ORIGINAL ARTICLE

HSR Proc Intensive Care Cardiovasc Anesth. 2013; 5(1): 40-54

Comparative effectiveness of novel oral anticoagulants for atrial fibrillation: evidence from pair-wise and warfarin-controlled network meta-analyses

G. Biondi-Zoccai[1], V. Malavasi[2], F. D'Ascenzo[3], A. Abbate[4], P. Agostoni[5], M. Lotrionte[6], D. Castagno[3], B. Van Tassell[4], E. Casali[2], M. Marietta[7], M.G. Modena[2], K.A. Ellenbogen[4], G. Frati[1,8]

[1]Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome, Italy; [2]Division of Cardiology, University of Modena and Reggio Emilia, Modena, Italy; [3]Division of Cardiology, University of Turin, Turin, Italy; [4]VCU Pauley Heart Center, Richmo-nd, VA, USA; [5]Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands; [6]Division of Cardiology, Catholic University, Rome, Italy; [7]Hemostasis/Thrombosis Unit, University of Modena and Reggio Emilia, Modena, Italy; [8]Department of AngioCardioNeurology, IRCCS Neuromed, Pozzilli, Italy

HSR Proc Intensive Care Cardiovasc Anesth. 2013; 5(1): 40-54

ABSTRACT

Introduction: Novel oral anticoagulants have been tested against warfarin for atrial fibrillation, yet no direct comparison is available. We thus aimed to perform pair-wise (direct) and warfarin-adjusted network (i.e. indirect) meta-analyses of novel oral anticoagulants for atrial fibrillation.
Methods: Databases were searched for randomized warfarin-controlled trials of novel anticoagulants for non-valvular atrial fibrillation. The primary end-point was long-term stroke/systemic embolism. Odds ratios (95 % intervals) were computed with RevMan and WinBUGS.
Results: Seven trials (52701 patients) were included, focusing on apixaban, dabigatran, edoxaban and rivaroxaban. Pair-wise meta-analysis showed that after a weighted average of 23 months these novel anticoagulants lead to significant reductions in the risk of stroke/systemic embolism (odds ratio = 0.81 [0.71-0.92], I2 = 23 %) and all cause death (odds ratio = 0.88 [0.82-0.95], I2 = 0 %) in comparison to warfarin. Network meta-analysis showed that apixaban and dabigatran proved similarly superior to warfarin in preventing stroke/systemic embolism (odds ratio = 0.78 [0.62-0.96] for apixaban vs warfarin; odds ratio = 0.66 [0.52-0.84] for high-dose dabigatran vs warfarin; odds ratio for apixaban vs high-dose dabigatran = 1.17 [0.85-1.63]), but apixaban was associated with fewer major bleedings (odds ratio = 0.73 [0.57-0.93]) and drug discontinuations (odds ratio = 0.64 [0.52-0.78]) than dabigatran. Rivaroxaban did not reduce stroke/systemic embolism (odds ratio = 0.87 [0.71-1.07]) or major bleedings in comparison to warfarin (odds ratio = 0.87 [0.71-1.07]) and was associated with more major bleedings in comparison to apixaban (odds ratio = 1.52 [1.19-1.92]). Data for edoxaban were inconclusive.
Conclusions: Novel oral anticoagulants appear as a very promising treatment option for atrial fibrillation.

Keywords: *apixaban, atrial fibrillation, dabigatran, meta-analysis, rivaroxaban, systematic review, warfarin.*

INTRODUCTION

Atrial fibrillation is the most common clinically relevant arrhythmia (1), and its management is based on rate control (2), and antithrombotic therapy (3). Stroke and systemic embolism are the most feared com-

Corresponding author:
Giuseppe Biondi Zoccai
Department of Medico-Surgical Sciences and Biotechnologies
Sapienza University of Rome
Corso della Repubblica, 79 - 04100 Latina, Italy
e-mail: gbiondizoccai@gmail.com

plications of atrial fibrillation. Warfarin and other oral vitamin K antagonists have been proved effective and relatively safe in the prevention of thromboembolic risk of patients without bleeding diathesis but at moderate or high risk of stroke (4).

