Venice Arrhythmias 2015

Rivaroxaban in Arrhythmology:
From Evidence Based Medicine to Real Life Experience

Patients undergoing AF ablation

Dr Sakis Themistoclakis

Head, Unit of Electrophysiology and Cardiac Pacing

Department of Cardiothoracic & Vascular Medicine
Ospedale dell'Angelo, Mestre-Venice, Italy

CONFLICTS OF INTEREST TO DISCLOSE:

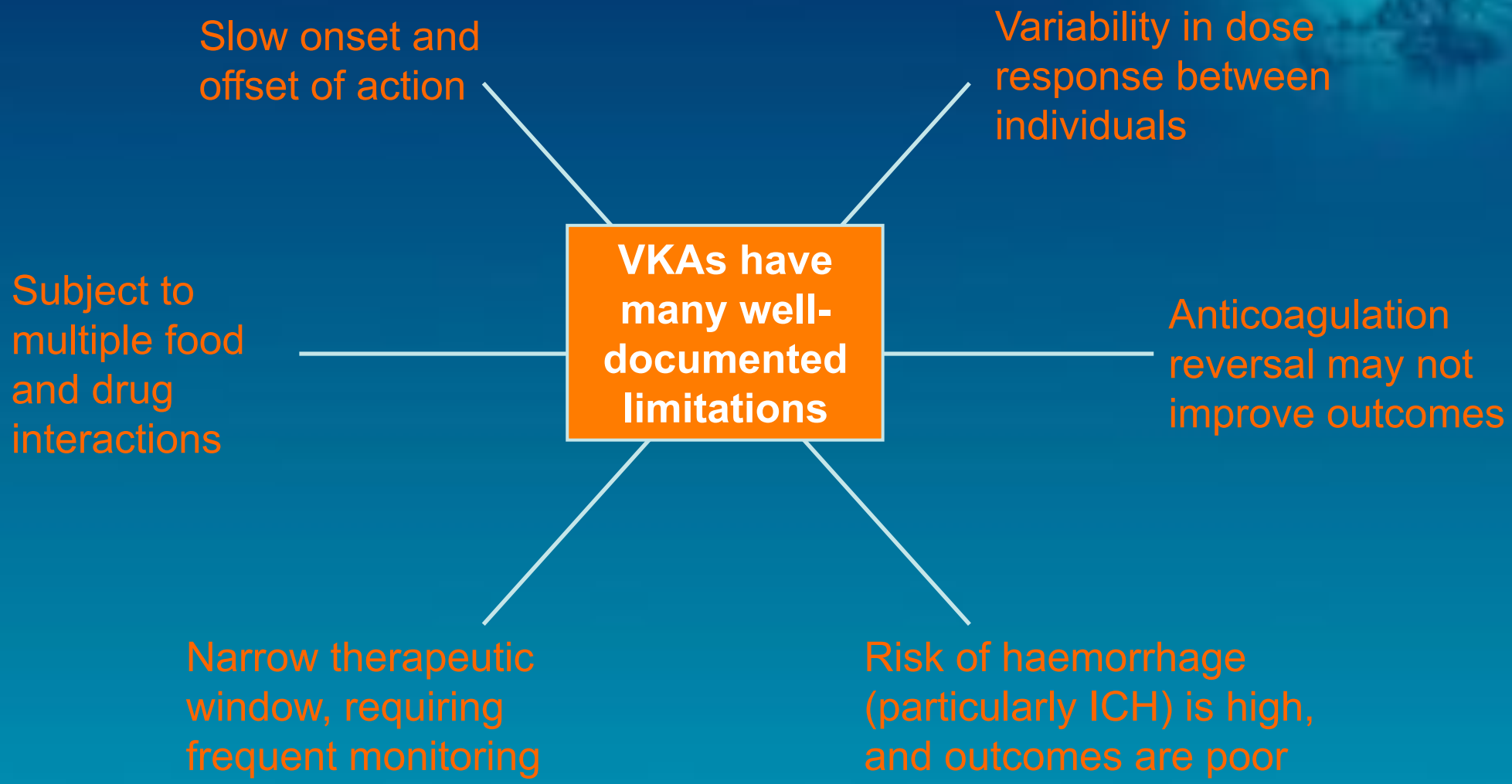
Consultant: Biosense Webster, Daiichi Sankyo

Research Grant:

- Bayer Pharma: X-VERT Trial (Local PI)
- Biosense Webster: OAT Study (Steering Committee)
- BMS/Pfizer: AEGEAN Trial (Local PI)
- Daiichi Sankyo: ENSURE AF Trial (National PI, Steering Committee)
- Boheringher Ingelheim: RE-CIRCUIT Trial (National PI)
- AF-NET, BMS/Pfizer: AXAFA Trial (National PI)

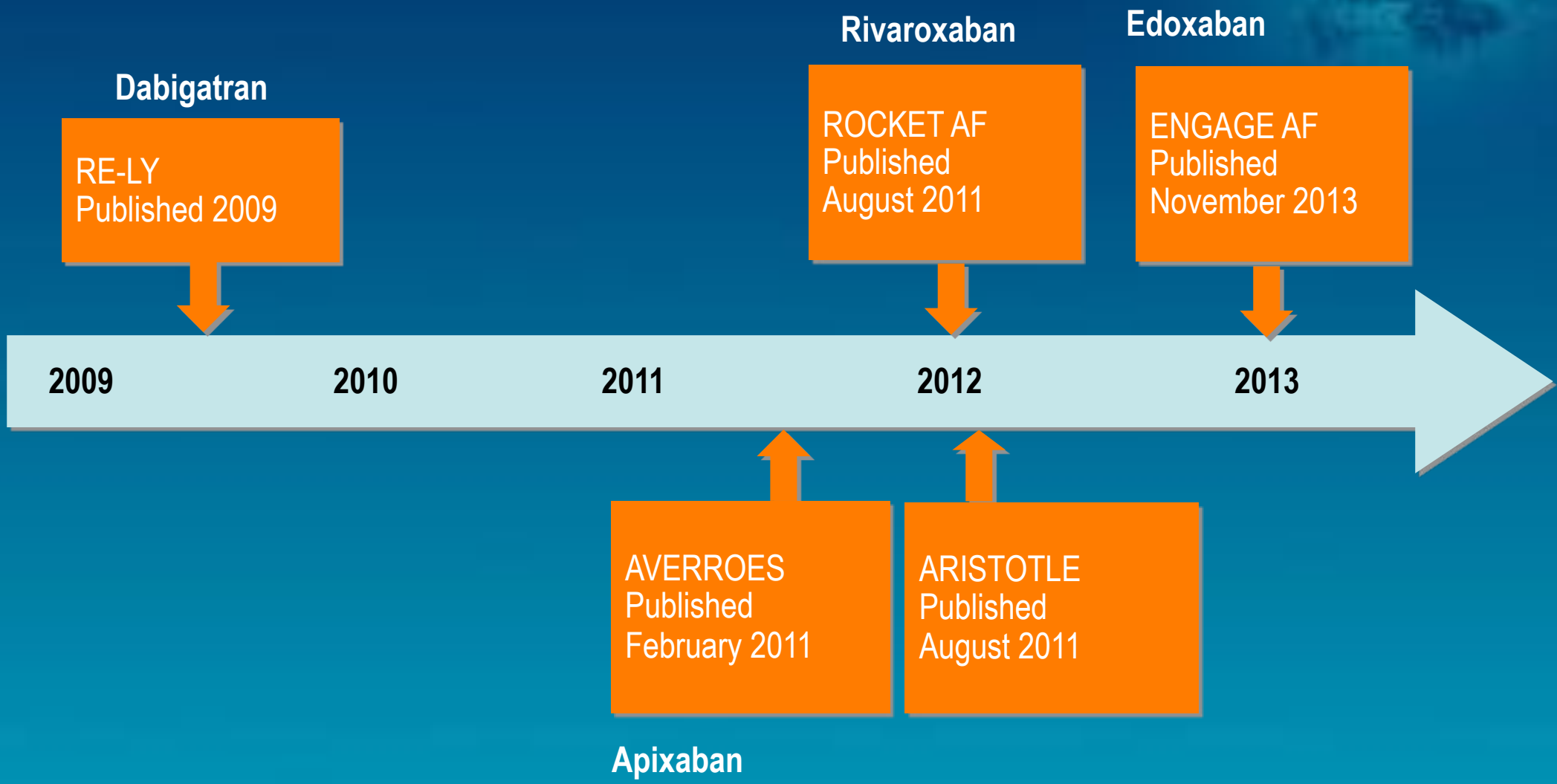
Speaker Honoraria: Bayer Pharma, Boheringher Ingelheim, Daiichi Sankyo

Challenges and limitations of VKAs



Adapted from Connolly SJ et al. *Circulation* 2007;116:449–55

NOAC in patients with Non Valvular Atrial Fibrillation
Phase 3 Study Timelines



Periprocedural Stroke and Management of Major Bleeding Complications in Patients Undergoing Catheter Ablation of Atrial Fibrillation

The Impact of Periprocedural Therapeutic International Normalized Ratio

Luigi Di Biase, MD; J. David Burkhardt, MD; Prasant Mohanty, MBBS, MPH; Javier Sanchez, MD; Rodney Horton, MD; G. Joseph Gallinghouse, MD; Dhanunjay Lakkireddy, MD; Atul Verma, MD; Yaariv Khaykin, MD; Richard Hongo, MD; Steven Hao, MD; Salwa Beheiry, RN; Gemma Pelargonio, MD; Antonio Dello Russo, MD; Michela Casella, MD; Pietro Santarelli, MD; Pasquale Santangeli, MD; Paul Wang, MD; Amin Al-Ahmad, MD; Dimpi Patel, DO; Sakis Themistoclakis, MD; Aldo Bonso, MD; Antonio Rossillo, MD; Andrea Corrado, MD; Antonio Raviele, MD; Jennifer E. Cummings, MD; Robert A. Schweikert, MD; William R. Lewis, MD; Andrea Natale, MD, FHRS, FACC

- Group 1: Ablation with an 8-mm catheter off warfarin
- Group 2: Ablation with an open irrigated catheter off warfarin
- Group 3: Ablation with an open irrigated catheter on warfarin

Circulation 2010; 121: 2550-6

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Complication	Group 1 (n=2488), n (%, 95% CI)	Group 2 (n=1348), n (%, 95% CI)	Group 3 (n=2618), n (%, 95% CI)	*P*, Multiple Comparison Between Group 3 and Groups 1 and 2
Stroke/TIA	27 (1.1, 0.72–1.58)	12 (0.9, 0.46–1.56)	0 (0)	<0.05
Minor bleeding	498 (20, 18.3–21.9)	256 (19, 16.7–21.5)	105 (4, 3.3–4.9)	<0.05
Major bleeding	10 (0.4, 0.19–0.74)	11 (0.8, 0.41%–1.46%)	10 (0.4, 0.18–0.70)	>0.05
Pericardial effusion	11 (0.4, 0.22–0.79)	11 (0.8, 0.41–1.46)	12 (0.5, 0.24–0.80)	>0.05

