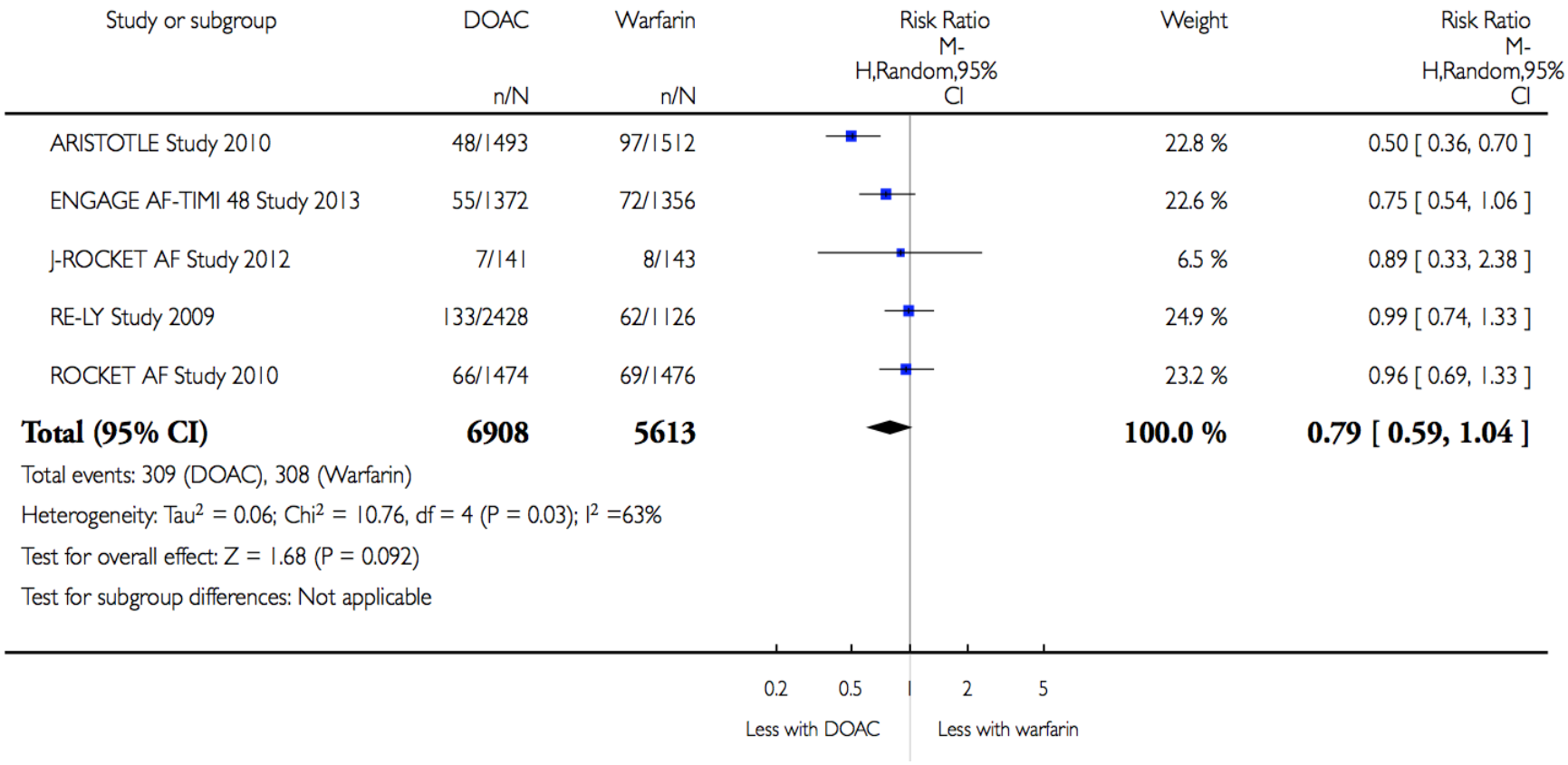


Kimaki et al; Cochrane 2017

Patients with Chronic Renal Failure

Major Bleeding

Cochrane Library



Kimaki et al; Cochrane 2017

Pharmacological Characteristics of the NOACs

	Xabans			DTI
	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Target	Factor Xa			Thrombin
Prodrug	No	No	No	Yes
Oral bioavailability	80–100%*	50%	62%	6.5%
Renal clearance of absorbed active drug	~33%	~27%	~55–60%	>80%
T_{max} (h)	2–4	3–4	1–2	2–6#
Half-life (h)	5–13	12	10–14	12–14
Fixed dosing (AF indication)	od	bid	od	bid