Warfarin has several limitations (1). First, it has a narrow therapeutic window and requires frequent monitoring of the international normalized ratio (INR). In addition, it has highly variable response (5), as well as multiple drug and food interactions (6). Finally, despite optimal warfarin treatment, thromboembolic events still occur in several patients (7, 8).

Novel oral anticoagulants have been recently developed and formally tested in warfarin-controlled phase III randomized trials (9-11), and others are currently completing pivotal trials (12-14). Specifically, apixaban (Eliquis; Bristol-Myers Squibb and Pfizer), edoxaban (Lixiana, Daiichi Sankyo and Eli Lilly) and rivaroxaban (Xarelto; Bayer and Johnson & Johnson) are oral direct Factor Xa (FXa) inhibitors, whereas dabigatran etexilate (Pradaxa, Pradax or Prazaxa; Boehringer Ingelheim) is an oral prodrug which is converted by plasma and hepatic esterases to dabigatran, a direct Factor IIa (FIIa, i.e. thrombin) inhibitor (*Table 1*) (15). Promising data have been reported for all such novel drugs when compared to warfarin in patients with atrial fibrillation, yet it is unclear whether they do really represent a favorable breakthrough in the management of atrial fibrillation. In addition, the practicing physician remains uncertain about the relative strengths and weaknesses of each of these new treatment options as no direct comparison among them is available nor is foreseeable in the next future.

Network meta-analyses, as mixed treatment comparisons, are novel research designs capable of comparing different treatments exploiting common comparators, and their role in clinical research and practice has already been established (16). Whereas other network meta-analyses have already been reported focusing on dabigatran and antiplatelet therapy (17, 18), no study is available comparing novel oral anticoagulants for atrial fibrillation.

We thus aimed to perform pair-wise and warfarin-controlled network meta-analyses of novel oral anticoagulants for atrial fibrillation.

METHODS

Design and registration. The present review was performed according to the Cochrane Collaboration and PRISMA statements (19, 20). In addition, it was prospectively registered on metcardio.org (protocol #3/2010).

Search. MEDLINE/PubMed was searched according to this highly sensitive strategy, modified by Biondi-Zoccai et al (21), on September 10, 2011: (apixaban OR rivaroxaban OR dabigatran OR (novel AND oral AND anticoagulant*)) AND atrial AND fibrillation AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]) NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt])). In addition, Google Scholar, The Cochrane Library, and Scopus were also searched for pertinent citations.

Table 1 - *Pharmacokinetics of the novel oral anticoagulants.*

	Apixaban[d]	Dabigatran[d,e]	Edoxaban	Rivaroxaban
Target	Factor Xa	Factor IIa	Factor Xa	Factor Xa
Dose[a]	5 mg	75-150 mg	30-60 mg	20 mg
Frequency	Twice daily	Twice daily	Daily	Daily
Effect of Food	None	May delay (but not limit) absorption	None	None
$T_{1/2}$	12 h	12-17 h	6-10 h	5-9 h
T_{MAX}	1-3 h	1 h	1-2 h	2-4 h
Metabolism	Hepatic (CYP3A4 - major)	Activation by esterases - renal	Renal – hepatic (CYP3A4 - minor)	Hepatic (CYP3A4 -major) - renal
Renal Impairment	Use 2.5 mg twice daily if SCr ≥1.5 mg/dL	Use 75 mg twice daily if CrCl = 15-30 mL/min*m^2	Avoid use if CrCl < 30 mL min*m^2	Use 15 mg daily if CrCl = 30-49 mL/min*m^2 - avoid use if CrCl < 30 mL/min*m^2
Hepatic Impairment	Use with caution in mild to moderate (Child-Pugh B) - avoid use in severe (Child-Pugh C)	N/A	Unknown	Avoid use in moderate (Child-Pugh B) or severe (Child-Pugh C)
Drug Interactions	CYP3A4 inhibitors or inducers - P-glycoprotein inhibitors or inducers	P-glycoprotein inhibitors or inducers	P-glycoprotein inhibitors or inducers	CYP3A4 inhibitors or inducers - P-glycoprotein inhibitors or inducers
Monitoring[b]	Anti-Xa	aPTT, ECT	Anti-Xa	Anti-Xa
Overdose management[c]	Unknown	Unknown (can be dialyzed)	Unknown	Unknown (likely not dialyzable – possibly protrombin complex concentrate[f]