Circulation 2010; 121: 2550-6

Periprocedural Stroke and Management of Major Bleeding Complications in Patients Undergoing AF Catheter Ablation

The Impact of Periprocedural Therapeutic INR

Complication	Group 1 (n=2488), n (%, 95% CI)	Group 2 (n=1348), n (%, 95% CI)	Group 3 (n=2618), n (%, 95% CI)	*P*, Multiple Comparison Between Group 3 and Groups 1 and 2
Stroke/TIA	27 (1.1, 0.72–1.58)	12 (0.9, 0.46–1.56)	0 (0)	<0.05
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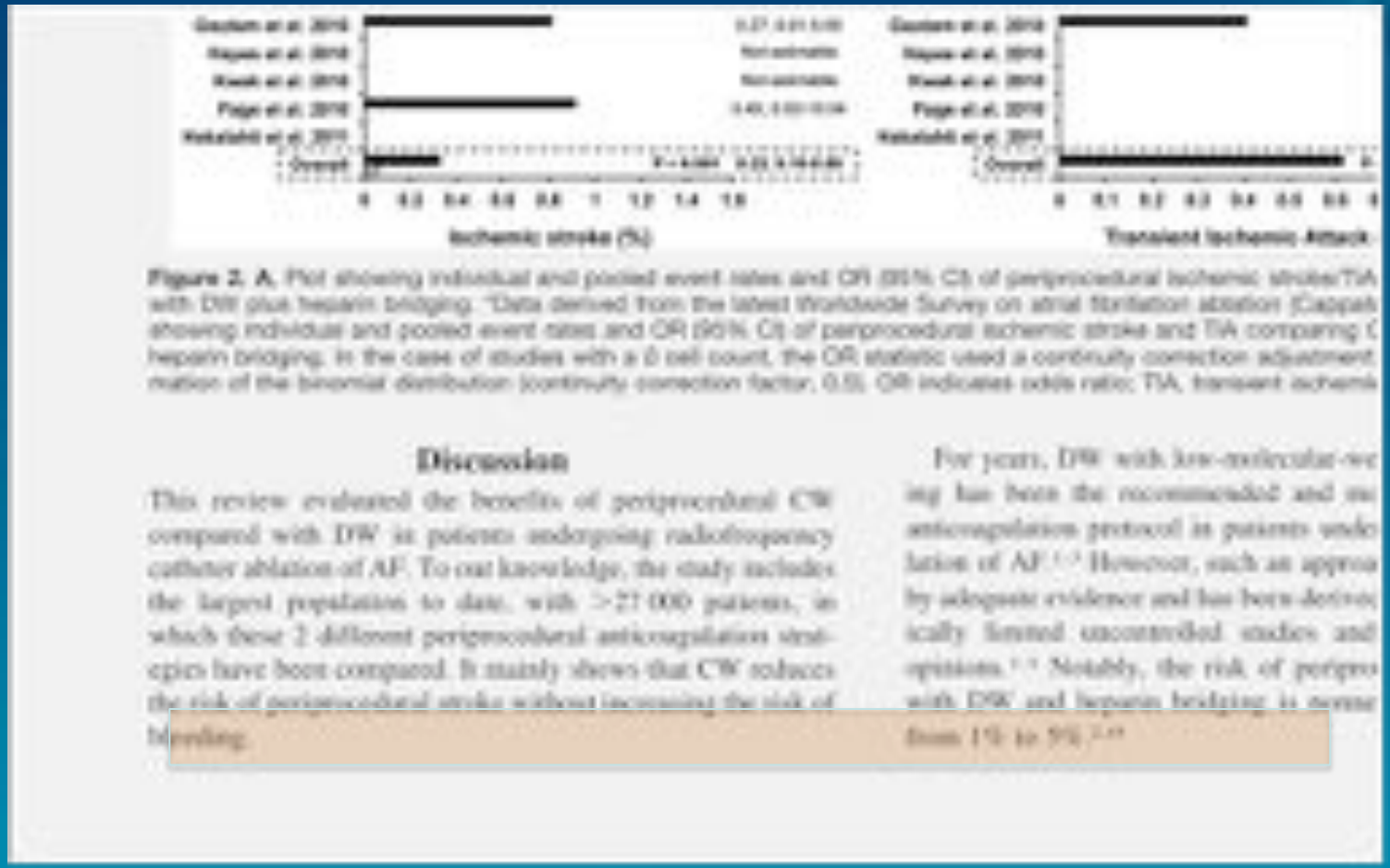
Di Biase et al. *Circulation* 2010; 121: 2550-6

Pericardial Effusion Management

	Patients off Warfarin (n=3836)	Patients on Warfarin (n=2618)	P
Patients with pericardial effusion, n (%, 95% CI)	22 (0.57, 0.36–0.87)	12 (0.46, 0.24–0.80)	0.602
Requiring pericardiocentesis, n (%, 95% CI)	9 (0.23, 0.11–0.45)	8 (0.31, 0.13–0.66)	0.626
Requiring fresh frozen plasma, n (%, 95% CI)	0	8 (0.31, 0.13–0.66)	<0.001
Median blood units for transfusion, n (%, 95% CI)	1 (0.03, 0.00–0.15)	3 (0.11, 0.02–0.33)	0.043
Requiring surgery, n (%, 95% CI)	3 (0.08, 0.02–0.23)	1 (0.04, 0.00–0.21)	0.651
Mean pericardial fluid aspiration, cm^3	700 ± 300	1200 ± 200	<0.001
Mean protamine for reversal, mg	45 ± 15	70 ± 15	<0.001

Di Biase et al. *Circulation* 2010; 121: 2550-6

Periprocedural ischemic stroke/TIA in AF ablation on &off warfarin



Ischemic stroke (%)

Transient Ischemic Attack

Figure 2. A. Plot showing individual and pooled event rates and OR (95% CI) of periprocedural ischemic stroke/TIA with DW plus heparin bridging. [illegible] showing individual and pooled event rates and OR (95% CI) of periprocedural ischemic stroke and TIA comparing [illegible] heparin bridging. In the case of studies with a 0 cell count, the OR statistic used a continuity correction adjustment [illegible] mation of the binomial distribution (continuity correction factor, 0.5). OR indicates odds ratio; TIA, transient ischemia

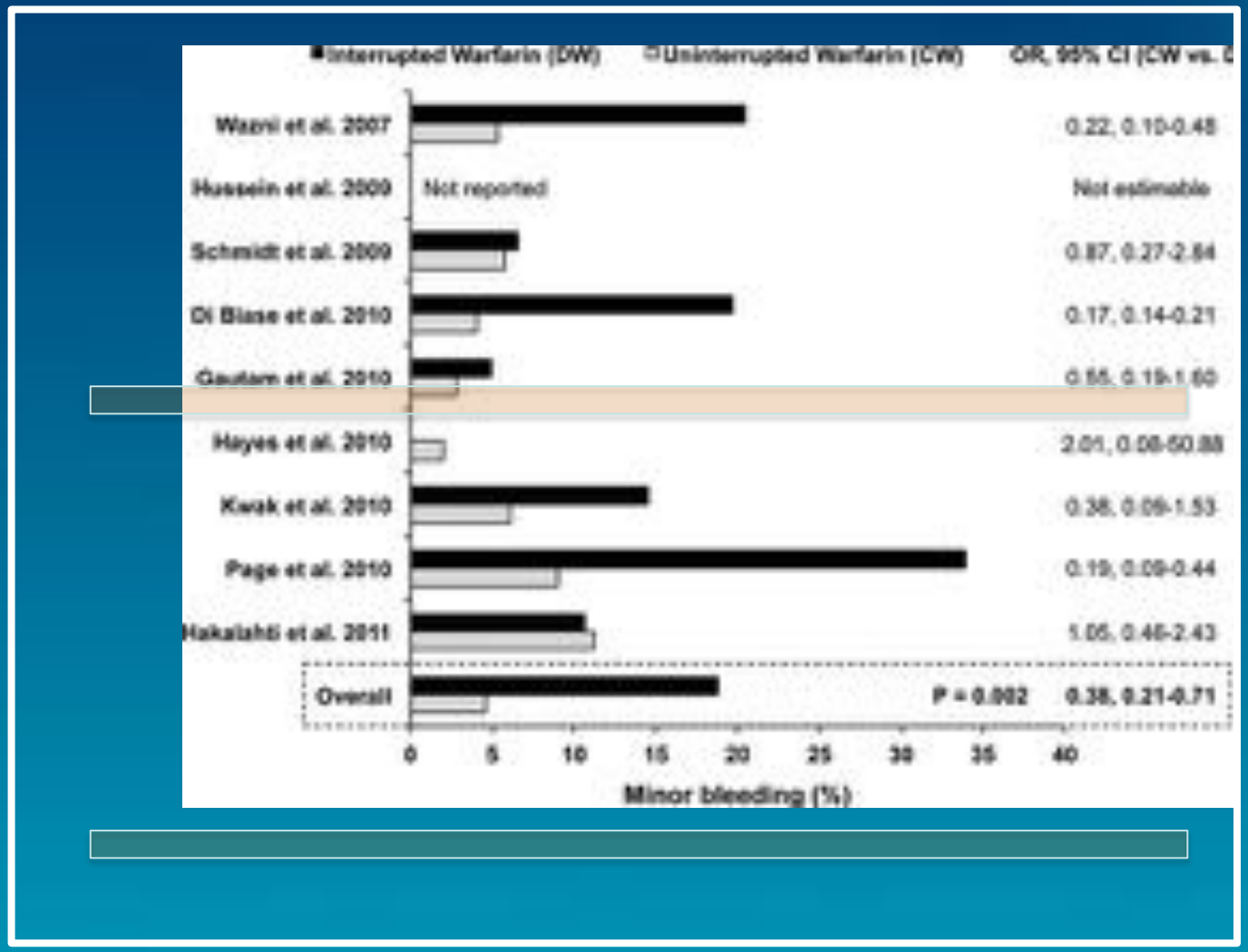
Discussion

This review evaluated the benefits of periprocedural CW compared with DW in patients undergoing radiofrequency catheter ablation of AF. To our knowledge, the study includes the largest population to date, with >27 000 patients, in which these 2 different periprocedural anticoagulation strategies have been compared. It mainly shows that CW reduces the risk of periprocedural stroke without increasing the risk of bleeding.