*15–20 mg to be taken with food; #Postoperative period;

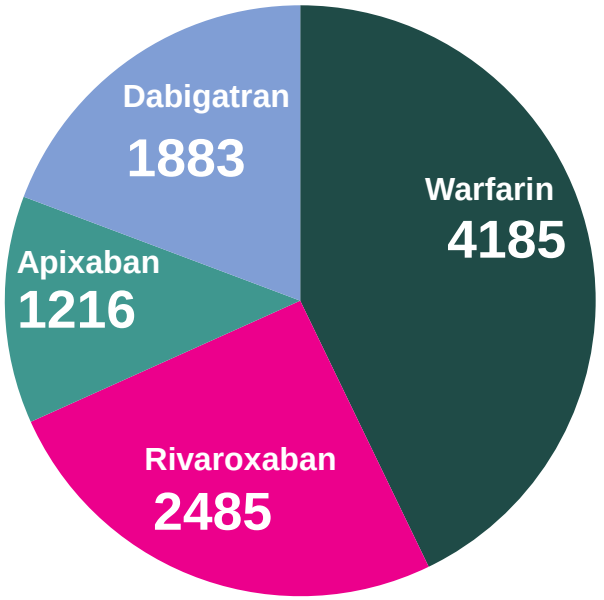
1. Dabigatran SmPC; 2. Apixaban SmPC; 3. Rivaroxaban SmPC; 4. Edoxaban SmPC

DOACs and Warfarin Real World Data in AF Patients: Different impact on adverse renal outcomes

9,769 patients with nonvalvular AF
New users of oral anticoagulants between 10/1/2010-4/30/2016

Propensity scores and inverse probability treatment weights (IPTW)

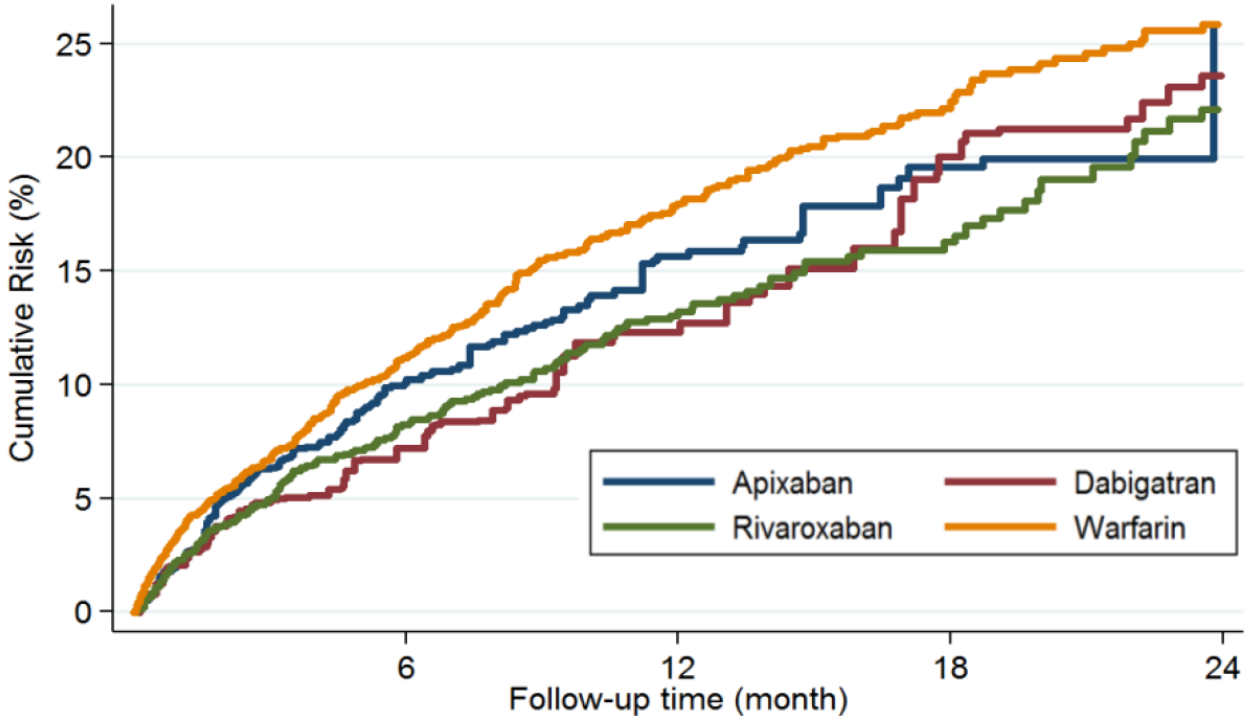
Patients in the four treatment groups (apixaban, dabigatran, rivaroxaban and warfarin) were balanced on over 60 baseline characteristics
Cox proportional hazards regression to compare treatments