[a]dose for atrial fibrillation; [b]routine monitoring not recommended due to linear dose response; [c]activated prothrombin complex concentrate and recombinant factor VIIa have been proposed in overdose management; [d]approved by the FDA for use in patients with non-valvular atrial fibrillation in the USA; [e]capsules should be swallowed, do not chew, break, or open capsules; [f]a single study showed reversibility of rivaroxaban effect (and not of dabigatran effect) using protrombin complex concentrate (Eerenberg et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011; 124: 1573-79); CrCl = creatinine clearance; CY = cytochrome; ECT = ecarin clotting time; N/A = not applicable or available; SC_r = serum creatinine; aPTT = activated partial thromboplastin time.

References of retrieved studies were checked for additional studies (backward snowballing) and 2008-2011 conference proceedings of the American College of Cardiology, American Heart Association, and European Society of Cardiology scientific sessions were also manually searched. No language restriction was enforced.

Selection. Study selection was performed by two independent reviewers (GBZ, ML), with divergences resolved by consensus. Citations were first scanned at the title/abstract level. Shortlisted studies were then retrieved in full text.

They were considered suitable for inclusion if: reporting on randomized trials,

comparing warfarin versus novel oral anticoagulants, enrolling patients with atrial fibrillation (all the criteria had to be satisfied for inclusion). Studies were excluded if non-randomized, used other controls than warfarin, included patients without atrial fibrillation, or focused on ximelagatran/melagatran, which is no longer developed given severe liver toxicity (22).

Abstraction and appraisal. Data abstraction and study appraisal were performed by two independent reviewers (GBZ, ML), with divergences resolved by consensus. Key study and patient characteristics were extracted, including the following outcomes, reported at the longest available follow-up according to intention-to-treat principles:

1) stroke or systemic embolism (primary end-point);
2) all-cause death;
3) major bleeding defined according to the Thrombolysis in Myocardial Infarction (TIMI) definition;
4) drug discontinuation.

In addition, study validity was appraised according to the risk of bias tool recommended by The Cochrane Collaboration (23). All corresponding authors of short-listed studies were directly contacted for data quality and completeness.

Analysis. Categorical variables are reported as events/patients at risk and were compared with odds ratios (OR) with 95% confidence/credible intervals. Overall pairwise meta-analyses were performed with DerSimonian-Laird method and random-effect model by means of RevMan 5.0.24 (The Cochrane Collaboration, Copenhagen, Denmark), checking statistical consistency by means of I^2 (24).

In addition, small study effects were appraised by visual inspection of funnel plots. Notably, no formal test for publication bias was used given the few included studies and variable comparators included. Subsequently, warfarin-adjusted network meta-analyses (actually indirect treatment comparisons, given the star-shaped network) were performed using a fixed-effect model with WinBUGS 1.4.3, which behaves similarly to an indirect comparison method given the star shape. Each analysis was based on non-informative priors for effect sizes. Convergence and lack of auto-correlation were checked and confirmed after a 100,000-simulation burn-in phase, and, finally, direct probability statements were based on an additional 500,000-simulation phase. Deviance and deviance information criterion (DIC) were used to appraise model fit in comparison to a random-effect model. Comparisons are presented throughout using warfarin as reference treatment and ordering experimental treatments alphabetically.

RESULTS

Studies. From a total of 7114 citations, 7 trials were finally included (*Tables 2-6*).

Specifically, two trials focused on apixaban (10, 25), two trials focused on dabigatran at variable dosages (9, 26), two trials focused on edoxaban at variable dosages (12, 13), and one trial focused on rivaroxaban (*Tables 2-4*) (11).

All included studies were randomized clinical trials, varying from small phase II dose-finding studies (12-13, 25-26), from large phase III pivotal studies with a non-inferiority scope (9, 11). Inclusion and exclusion criteria were largely similar, but patients enrolled in the ROCKET AF trial of rivaroxaban versus warfarin had a higher prevalence of adverse clinical features, including a higher CHADS2 score (*Tables 2-4*).