For years, DW with low-molecular-we[illegible] ing has been the recommended and mo[illegible] anticoagulation protocol in patients unde[illegible] lation of AF.[1–3] However, such an approa[illegible] by adequate evidence and has been derive[illegible] ically limited uncontrolled studies and [illegible] opinions.[1–3] Notably, the risk of periproc[illegible] with DW and heparin bridging is report[illegible] from 1% to 5%.[4–15]

Santangeli P et al. *Circ Arrhythm Electrophysiol. 2012;5:302-311*

Major bleeding / cardiac tamponade in AF ablation on & off warfarin



Santangeli P et al. *Circ Arrhythm Electrophysiol. 2012;5:302-311*

Minor bleeding in pts with & without periprocedural bridging with LMWH

range of upper CI limits excluding each study in turn, 0.55–1.10). In this regard, the use of ICE may be of significant value in less-experienced centers, especially when a CW strategy is implemented, although it necessitates additional expertise and increases the cost of the procedure.

With regard to the management of major bleeding complications, most studies adopted therapeutic warfarin reversal with either fresh frozen plasma or infusion of prothrombin complex concentrate on top of heparin reversal with protamine. The need for fresh frozen plasma and prothrombin

accepted.

Another point is whether a thromboembolic protection v feasible. When the risks of ev periprocedural thromboembo may provide relevant findin domized trials. The pooled e 0.94%, and a randomized tria α=0.05) to demonstrate a thr would need to enroll 3130 pa

Santangeli P et al. *Circ Arrhythm Electrophysiol. 2012;5:302-311*

warfarin or on-warfarin arm. The incidence of thromboembolic events in the 48 hours after ablation was the primary end point of the study. The study enrolled 1584 patients: 790 assigned to discontinue warfarin (group 1) and 794 assigned to continuous warfarin (group 2). No statistical difference in baseline characteristics was observed. There were 39 thromboembolic events (3.7% strokes [n=29] and 1.3% transient ischemic attacks [n=10]) in group 1: two events (0.87%) in patients with paroxysmal AF, 4 (2.3%) in patients with persistent AF, and 33 (8.5%) in patients with long-standing persistent AF. Only 2 strokes (0.25%) in patients with long-standing persistent AF were observed in group 2 (P<0.001). Warfarin discontinuation emerged as a strong predictor of periprocedural thromboembolism (odds ratio, 13; 95% confidence interval, 3.1–55.6; P<0.001).

Conclusion—This is the first randomized study showing that performing catheter ablation of AF without warfarin discontinuation reduces the occurrence of periprocedural stroke and minor bleeding complications compared with bridging with low-molecular-weight heparin.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01006876.

(*Circulation*. 2014;129:2638-2644.)

Key Words: atrial fibrillation ■ catheter ablation ■ catheter ablation, radiofrequency ■ stroke ■ transient ischemic attack ■ warfarin

Radiofrequency catheter ablation for atrial fibrillation (AF) is an effective therapeutic option for the treatment of the procedure and its operator dependency expose patients to a considerable number of potential complications.[1-3]

with continuous warfarin (group 2, n=794; Figure

The baseline characteristics and risk factors we anced between the 2 groups. In group 1, the avera 61±10 years; 76% were male; 29% had paroxysm had persistent AF; 49% had long-standing persis AF; the left atrial size was 44.8±7 mm; and the left ejection fraction was 53±12%.

Patients in group 2 were 62±12 years of age; male; 25% had paroxysmal AF; 24% had persiste had LSP AF; the left atrial size was 45.1±7 mm; ventricular ejection fraction was 52±13%.

In group 1, 561 patients (71%) had a CHADS compared with 588 (74%) in group 2 (P=0.17)

Di Biase et al. Circulation. 2014;129:2638-44

for atrial fibrillation (AF). The periprocedural anticoagulation management could play a role in the incidence of these complications. Although ablation procedures performed without warfarin discontinuation seem to be associated with lower thromboembolic risk, no randomized study exists.

Methods and Results—This was a prospective, open-label, randomized, parallel-group, multicenter study assessing the role of continuous warfarin therapy in preventing periprocedural thromboembolic and hemorrhagic events after radiofrequency catheter ablation. Patients with $CHADS_2$ score ≥1 were included. Patients were randomly assigned in a 1:1 ratio to the uninterrupted warfarin or no-warfarin arms. The incidence of thromboembolic events in the 48 hours after ablation was the primary end point of the study. The study enrolled 1584 patients: 790 assigned to discontinue warfarin (group 1) and 794 assigned to continue warfarin (group 2). No statistical difference in baseline characteristics was observed. There were 39 thromboembolic events (3.7% strokes [n=29] and 1.3% transient ischemic attacks [n=10]) in group 1: two events (0.07%) in patients with paroxysmal AF, 4 (2.3%) in patients with persistent AF, and 33 (8.5%) in patients with long-standing persistent AF. Only 2 strokes (0.25% in patients with long-standing persistent AF were observed in group 2 ($P<0.001$). Warfarin discontinuation emerged as a strong predictor of periprocedural thromboembolism (odds ratio, 13; 95% confidence interval, 3.1–53.6; $P<0.001$).

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Radiofrequency catheter ablation for atrial fibrillation (AF) is an effective therapeutic option for the treatment of symptomatic drug-refractory AF.[1] The complexity of the procedure and its operator dependency expose patients to a considerable number of potential complications.[2] Periprocedural thromboembolic events represent one of the

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From the Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin, TX (A.D.B., J.D.B., P.S., P.M., J.L.S., B. Shelton, G.J.G., J.J., R.R., S.M., A.N.); Albert Einstein College of Medicine, Montefiore Hospital, New York, NY (J.D.); Department of Biomedical Engineering, University of Texas, Austin (J. D., A.N.); Department of Cardiology, University of Perugia, Perugia, Italy (L.D.B., P.L.); Ospedale dell'Angelo, Mestre-Venice, Italy (S.T., A.B.); University of Kansas, Kansas City (D.L., M.B.); California Pacific Medical Center, San Francisco (H.H., B. Hongo, S.E., A.N.); University of Kentucky, Lexington (C.A.); University of Tor Vergata, Rome, Italy (G. Fedele, C.T.); Fatebenefratelli, Rome, Italy (G.P., M.C.N.); Cardiac Arrhythmia Research Center, Cardiologico Monzino IRCCS, Milan, Italy (A.G.R., M.C., G. Fassini, C.T.); Alpert General Hospital, Alpert, OH (R.A.S.); Division of Cardiology, Stanford University (C.A.J.L.N.); Case Western Reserve University, Cleveland, OH (A.N.); and Interventional Electrophysiology, Scripps Clinic, La Jolla, CA (A.N.).

Correspondence to Andrea Natale, MD, FACC, FHRS, FESC, 1000 N I-35, Ste 726, Austin, TX 78705. E-mail dr.natale@gmail.com

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Compare Trial

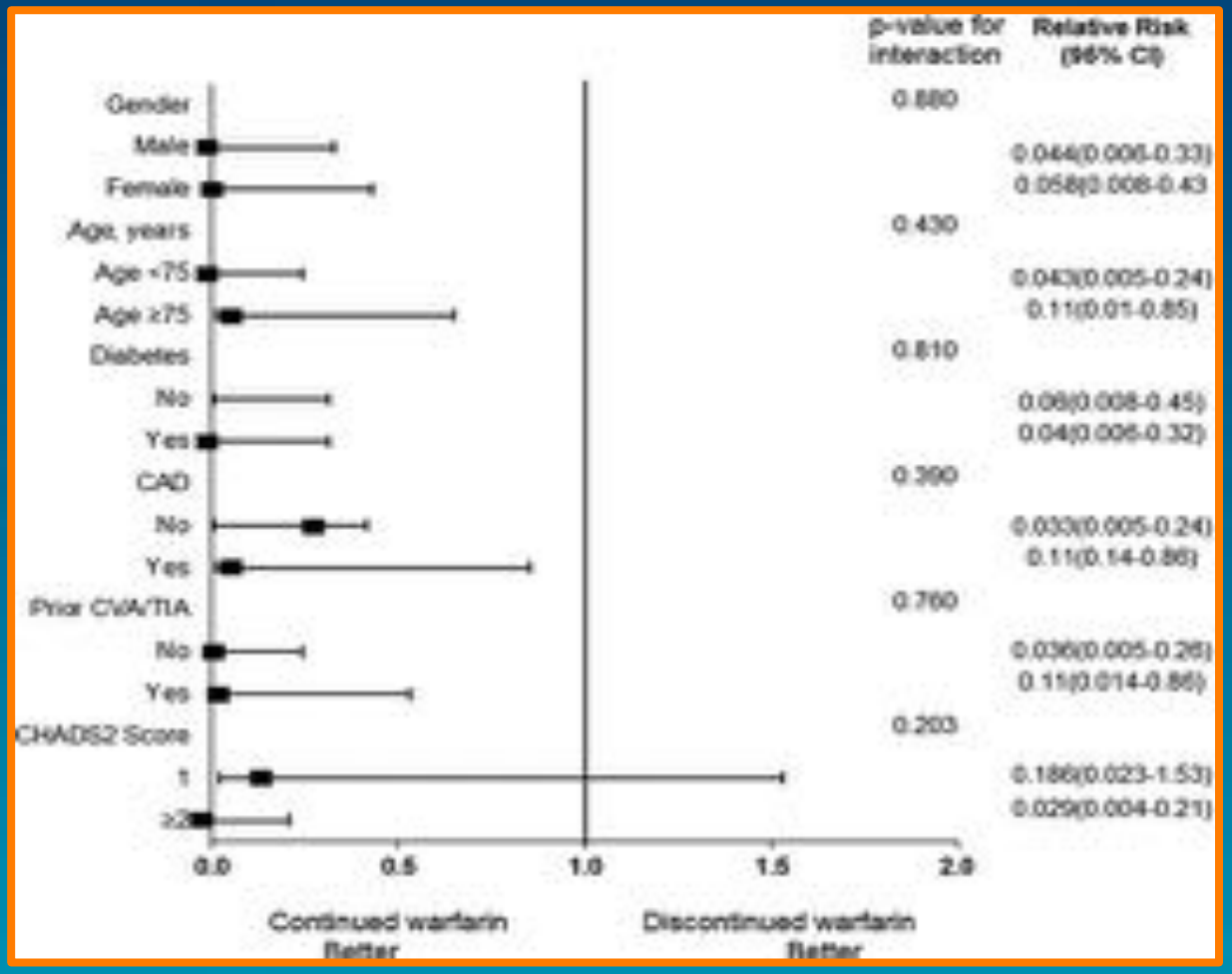
Periprocedural TE and bleeding complications:

Figure 2. Incidence of periprocedural thromboembolic
bleeding complications were more frequent in the off-
population (group 1). Patients on warfarin (group 2) ha
relative risk reduction in stroke/transient ischemic atta
81% relative risk reduction in minor bleeding, and 50%
risk reduction in major bleeding compared with group
represent 95% confidence interval of the relative risk

Di Biase et al. Circulation. 2014;129:2638-44

Compare Trial

Relative risk for different categories:



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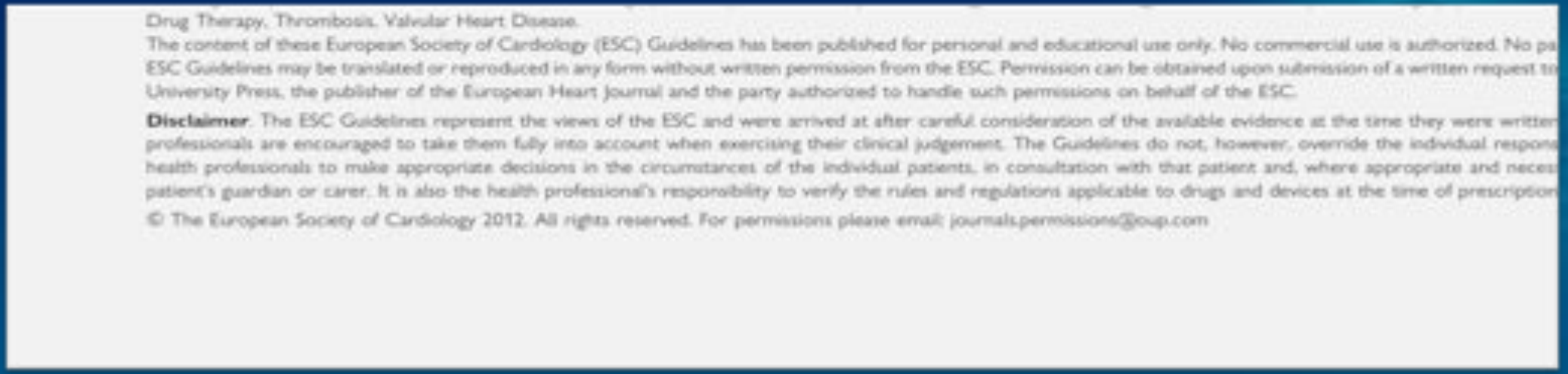
Drug Therapy, Thrombosis, Valvular Heart Disease.

Disclaimer. The ESC Guidelines represent the views of the ESC and were arrived at after careful consideration of the available evidence at the time they were written
professionals are encouraged to take them fully into account when exercising their clinical judgement. The Guidelines do not, however, override the individual respons
health professionals to make appropriate decisions in the circumstances of the individual patients, in consultation with that patient and, where appropriate and neces
patient's guardian or carer. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription

- At present, for patients on OAC with VKA, we recommend undertaking catheter ablation of AF on continuous anticoagulation. Anticoagulant therapy should be kept at low therapeutic levels (such as an INR of 2 to 2.5) throughout ablation. Such a regimen may help to reduce periprocedural strokes, possibly including silent cerebral infarcts

- There are currently no controlled data on the risk-benefit profile of catheter ablation on uninterrupted NOACs.

AF Catheter ablation

Periprocedural Anticoagulation protocols using NOACs

Summary:

- Discontinuation of NOAC without peri-operative bridging with LMWH
- Pre-operative discontinuation of NOAC, bridging with LMWH, and subsequent resumption of NOACs without bridging;
- Ablation performed without NOAC discontinuation;
- Discontinuation of NOAC and bridging with VKA.

Recommendations for stopping and starting NOACs after AF ablation procedures

- Limited available data.
- Recommend strategy of bridging and restarting of NOACs.
- A too aggressively shortened periprocedural cessation of NOACs and/or no bridging may be less safe when compared to continued VKA administration and ablation under an INR between 2.0 and 3.0, both concerning bleeding and cardioembolic complications.

Europace 2013; 15: 625–651

During a 12-month time interval, the use of the NOACs in this population rose from <10 to 70%.

Baseline haemoglobin (g/dL)	14.7 ± 1.3	14
Indexed left atrial volume (mL/m^2)	45.7 ± 16.5	47
Left ventricular ejection fraction (%)	62.4 ± 8.7	61

VKA, vitamin K antagonists; AF, atrial fibrillation; TIA, transien
Reference values for haemoglobin: 13.5–17.5 g/dL; C-reactive
The observed differences were significant for the following su

Providencia et al. Europace Feb 2014

Safety and efficacy of dabigatran etexilate during catheter ablation of atrial fibrillation:
A meta-analysis of the literature

Thrombo-embolic events:

Lakkireddy	12	145	8	145	11.1%	1.55 [0.61, 3.90]
Maddox	0	0	0	0		Not estimable
Nin	19	45	9	45	7.8%	2.92 [1.14, 7.48]
Snipielsky	6	31	21	125	10.1%	1.19 [0.43, 3.25]
Yamaji	2	106	11	397	6.9%	0.67 [0.15, 3.09]
Total (95% CI)		**1195**		**1990**	**100.0%**	**0.95 [0.67, 1.35]**
Total events	63		103			

Heterogeneity: $\chi^2 = 12.99$, df = 8 ($P = 0.11$); $I^2 = 38\%$

Test for overall effect: $Z = 0.28$ ($P = 0.78$)

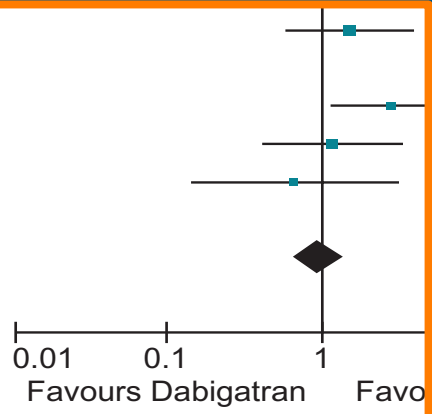

Figure 3 Minor bleeding.

A total of 3648 patients were included: 2241 were receiving warfarin and 1407 dabigatran

Hohnloser et al. Europace 2013; 15: 1407–1411

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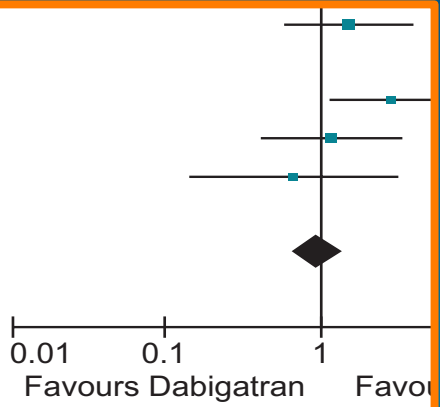

Figure 3 Minor bleeding.

Hohnloser et al. Europace 2013; 15: 1407–1411

Safety and efficacy of dabigatran etexilate during catheter ablation of atrial fibrillation: a meta-analysis of the literature

Conclusions:

- There is limited experience with dabigatran and other NOACs for peri-procedural management of anticoagulation in patients undergoing ablation for AF.
- Although meta-analysis of 10, mainly observational, studies found no statistically significant difference in the rates of thromboembolic events and major and minor bleeding between patients managed on dabigatran compared with warfarin, **this meta-analysis has not enough power to firmly establish the efficacy and safety of dabigatran in the setting of catheter ablation of AF.**
- This implies the need for a well-designed large-scale clinical trial to firmly establish the safety (and possibly the efficacy) of dabigatran (and other NOACs) in the setting of AF ablation.

Hohnloser et al. Europace 2013; 15: 1407–1411

in patients with AF undergoing catheter ablation.

Methods

We searched the published literature from January 1, 2001 through July 30, 2013 using the following key words: dabigatran, oral thrombin inhibitors, atrial fibrillation, and ablation. PubMed, The Cochrane Library (Cochrane Data-

excluded studies without a comparator group, and studies that did not report clinical outcomes, we tried contact the individual corresponding authors for furt details.

Two reviewers (RN and PS) independently extracted data from the eligible studies using the standardized p lished protocol at PROSPERO, and disagreements w

higher risk of stroke or TIA was observed with dabigatran compared with warfarin (POR 3.58, 95% CI 1 .32 to 9.70) in the United States population. A consistent high risk for stroke or TIA with dabigatran was observed in most of our important sensitivity analysis: studies published as full-text reports, studies with low or intermediate risk of bias, observational studies only, studies with follow-up of at least 30 days, studies with interrupted dabigatran therapy, and studies with bridging low-molecular-weight heparin (Supplementary Table 2, online only). Sensitivity analyses for major bleeding showed a comparable bleeding risk with dabigatran and warfarin in all subgroup analyses (data not shown). Sensitivity analyses by sequentially dropping each individual study and evaluating the overall outcomes failed

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Am J Cardiol 2014; in press

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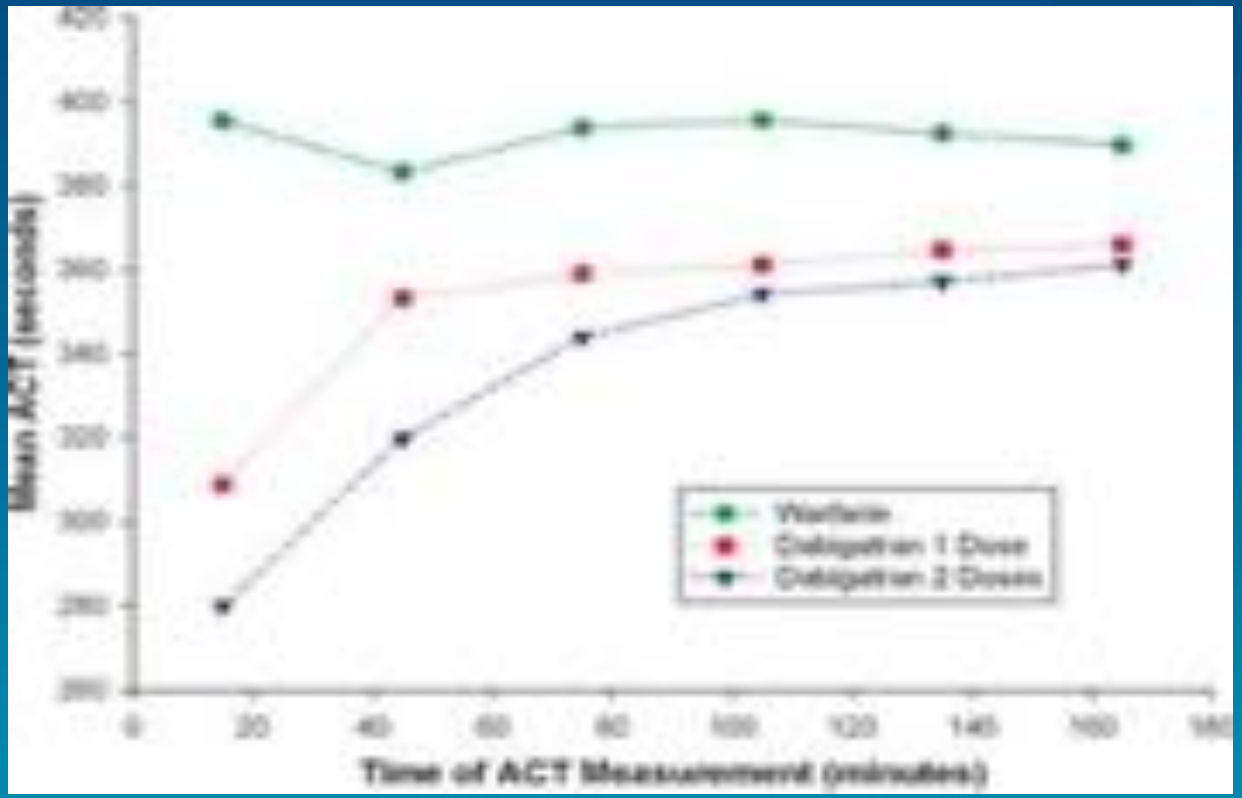
Limitations:

- Observational studies
- Differences in the study protocol, definitions for safety and efficacy outcomes, and baseline characteristics of the patients.
- Reported incidence of a few of our outcomes was very low, and some of our results showed wide CI
- The higher incidence of stroke or TIA with dabigatran might be observed by chance in our analysis indicated also by study sequential analyses for a 150% POR increase.