Adapted from Yao X *et al. J Am Coll Cardiol* 2017;70:2621–2632

DOACs and Warfarin Real World Data in AF Patients: Different impact on adverse renal outcomes

≥30% Decline in eGFR



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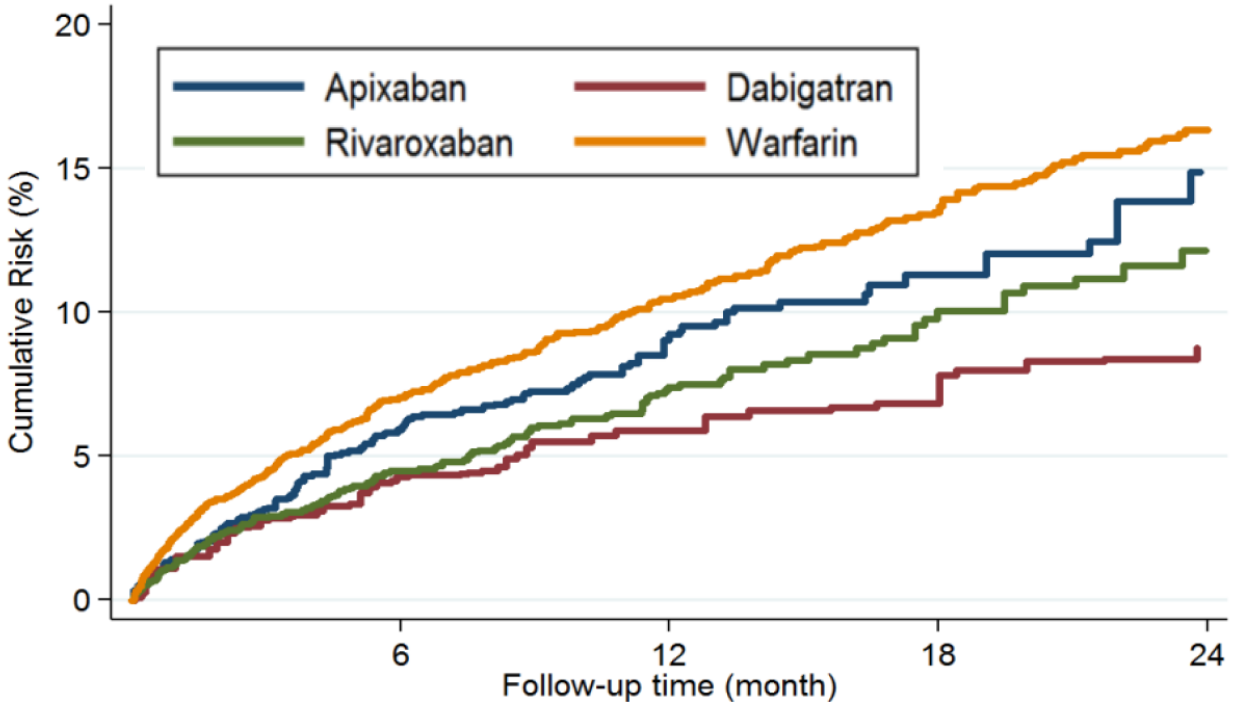
DOACs and Warfarin Real World Data in AF Patients: Different impact on adverse renal outcomes