Despite this, enrolment criteria were sufficiently homogeneous (i.e. all studies included patients in whom warfarin was considered beneficial) to ensure that the key assumption of any network meta-analysis

Table 2 - *Main features of included studies.*

Study	Design	Patients	Location	Drug	Follow-up (months)	Primary end-point
ARISTOTLE	Non-inferiority RCT	18,201	Worldwide	Apixaban 5 mg BID (2.5 mg in patients with two or more of the following: age ≥80 years, body weight ≤60 kg, or SCr ≥1.5 mg/dL (133 µmol/L) vs warfarin (target INR 2.0-3.0)	22	Stroke or systemic embolism
ARISTOTLE-J	Phase II RCT	222	Japan	Apixaban 2.5 mg BID vs apixaban 5 mg BID vs warfarin (target INR 2.0-3.0)	3	Major bleeding and clinically relevant non-major bleeding
Chung 2011	Phase II RCT	253	Asia	Edoxaban 30 mg QD vs edoxabn 60 mg QD vs warfarin (target INR 2.0-3.0)	3	Major, clinically relevant non-major and minor bleeding
PETRO	Phase II RCT	502	Worldwide	Dabigatran 50 mg QD vs dabigatran 50 mg BID vs dabigatran 150 mg BID vs dabigatran 300 mg BID vs warfarin (target INR 2.0-3.0)	3	Bleeding events
RE-LY	Non-inferiority RCT	18,113	Worldwide	Dabigatran 150 mg BID vs dabigatran 110 mg BID vs warfarin (target INR 2.0-3.0)	24	Stroke or systemic embolism
ROCKET-AF	Non-inferiority RCT	14,264	Worldwide	Rivaroxaban 20 mg QD (15 mg if CrCl between 30-49 ml per minute) vs warfarin (target INR 2.0-3.0)	24	Stroke (ischemic or hemorrhagic) and systemic embolism
Weitz 2010	Phase II RCT	1,146	Worldwide	Edoxaban 30 mg QD vs edoxaban 30 mg BID vs edoxaban 60 mg QD vs edoxaban 60 mg BID vs warfarin (target INR 2.0-3.0)	3	Major and/or clinically relevant non-major bleeding

BID = bis in die; CrCl = creatinine clearance; INR = international normalized ratio; QD = quoque die; RCT = randomized clinical trial; SC_r = serum creatinine.

Table 3 - *Key selection criteria of included studies.*

Study	Inclusion	Exclusion
ARISTOTLE	AF with CHADS2≥1	AF due to a reversible cause, moderate or severe mitral stenosis, conditions other than AF that required anticoagulation (e.g., a prosthetic heart valve), stroke within the previous 7 days, a need for aspirin at a dose of > 165 mg a day or for both aspirin and clopidogrel, calculated creatinine clearance of < 25 ml per minute.
ARISTOTLE-J	AF with CHADS≥1	Recent stroke or TIA, valvular heart disease; sick sinus syndrome or severe conduction disturbance; non-cardiogenic stroke requiring aspirin > 100 mg/day or concomitant aspirin and antiplatelet agents; contraindications for warfarin use; severe or refractory hypertension; New York Heart Association class IV heart failure; current thrombocytopenia: alanine aminotransferase or aspartate aminotransferase ≥2 × upper limit of normal; creatinine clearance < 25 ml/min by Cockcroft Gault calculation; known or suspected hereditary bleeding tendencies; and scheduled electrical, pharmacological, or surgical cardioversion during the treatment period.
Chung 2011	AF with CHADS2≥1	Previous valve surgery, contraindication to anticoagulants, known bleeding disorder, conditions associated with high risk of bleeding (e.g. past history of major bleeding; uncontrolled hypertension; uncontrolled diabetes; haemorrhagic disorder; significant thrombocytopenia), ongoing treatment with an antiplatelet agent, AF secondary to other reversible disorders, acute coronary syndrome or revascularization procedures, stroke, transient ischaemic attack, any major surgery within the previous 30 days, left ventricular aneurysm or atrial myxoma, impaired hepatic function, serum creatinine ≥1.5 mg/dl, women of child-bearing potential without adequate contraception, pregnancy or lactation.
PETRO	AF with CHADS2≥1	Mitral stenosis, prosthetic heart valves, planned cardioversion, recent (< 1 month) myocardial infarction, recent stroke or TIA, coronary stent placement within 6 months, any contraindication to or another indication for anticoagulant therapy, major hemorrhage in the past 6 months, glomerular filtration rate < 30 ml/min, abnormal liver function, risk of pregnancy, investigational drug use within 30 days, or any other condition that would not allow participation in the study.
RE-LY	AF with CHADS2≥1	Severe heart-valve disorder, stroke within 14 days or severe stroke within 6 months before screening, a creatinine clearance < 30 ml per minute, active liver disease, and pregnancy.
ROCKET-AF	AF with CHADS2≥2	Mitral valve stenosis, prosthetic heart valve; planned cardioversion (electrical or pharmacological); AF due to a reversible cause; active endocarditis; active internal bleeding; platelet count < 90,000/μL at the screening visit; sustained uncontrolled hypertension; severe, disabling stroke within 3 months or any stroke within 14 days before the randomization visit; TIA within 3 days before the randomization visit; indication for anticoagulant therapy for a condition other than atrial fibrillation; aspirin > 100 mg daily; aspirin in combination with thienopyridines within 5 days before randomization; intravenous antiplatelets within 5 days before randomization; fibrinolytics within 10 days before randomization; systemic treatment with a strong inhibitor or inducer of cytochrome P450 3A4, such as ketoconazole or protease; hemoglobin < 10 g/dL at the screening visit; pregnancy or breast-feeding: any other contraindication to warfarin; known HIV infection at time of screening; renal clearance < 30 mL/min at the screening visit; known significant liver disease.