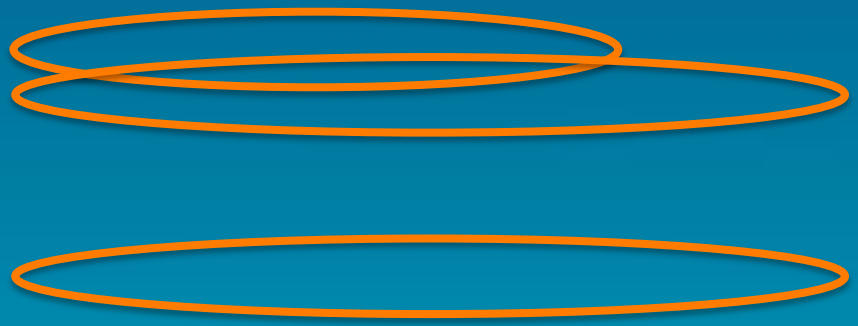
Am J Cardiol 2014

Mean intraprocedural activated clotting time (ACT) measurements throughout the pulmonary vein isolation procedure.



Bassiouny M et al. Circ Arrhythm Electrophysiol 2013;6:460-466

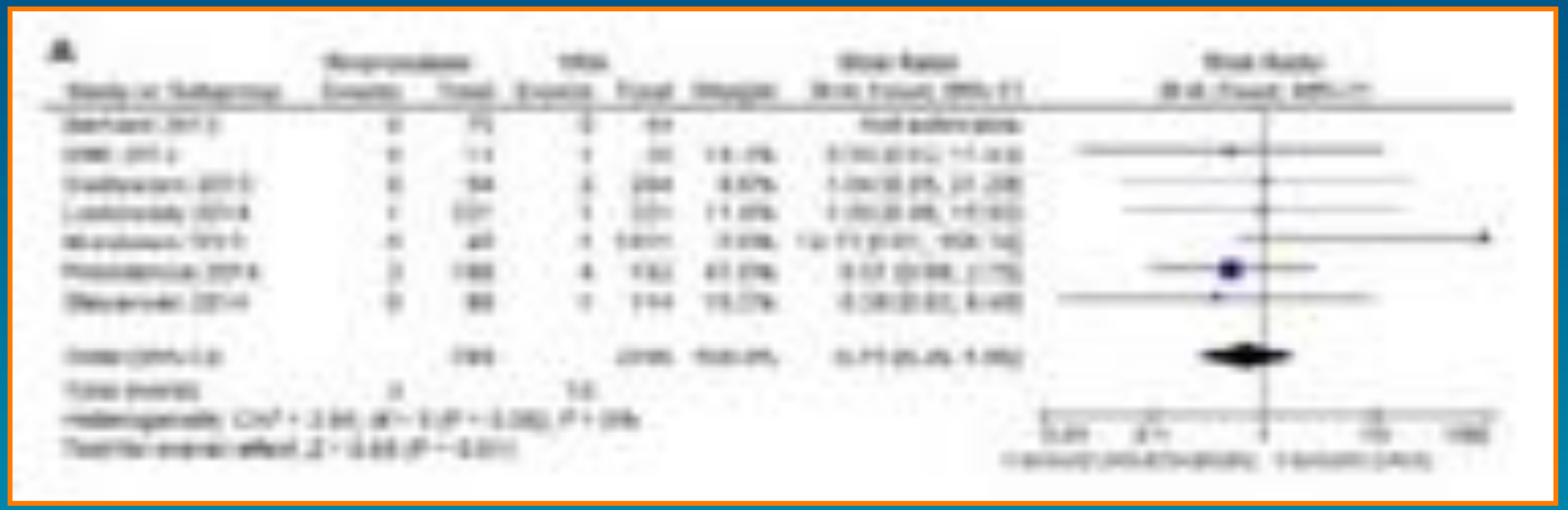
Feasibility & Safety of Uninterrupted Rivaroxaban for Periprocedural Anticoagulation in Patients Undergoing Radiofrequency Ablation for Atrial Fibrillation: Results from a Multicenter Prospective Registry



Lakkireddy D et al. J Am Coll Cardiol 2014, doi: 10.1016/j.jacc.2013.11.039

Comparision of rivaroxaban versus warfarin in patients undergoing AF catheter ablation

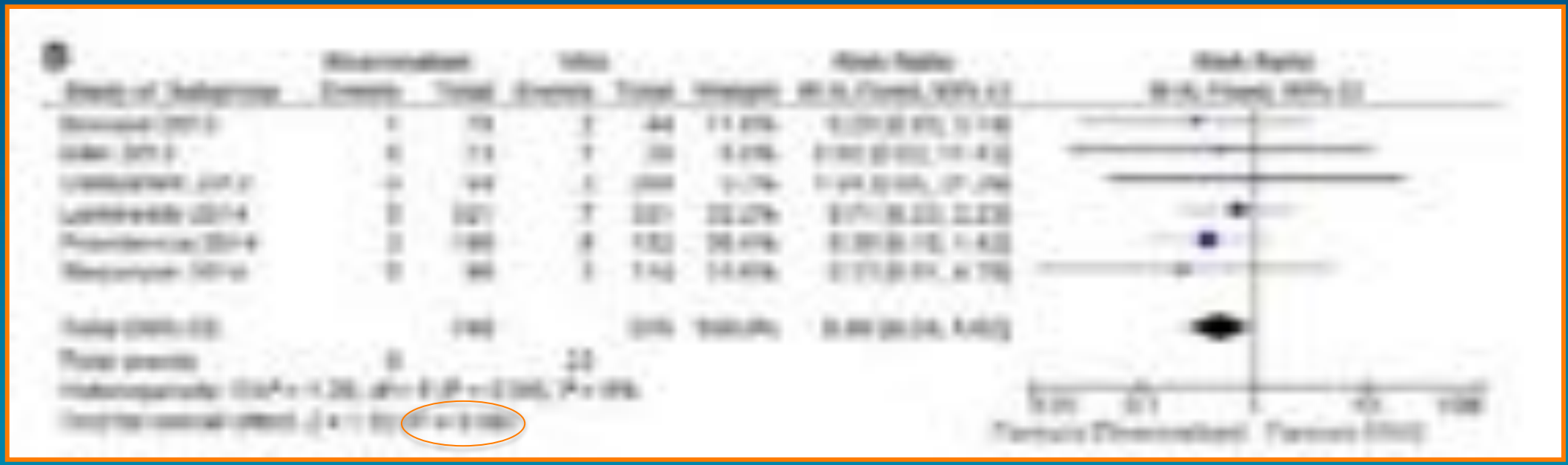
Thromboembolic events:



Aryal et al. Am J Cardiol 2014;114:577-582

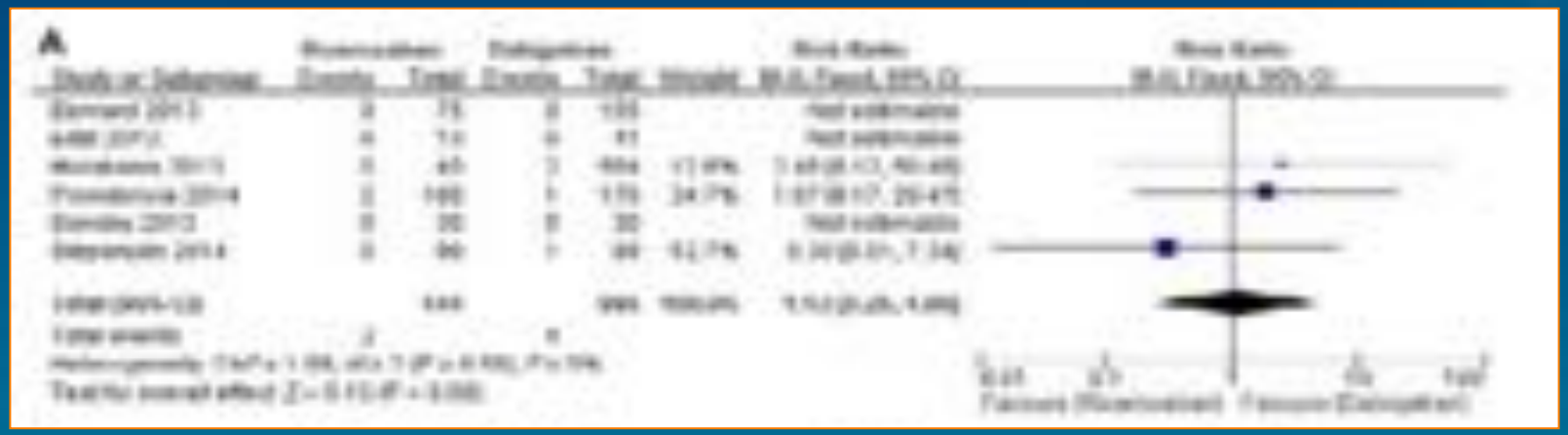
Comparision of rivaroxaban versus warfarin in patients undergoing AF catheter ablation

Major bleeding :

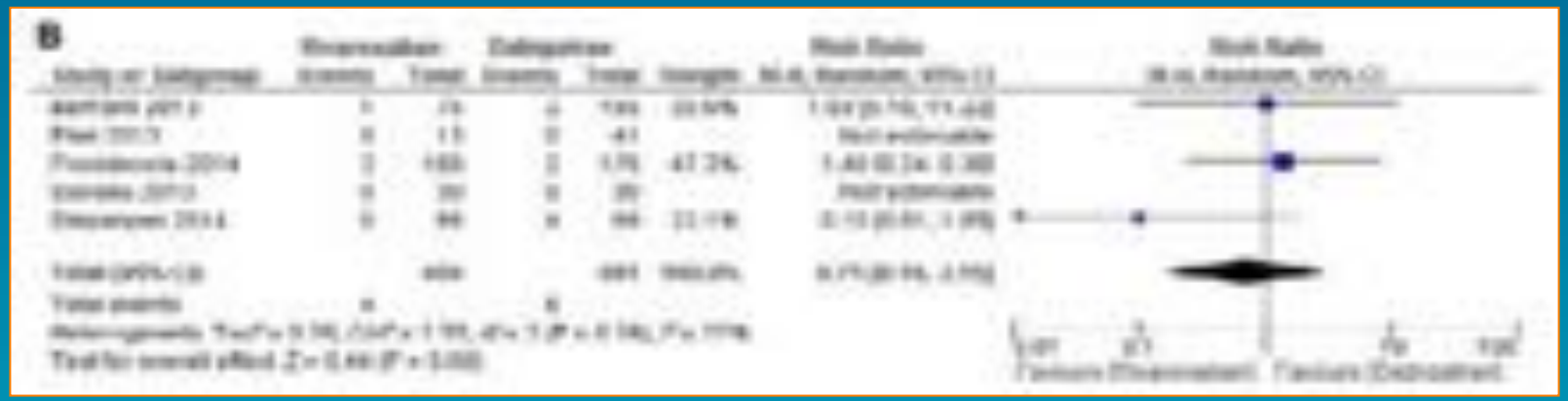


Aryal et al. Am J Cardiol 2014;114:577-582

Comparision of rivaroxaban versus dabigatran in patients undergoing AF catheter ablation



Thromboembolic events



Major bleeding

Aryal et al. Am J Cardiol 2014;114:577-582

Meta-analysis of risk of stroke and thrombo-embolism with rivaroxaban vs VKA in ablation and cardioversion of AF

Stroke:

On the contrarian side, it was suggested in a retrospective study that use of open irrigated tip radiofrequency catheters together with interrupted OAC and bridging with heparin had equal thrombo-embolic events as uninterrupted OAC and that the interrupted approach for anticoagulation provides better outcomes of major bleeding episodes especially in the case of new oral anticoagulants with no established reversing agent [18].