Acute Kidney Injury



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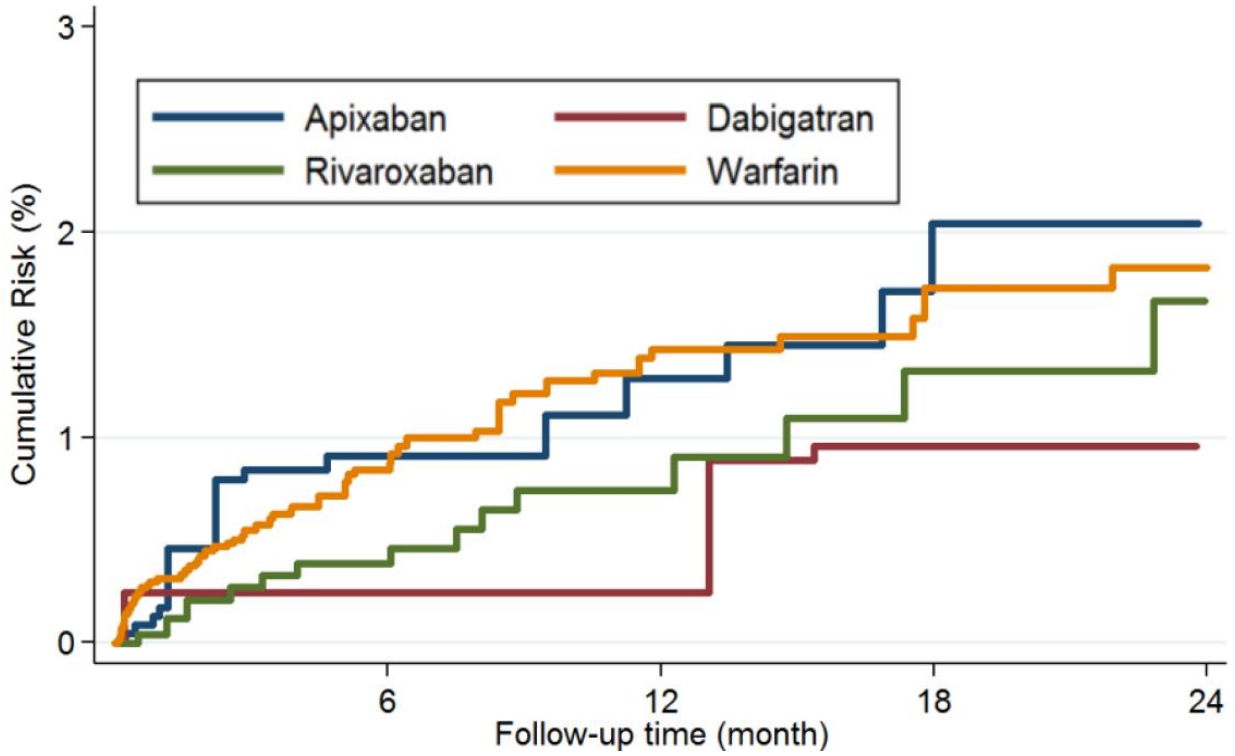
DOACs and Warfarin Real World Data in AF Patients: Different impact on adverse renal outcomes

Kidney Failure



Adapted from Yao X *et al. J Am Coll Cardiol* 2017;70:2621–2632

Take home messages

- Ruolo centrale del Clinico.
- DOACs almeno ugualmente efficaci e sicuri rispetto a AVK nelle diverse situazioni cliniche.
- “Monitoraggio” periodico della terapia anticoagulante è utile nella maggior parte dei nostri pazienti.