Weitz 2010	AF with CHADS2≥2	Mitral valve disease, endocarditis, or a mechanical valve; contraindications to anticoagulation therapy, including a known bleeding disorder, recent major bleeding, uncontrolled hypertension, haemoglobin < 10.0 g/dl, platelet count < 100,000/µl or a white blood cell count < 3,000/µl; a requirement for ongoing treatment with a thienopyridine; AF secondary to reversible disorders (e.g., thyrotoxicosis); left ventricular aneurysm or atrial myxoma; an estimated life expectancy < 12 months; planned surgery or intervention within the study period; a history of hepatitis B or C or HIV infection; creatinine clearance < 30 ml/minute (min); a cardiac pacemaker or implantable cardioverter-defibrillator; investigational drug treatment (including edoxaban) or device implantation in the last three months, or plan to receive such therapy during the study period. impaired hepatic function.

AF = atrial fibrillation; TIA = transient ischemic attack; CHADS2 = Congestive heart failure, hypertension, age, diabetes, stroke score.

Table 4 - *Key patient characteristics of included studies.*

Study	Age (years)	Female gender	HTN	Diabetes	Heart failure	Prior-myocardial infarction	Parox-smal AF	Prior stroke or TIA	Warfarin naïve patients	$CHADS_2$ score > 2
ARISTOTLE	70	36 %	87 %	25 %	36 %	15 %	16 %	20 %	57 %	30 %
ARISTOTLE-J	70	20 %	83 %	23 %	1 %	NA	0	28 %	16 %	57 %
Chung 2011	65	36 %	71 %	30 %	28 %	NA	NA	19 %	NA	49 %
PETRO	70	18 %	71 %	25 %	29 %	NA	23 %	17 %	NA	NA
RE-LY	72	37 %	79 %	23 %	79 %	17 %	33 %	20 %	50 %	33 %
ROCKET-AF	73	40 %	90 %	40 %	63 %	17 %	18 %	55 %	62 %	100 %
Weitz 2010	65	41 %	NA	NA	NA	NA	NA	NA	66 %	100 %

AF = atrial fibrillation; $CHADS_2$ = Congestive heart failure, hypertension, age, diabetes, stroke score; HTN = hypertension; NA = not available or applicable; TIA = transient ischemic attack.

(namely the focus on a common patient subset treated with the same comparator) hold true. The internal validity of included studies was high, especially given the logistical challenges involved in the conduct of a double-blind trial when warfarin is the control treatment (*Table 5*).