Cardioversion trials included in this analysis had patients on uninterrupted anticoagulation strategy and trans-esophageal echocardiograms were sometimes done in certain occasions prior to the procedure. Of the few studies that compared the use of rivaroxaban to VKA in cardioversion and in ablation, only two were randomized trials while the rest were observational. The recently published randomized trial (X-VERT) showed equal thrombo-embolic and bleeding events between rivaroxaban and warfarin in cardioversion. It also showed that rivaroxaban was associated with a significantly shorter time to cardioversion compared to warfarin

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Nairooz et al. Int J Cardiol 2015;187: 345–53

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Nairooz et al. Int J Cardiol 2015;187: 345–53

Feasibility and safety of uninterrupted peri-procedural apixaban administration in pts undergoing AF ablation

Complication n (%)	Apixaban (N=200)	Warfarin (N=200)	p-value
Major Bleeding Complications	**2 (1.0)**	**1 (0.5)**	**1.0**
Early Pericardial effusion	1 (0.5)	1 (0.5)	1.0
Delayed Pericardial effusion	1 (0.5)	0 (0)	1.0
Minor Bleeding Complications	**7 (3.5)**	**5 (2.5)**	**0.56**
Pericardial Effusion w/out Tamponade and no clinical relevance	3 (1.5)	2 (1.0)	1.0
Groin Hematoma	3 (1.5)	2 (1.0)	1.0
Other	1 (0.5) (GI bleeding)	1 (0.5) (Hematuria)	1.0
Total Bleeding Complications	**9 (4.5)**	**6 (3.0)**	**0.43**
Thromboembolic complications (TIA/Stroke)	**0**	**0**	—
Composite of bleeding and embolic complications	**9 (4.5)**	**6 (3.0)**	**0.43**

Di Biase et al. H. Rhythm Published online: Feb 26, 2015

Feasibility and safety of uninterrupted peri-procedural apixaban administration in pts undergoing AF ablation

Values are reported as mean ± SD or n (%)
ACT: activated clotting time; INR: international normalized ratio.

Table 3

Comparison Complications between Patients on Apixaban

Complication n (%)	Apixaban (N=200)	Warfarin (N=200)

Di Biase et al. H. Rhythm Published online: Feb 26, 2015

oagulation (OAC) with vitamin K antagonists (VKAs) due to fewer thromboembolic and bleeding complications as compared with a bridging regimen with low-molecular-weight heparin (LMWH).[1–3]

cerns about potentially increased bleeding rates in cas
tions or invasive procedures. *Post hoc* analyses of
indicate similar rates of perioperative bleeding ar

* Corresponding author. Tel: +49 341 8651413; fax: +49 341 8651460, Email: charlotteeitel@gmx.de

- Prospective study enrolling 259 patients undergoing AF catheter ablation.
- Patients treated with warfarin and stable INR values before the procedure were excluded from the study
- Patients already on NOACs or LMWH received their last dose the day before the ablation procedure.
  - The last dose of dabigatran was given the evening before the procedure.
  - The last rivaroxaban dose was given the day before the procedure in the morning.
- After the ablation procedure, NOACs were started the same evening depending on the status of femoral puncture sites, otherwise LMWH was given (enoxaparin 0.5 mg/kg) and NOACs were started the day after the intervention.
- Novel oral anticoagulants were given for at least 3 months post-ablation.
- After ablation 38% of patients received dabigatran 110 mg, 56% 150 mg, and 6% received rivaroxaban 20 mg.

Europace 2013; 15: 1587-1593

Novel oral anticoagulants in a real-world cohort of patients undergoing catheter ablation of atrial fibrillation

Results:

- During a mean follow-up of 311 days no stroke, systemic embolism, or major haemorrhage were reported.

- No differences were observed in patients on dabigatran 150, 110 mg, and on rivaroxaban with respect to premature discontinuation due to adverse effects.

Eitel C et al. Europace 2013; 15: 1587-1593

Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia in clinical practice.[1] Catheter ablation of AF has been established as the most effective therapy for the treatment of symptoms in these patients.[1] However, this procedure is associated with a significant thromboembolic risk during and shortly after the procedure, requiring an effective anticoagulation.[2] Vitamin K antagonists (VKA) have been traditionally used to prevent procedure-related thromboembolism.[4]

Recently, novel oral anticoagulants (NOACs) offering important advantages beyond their easiness of administration, like less interactions and no need of laboratory monitoring, have become available and appear as an attractive alternative in this setting. The impact of the wide availability of these NOACs in preventive anticoagula[illegible] treatment of patients that are currently being referred to catheter ab[illegible] lation of AF is currently unknown.

Dabigatran (a direct thrombin inhibitor) has displayed reassur[illegible] safety and efficacy data, suggesting that it might be used as an alterna[illegible] tive to VKA.[5,6] However, data are almost absent concerning rivaroxaban, another NOAC with a different mechanism of action (a facto[illegible] Xa inhibitor) which is being increasingly used worldwide.

Aim

We aimed to (i) observe the change in the pattern of anticoagula[illegible] prescription in patients referred for catheter ablation of AF in ou[illegible]

* Corresponding author. Tel: [illegible]; Fax: [illegible]; Email: [illegible]

Different treatment regimens and timing of drug interruption and restart, as well as bridging heparin therapy.

Providencia et al. Europace Feb 2014

Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia in clin-

the wide availability of these NOACs in preventive anticoag
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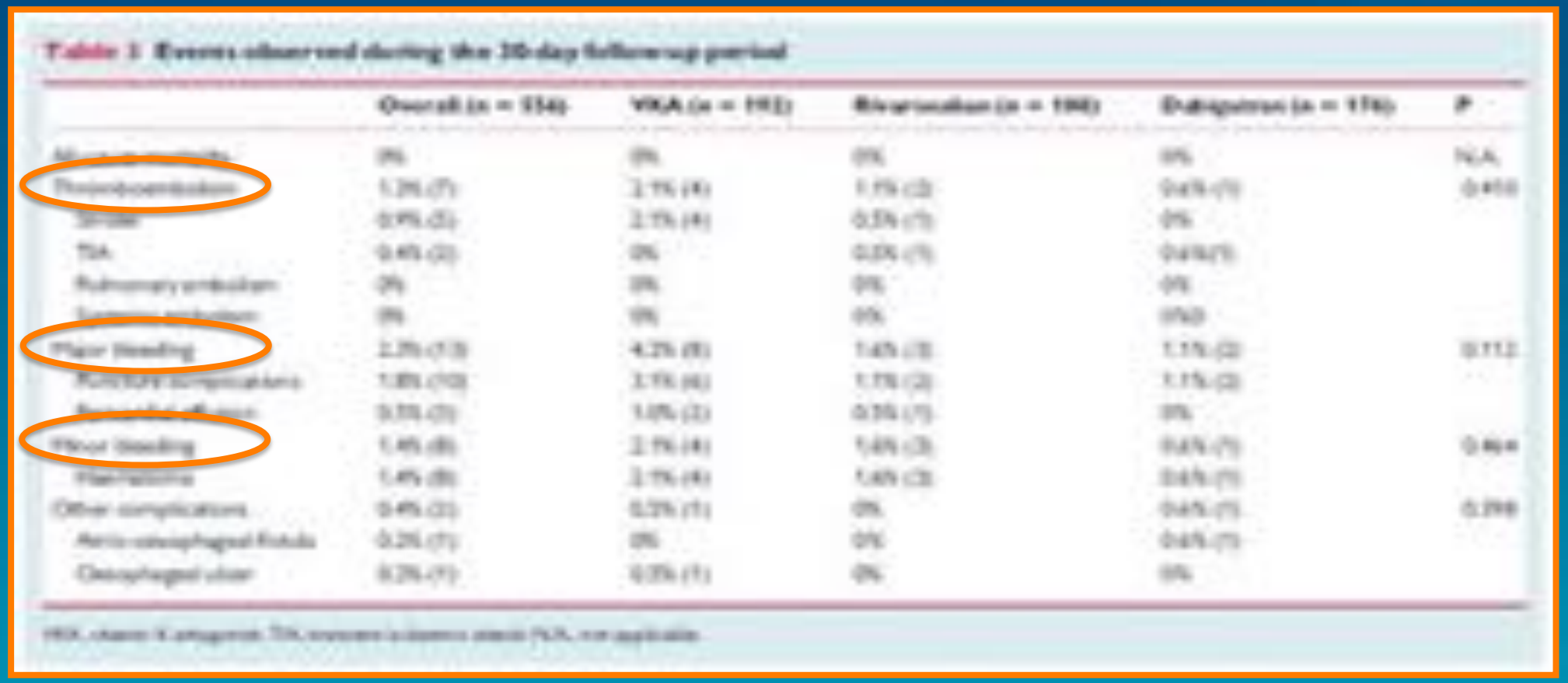


	Overall (n = 554)	VKA (n = 192)	Rivaroxaban (n = 190)	Dabigatran (n = 176)	P
	0%	0%	0%	0%	N.A.
Thromboembolism	1.2% (7)	2.1% (4)	1.1% (2)	0.6% (1)	0.410
Stroke	0.9% (5)	2.1% (4)	0.5% (1)	0%	
TIA	0.4% (2)	0%	0.5% (1)	0.6% (1)	
Pulmonary embolism	0%	0%	0%	0%	
Systemic embolism	0%	0%	0%	0%	
Major bleeding	2.3% (13)	4.2% (8)	1.6% (3)	1.1% (2)	0.112
Pericardial complications	1.8% (10)	3.1% (6)	1.1% (2)	1.1% (2)	
Pericardial effusion	0.5% (3)	1.0% (2)	0.5% (1)	0%	
Minor bleeding	1.4% (8)	2.1% (4)	1.6% (3)	0.6% (1)	0.864
Hematoma	1.4% (8)	2.1% (4)	1.6% (3)	0.6% (1)	
Other complications	0.4% (2)	0.5% (1)	0%	0.6% (1)	0.398
Aorto-esophageal fistula	0.2% (1)	0%	0%	0.6% (1)	
Oesophageal ulcer	0.2% (1)	0.5% (1)	0%	0%	

VKA, vitamin K antagonist; TIA, transient ischaemic attack; N.A., not applicable.