Pair-wise meta-analysis. First, we conducted a standard pair-wise meta-analysis pooling all novel oral anticoagulants together and comparing them against warfarin performing a random-effect model. After a weighted average follow-up of 23 months, novel oral anticoagulants were associated with significant reductions in the risk of stroke or systemic embolism (OR = 0.81 [0.71-0.92], I^2 = 23 %) all cause death (OR = 0.88 [0.82-0.95], I^2 = 0 %), in comparison to warfarin, with a favorable trend for major bleeding (OR = 0.83 [0.68-1.02], I^2 = 73 %). Conversely, aggregate analysis showed a similar or slightly increased risk of study drug discontinuation with novel oral anticoagulants (OR = 1.18 [0.96-1.46], I^2 = 92 %) versus warfarin. However, both estimates regarding major bleeding and drug discontinuation were statistically inconsistent, suggesting different effects of the different anticoagulants. Funnel plot inspection suggested the presence of small study effects due to the inclusion of phase II trials with a small sample size. However, sensitivity

Table 5 - *Risk of bias assessment of included studies.*

	Adequate sequence generation?	Allocation concealment used?	Blinding?	Concurrent therapies similar?	Incomplete outcome data ad dressed?	Uniform and explicit out come definitions?	Free of selective outcome reporting?	Free of other bias?	Over all risk of bias?
ARISTOTLE	Yes (computed generated sequence)	Yes (interactive voice response system)	Double blind, bouble dummy	Yes (differences < 1 %)	Yes	Yes	Yes	Yes	Low
ARISTOTLE-J	Unclear	Yes (interactive voice response system)	Double blind	Yes (differences < 3 %)	Not addressed	Yes	Unclear	Yes	Moderate
Chung 2011	Yes (computed generated sequence)	Yes (interactive voice response system)	Blind to dose of edoxaban, but open to identity of edoxaban warfarin	Yes (differences < 1 %)	Not addressed	Yes	Unclear	Yes	Moderate
PETRO	Unclear	Yes (interactive voice response system)	Double blind to dose of dabigatran but open to identity of dabigatran and warfarin	Yes (differences < 5 %)	Not addressed	Yes	Unclear	Yes	Moderate
RE-LY	Yes (computed generated sequence)	Yes (interactive voice response system)	Double blind	Yes (differences < 1 %)	Yes	Yes	Yes	Yes	Low
ROCKET-AF	Yes (computed generated sequence)	Yes (interactive voice response system)	Double blind, double dummy	Yes (differences < 1 %)	Yes	Yes	Yes	Yes	Low
Weitz 2010	Yes (computed generated sequence)	Yes (interactive voice response system)	Blind to dose of edoxaban, but open to identity of edoxaban and warfarin	Yes (differences < 5 %)	Not addressed	Yes	Yes	Yes	Low

Table 6 - *Key excluded studies.*

Study	Study drug	Reason for exclusion
AVERROES	Apixaban	Selective inclusion of warfarin ineligible patients
Ellis 2009	Tecarfarin	Non-randomized design
ENGAGE AF-TIMI 48	Edoxaban	Ongoing
RE-LY – CHADS2 substudy	Dabigatran	Duplicate publication
RE-LY – CHA2DS2-VASc substudy	Dabigatran	Duplicate publication
RE-LY – Prior stroke/TIA substudy	Dabigatran	Duplicate publication
ROCKET-AF – Renal failure substudy	Rivaroxaban	Duplicate publication

$CHADS_2$ = Congestive heart failure, hypertension, age, diabetes, stroke score; CHA2DS2-VASc = Congestive heart failure, hypertension, age, diabetes, stroke-vascular disease, age, sex category score; TIA = transient ischemic attack.

analysis excluding all studies with sample size ≤5,000 patients confirmed in magnitude and direction our overall findings. *Network meta-analysis*. Warfarin-controlled network meta-analysis enabled the head-to-head comparison of each novel oral anticoagulant against warfarin as well as against each other individual drug (*Table 7)*.

After a weighted average follow-up of 23 months, apixaban and high-dose dabiga-

Table 7 - *Clinical outcomes in included studies*.*

	Stroke or systemic embolism	Death	Major bleeding	Drug discontinuation
Apixaban	**OR = 0.78 (0.62-0.96) vs warfarin;** OR = 1.17 (0.85-1.63) vs HD dabigatran; OR = 0.85 (0.62-1.17) vs LD dabigatran; OR = 3.70 (0.43-50.1) vs HD edoxaban; OR = 1.43 (0.25-12.5) vs LD edoxaban; OR = 0.89 (0.65-1.20) vs rivaroxaban	OR = 0.89 (0.75-1.05) vs warfarin; OR = 1.01 (0.79-1.29) vs HD dabigatran; OR = 0.98 (0.77-1.25) vs LD dabigatran; OR = 2.78 (0.46-16.7) vs HD edoxaban; OR = 1.16 (0.20-5.26) vs LD edoxaban; OR = 1.07 (0.82-1.41) vs rivaroxaban	**OR = 0.68 (0.58-0.80) vs warfarin; OR = 0.73 (0.57-0.93) vs HD dabigatran;** OR = 0.85 (0.66-1.08) vs LD dabigatran; OR = 0.57 (0.26-1.30) vs HD edoxaban; OR = 1.19 (0.49-2.86) vs LD edoxaban; **OR = 0.66 (0.52-0.84) vs rivaroxaban**	OR = 0.90 (0.78-1.03) vs warfarin; **OR = 0.64 (0.52-0.78) vs HD dabigatran; OR = 0.66 (0.54-0.81) vs LD dabigatran; OR = 0.17 (0.02-0.78) vs HD edoxaban;** OR = 0.58 (0.05-4.17) vs LD edoxaban; OR = 0.82 (0.67-1.01) vs rivaroxaban
High-dose dabigatran	**OR = 0.66 (0.52-0.84) vs warfarin; OR = 0.72 (0.56-0.93) vs LD dabigatran;** OR = 3.13 (0.37-50.0) vs HD edoxaban; OR = 1.20 (0.21-10.3) vs LD edoxaban; OR = 0.76 (0.55-1.03) vs rivaroxaban	OR = 0.88 (0.74-1.05) vs warfarin; OR = 0.97 (0.81-1.16) vs LD dabigatran; OR = 2.86 (0.46-20.2) vs HD edoxaban; OR = 1.16 (0.21-5.56) vs LD edoxaban; OR = 1.06 (0.80-1.41) vs rivaroxaban	OR = 0.93 (0.77-1.12) vs warfarin; OR = 1.16 (0.96-1.41) vs LD dabigatran; OR = 0.78 (0.35-1.82) vs HD edoxaban; OR = 1.64 (0.66-4.07) vs LD edoxaban; OR = 0.91 (0.70-1.19) vs rivaroxaban	**OR = 1.41 (1.21-1.65) vs warfarin;** OR = 1.04 (0.89-1.20) vs LD dabigatran; OR = 0.27 (0.03-1.23) vs HD edoxaban; OR = 0.93 (0.08-6.67) vs LD edoxaban; **OR = 1.29 (1.05-1.60) vs rivaroxaban**
Low-dose dabigatran	OR = 0.91 (0.72-1.15) vs warfarin; OR = 4.39 (0.50-50.0) vs HD edoxaban; OR = 1.69 (0.29-14.3) vs LD edoxaban; OR = 1.04 (0.77-1.42) vs rivaroxaban	OR = 0.91 (0.76-1.09) vs warfarin; OR = 2.78 (0.44-1.67) vs HD edoxaban; OR = 1.13 (0.21-5.26) vs LD edoxaban; OR = 1.10 (0.83-1.45) vs rivaroxaban	**OR = 0.80 (0.66-0.97) vs warfarin;** OR = 0.67 (0.30-1.56) vs HD edoxaban; OR = 1.41 (0.57-3.45) vs LD edoxaban; OR = 0.78 (0.60-1.02) vs rivaroxaban	**OR = 1.36 (1.16-1.58) vs warfarin;** OR = 0.26 (0.03-1.19) vs HD edoxaban; OR = 0.88 (0.08-6.30) vs LD edoxaban; **OR = 1.24 (1.01-1.54) vs rivaroxaban**
High-dose edoxaban	OR = 0.21 (0.02-1.78) vs warfarin; OR = 0.40 (0.02-5.26) vs LD edoxaban; OR = 0.24 (0.02-2.04) vs rivaroxaban	OR = 0.32 (0.05-1.94) vs warfarin; OR = 0.44 (0.06-2.43) vs LD edoxaban; OR = 0.38 (0.06-2.44) vs rivaroxaban	OR = 1.19 (0.53-2.60) vs warfarin; OR = 2.04 (0.84-5.55) vs LD edoxaban; OR = 0.85 (0.39-1.99) vs rivaroxaban	**OR = 5.29 (1.15-49.7) vs warfarin;** OR = 3.33 (0.94-16.7) vs LD edoxaban; **OR = 4.76 (1.05-4.76) vs rivaroxaban**
Low-dose edoxaban	OR = 0.55 (0.07-3.10) vs warfarin; OR = 0.62 (0.07-3.70) vs rivaroxaban	OR = 0.78 (0.17-4.28) vs warfarin; OR = 0.93 (0.20-5.26) vs rivaroxaban	OR = 0.57 (0.24-1.37) vs warfarin; OR = 0.56 (0.22-1.37) vs rivaroxaban	OR = 1.53 (0.21-16.8) vs warfarin; OR = 1.41 (0.20-16.6) vs rivaroxaban
Rivaroxaban	OR = 0.87 (0.71-1.07) vs warfarin	OR = 0.83 (0.66-1.03) vs warfarin	OR = 1.02 (0.85-1.23) vs warfarin	OR = 1.09 (0.94-1.26) vs warfarin