Europace. 2014 Feb 18

In the last 10 years, catheter ablation has become an effective therapeutic option for treatment of symptomatic and drug-refractory AF. Nevertheless, this therapy may be associated with complications, mainly thromboembolic events, cardiac tamponade, and vascular complications.[1,3] Over the years, various antithrombotic treatments for use either during or after the procedure have been proposed to maximize protection against thromboembolic events and to reduce the risk of bleeding. However, the lack of prospective,

for replacement of coagulation factors reduced by warfarin in addition to protamine for reversal of heparin.[3,4]

The availability of NOACs has opened up new anticoagulation protocols during AF ablation. Given the rapid onset of action, these drug have the potential advantage of not requiring any bridging with heparin in the immediate post-operative period. At the same time however, the lack of an antidote makes it difficult to manage any major bleeding. In the last 2 years, several retrospective analyse

- The presence of controversial retrospective data with different anticoagulation protocols and the lack of randomized studies conducted on large patient populations suggest that, at this stage, a certain amount of caution should be exercised with regard to the use of dabigatran as a periprocedural antithrombotic therapy.

- Ablation of AF using uninterrupted warfarin seems to be the most appropriate strategy. Alternatively, discontinuation of NOACs 24 h before the procedure and their resumption a few hours after ablation to avoid the bridge with LMWH seems prudent.

- Further data from prospective randomized studies will be necessary to obtain a clearer picture on the periprocedural management of NOACs in patients undergoing AF ablation and, if appropriate, to propose these new drugs as alternatives to warfarin in electrophysiology laboratories.

Europace 2013; 15: 1535–1537

Dabigatran for Peri Procedural Anticoagulation during Radiofrequency Ablation of Atrial Fibrillation (DAPPARAF)

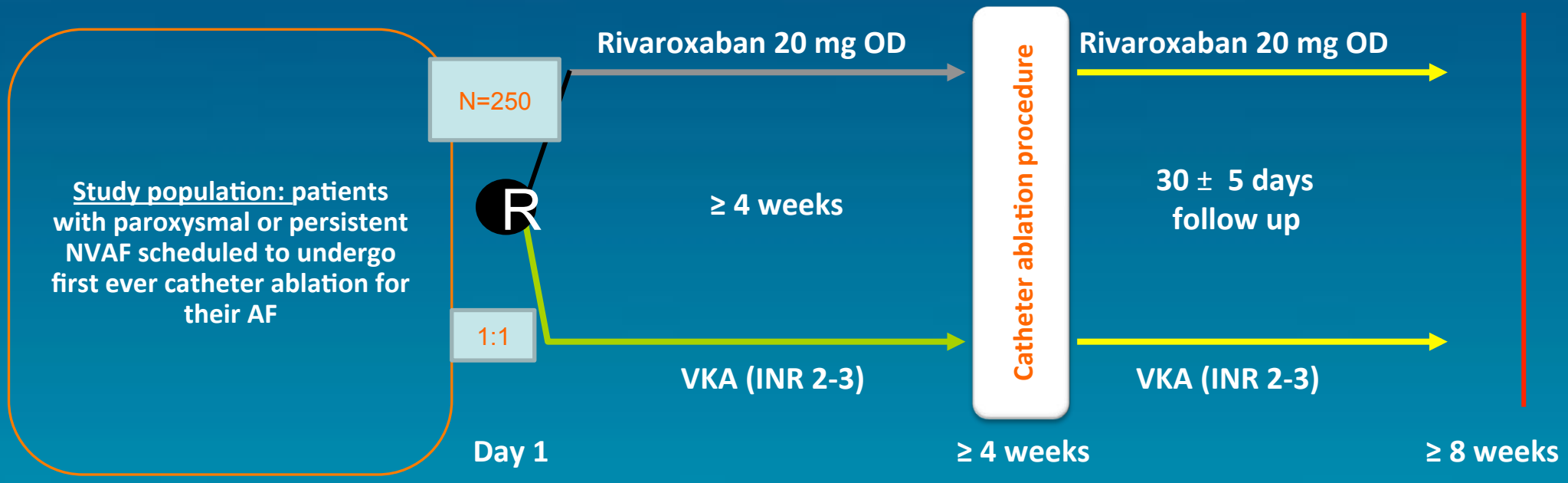
Estimated Enrollment: 200

- Dabigatran 150 mg BID initiated at least one month prior to the ablation procedure until the day before ablation. **On the day prior to ablation, patients will not take any Dabigatran**, nor will any be taken on the day of ablation, until after sheath removal.

- Dabigatran will be started at same dose as before the ablation procedure 8 hours post sheath removal and continued twice daily until 3rd month follow-up

VENTURE-AF

Randomized, open label, active controlled multi-center study to evaluate the safety of rivaroxaban and VKA in subjects undergoing catheter ablation for atrial fibrillation



Clinicaltrials.gov NCT01729871

Cappato et al. Eur Hart J May 2015

VENTURE-AF

Patient population:

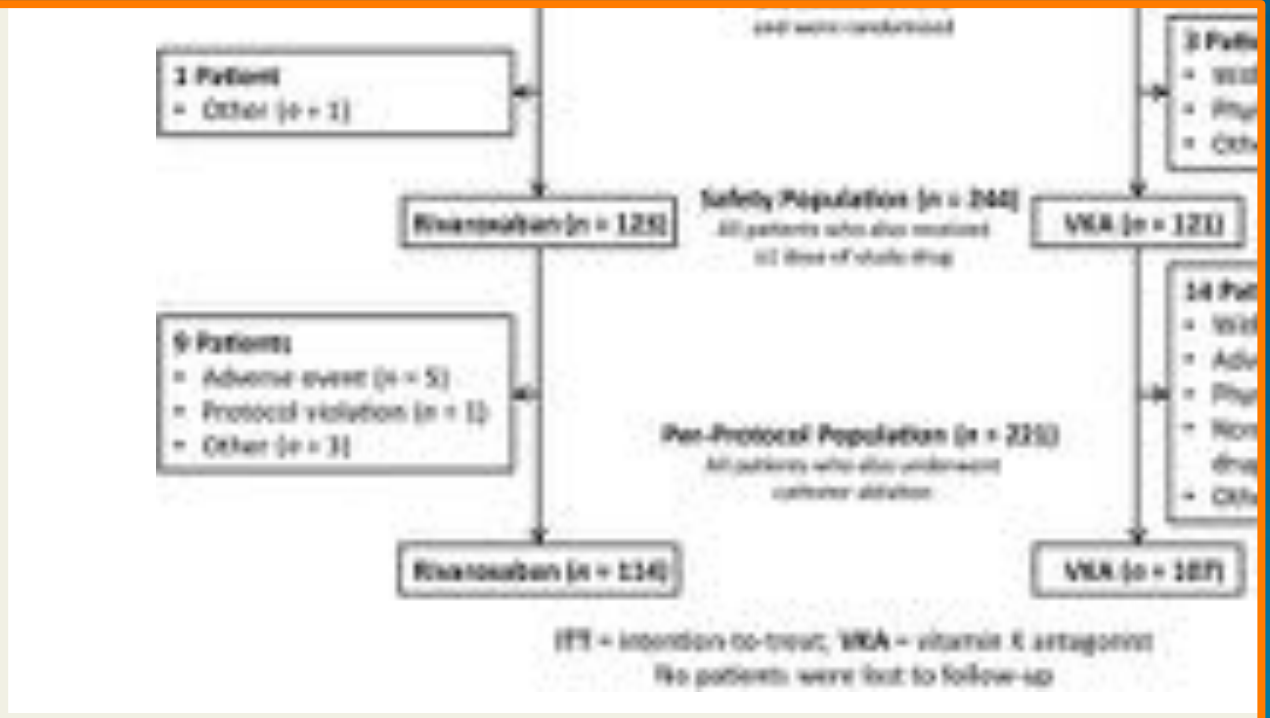


Figure 1 Patient disposition during the study.

Cappato et al. Eur Hart J May 2015

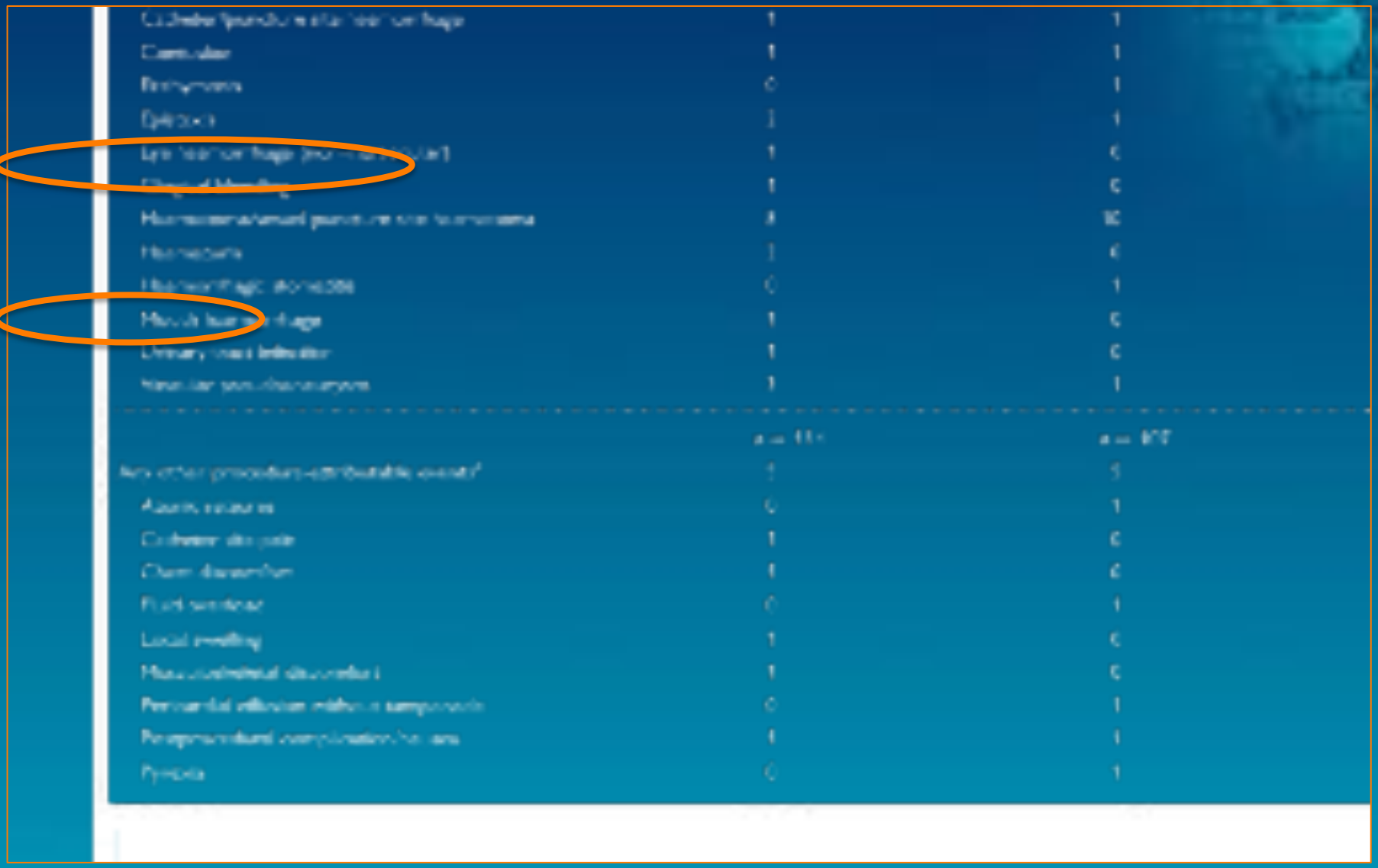
VENTURE-AF

Intraprocedural practical management of ACT:

N	114	107	221
Protamine for heparin reversal, n (%)	32 (28.1)	27 (25.2)	59 (26.7)

Cappato et al. Eur Hart J May 2015

VENTURE-AF: outcames



Cappato et al. Eur Hart J May 2015

Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation

to those for uninterrupted VKA therapy.

Name of the Trial Registry Clinicaltrials.gov trial registration number is NCT01729871.

Keywords Atrial fibrillation • Catheter ablation • Oral anticoagulant • Uninterrupted • Thromboembolism

* Corresponding author. Tel: +1 512 544 8186, Fax: +1 512 544 8184, Email: dr.natale@gmail.com

Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation catheter Ablation:

Comparison to vitamin K antagonist therapy

An Investigator-driven, Prospective, Parallel-group, Randomized, Open-label, Blinded Outcome Assessment (PROBE), Multi-centre Trial to determine the optimal anticoagulation therapy for patients undergoing catheter ablation of atrial fibrillation

Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation catheter Ablation:

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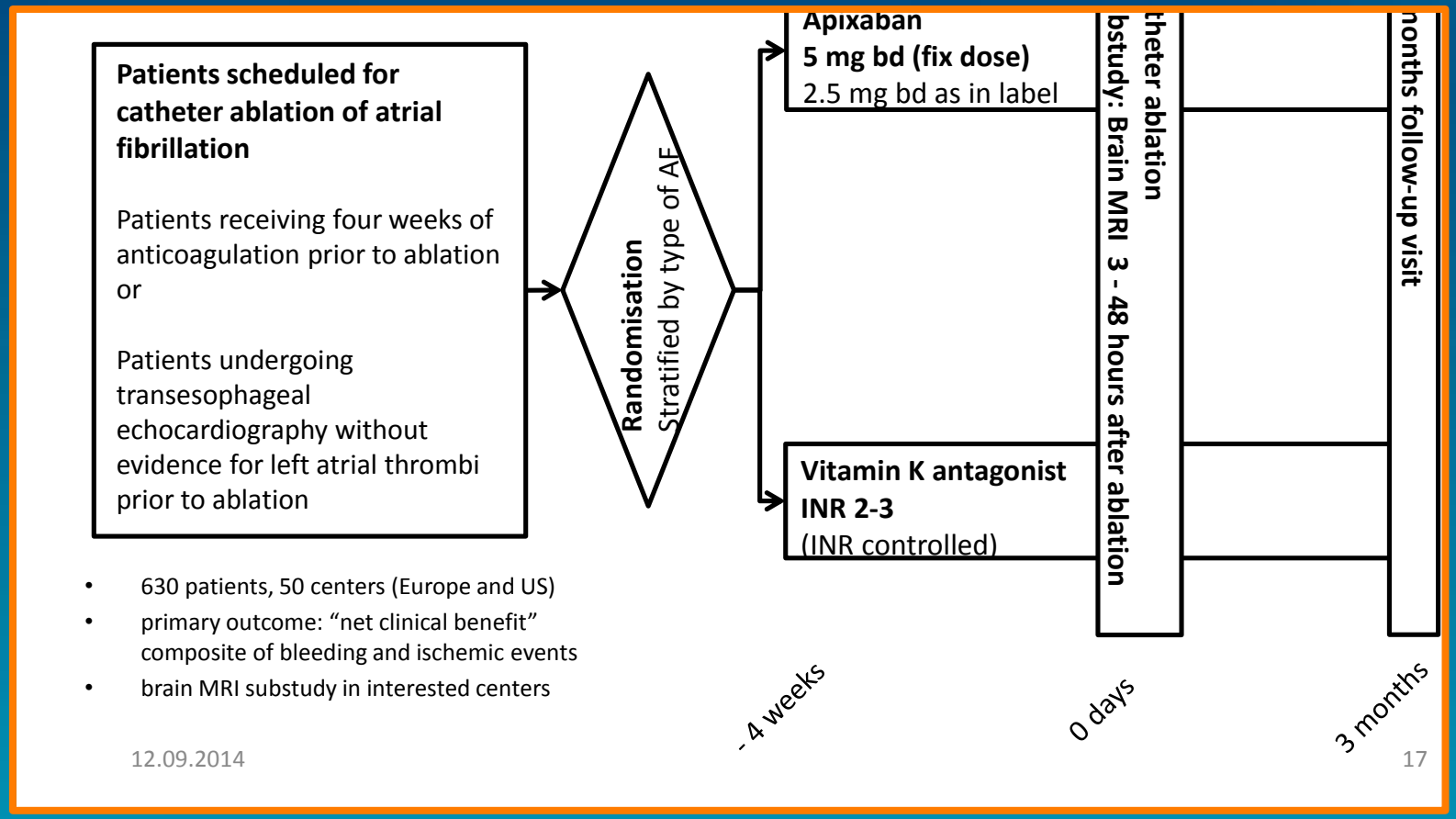

Randomised Evaluation of dabigatran etexilate Compared to warfarIn in pulmonaRy vein ablation: assessment of an uninterrupted periproCedUral antIcoagulation sTrategy (The RE-CIRCUIT Trial)

- Primary objective of this trial is to assess the safety of an uninterrupted dabigatran etexilate periprocedural anticoagulant regimen compared to an uninterrupted periprocedural warfarin regimen in NVAF patients undergoing AF ablation in a PROBE (**Prospective, randomized, open label, blinded end point**) active controlled study.

- Secondary objectives are to assess a composite of safety and efficacy in this clinical setting.

ClinicalTrials.gov: NCT02348723

Randomised Evaluation of dabigatran etexilate Compared to warfarIn in pulmonaRy vein ablation: assessment of an uninterrupted periproCedUral antIcoagulation sTrategy (The RE-CIRCUIT Trial)

Figure 3.1: 1 Treatment periods and treatment groups in the trial design

The screening period will consist of one visit (Visit 1). The patients will be ran
Visit 2. Screening and randomisation can be conducted on the same day.

Pre-ablation period
There will be a pre-ablation period of 4 to 8 weeks.

01-MCS-40-106-RD-03 (11.0

724 pts planned in US, Europe and Japan


Laurent Fauchier, (France), Deirdre Lane, (UK), Alvaro Avezum, (Brazil), Torben Bjerregaard Larsen, (Denmark), Guiseppe Boriani, (Italy), Vanessa Roldan-Schilling, (Spain), Bulent Gorenek, (Turkey), and Irene Save (UK, on behalf of EP-Europace)

While awaiting data from prospective trials, we recommend an institutional protocol for NOAC patients undergoing AF ablation. This may consist of:

- Changing patients to uninterrupted VKA,
- Uninterrupted NOAC therapy,
- Well-planned cessation of NOAC.

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Laurent Fauchier, (France), Deirdre Lane, (UK), Alvaro Avezum, (Brazil),
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A number of factors should be considered for the timing of last intake, such as

- renal function,
- CHA_2DS_2-VASc risk of the patient,
- experience of the operator,
- type and extent of additional ablation beyond PVI,
- presence of peri-procedural imaging to guide transseptal puncture

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- Meta-analysis data indicate that a last intake of NOAC 24 h before the procedure is a viable strategy.
- Continued intake until the evening before the procedure or even the morning of the procedure seems to be equally safe, especially in experienced centres but more data are needed to make firm statements on the best strategy.
- When NOAC is last taken ≥36 h before the intervention, a TOE should be considered before ablation.

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- During the ablation, IV heparin should be administered to achieve an ACT of 300 – 350 s. It seems reasonable to use the same target ACT levels for heparin titration in NOAC-treated patients as in patients on (uninterrupted) VKA.

- NOAC intake can be resumed a 3 -4 h after sheath removal if adequate haemostasis and the absence of pericardial effusion have been confirmed.

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(UK, on behalf of EP-Europace)

[1]Department of Cardiology – Arrhythmology, Hasselt University and Heart Center, Jessa Hospital, Stadsomvaart 11, 3500 Hasselt, Belgium; [2]Department of Cardi
University of Leuven, Belgium; [3]Department of Cardiology, Amphia Ziekenhuis, Breda, Netherlands; [4]Department of Cardiology, Klinikum Oldenburg, Oldenbur
[5]Department of Neurology, University Hospital Essen, University Duisburg-Essen, Germany; [6]Department of Neurology, Ruprecht Karls Universität, Heidelberg,
Clinical Research Center and Department of Medical Sciences, Uppsala University, Uppsala, Sweden; [8]Clinical Cardiology, St George's University, London, UK;
Birmingham Centre for Cardiovascular Sciences, Birmingham, UK; and [10]Department of Cardiology and Angiology, University of Münster, Germany

During the ablation, IV heparin should be administered to achieve an ACT of 300 – 350 s. It seems reasonable to use the same target ACT levels for heparine titration in NOAC-treated patients as in patients on (uninterrupted) VKA, as has been done by many investigators.

It has been noted that even in patients in whom the last NOAC dose was given in the morning of the procedure, the total need for heparin was higher and the time to target ACT lasted longer than in uninterrupted VKA patients. This likely reflects a difference in whole blood coagulability rather than a direct interaction between NOACs and the ACT test.

NOAC intake can be resumed a 3 – 4 h after sheath removal if adequate haemostasis and the absence of pericardial effusion have been confirmed

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