*reported as odds ratio (OR) with 95% credible intervals. Bold face highlights credibly different OR. HD = High-dose; LD = Low-dose.

tran proved similarly effective in preventing stroke or systemic embolism in comparison to warfarin (OR = 0.78 [0.62-0.96] for apixaban and OR = 0.66 [0.52-0.84] for high-dose dabigatran vs warfarin; indirect OR of apixaban versus high-dose dabigatran = 1.17 [0.85-1.63]). However, apixaban was associated with fewer major bleedings than high-dose dabigatran (OR = 0.73 [0.57-0.93]) and fewer drug discontinuations than either high-dose dabigatran (OR = 0.64 [0.52-0.78]) or low-dose dabigatran (OR = 0.66 [0.54-0.81]).

Low-dose dabigatran was associated with fewer major bleedings than warfarin (OR = 0.80 [0.66-0.97]), but was discontinued more frequently (OR = 1.36 [1.16-1.58]) than the older agent. Conversely, rivaroxaban did not appear to reduce the risk of stroke or systemic embolism (OR = 0.87 [0.71-1.07]) or major bleeding incomparison to warfarin (OR = 0.87 [0.71-1.07]) and was associated with credibly more major bleedings in comparison to apixaban (OR = 1.52 [1.19-1.92]).

Data for edoxaban were largely inconclusive, as the pertinent phase III pivotal trial is still ongoing (i.e. ENGAGE AF-TIMI 48). Nonetheless, high-dose edoxaban was discontinued more frequently than warfarin (OR = 5.29 [1.15-49.7]), apixaban (OR = 5.89 [1.28-50.1]) and rivaroxaban (OR = 4.76 [1.05-4.76]).

DISCUSSION

This systematic review provides direct evidence that novel oral anticoagulants represent a paradigm shift in the management of atrial fibrillation, as they are associated with significant benefits on the risk of stroke or systemic embolism and death. In addition, by exploiting the use of warfarin as a common comparator within the framework of a network meta-analysis, this study shows that both apixaban and high-dose dabigatran are superior to warfarin for the prevention of thromboembolism with a similar efficacy, and that apixaban appears to be better tolerated and associated with reduced bleeding when compared with dabigatran.

Apixaban is an inhibitor of coagulation factor Xa, orally bioavailable and mostly metabolized by the hepatic CYP3A4 system (15, 27). The recommended dose is 5 mg twice daily but the dose is to be reduced with renal impairment. The use of apixaban is discouraged in patients with severe liver disease, and caution should be used when CYP3A4 or P-glycoprotein inhibitors or inducers are used concomitantly. As for all factor Xa inhibitors routine monitoring of efficacy is not available, as anti-Xa activity may determined but it is often not available. To date, no specific antidote to reverse the effects of apixaban is known. The superior efficacy in preventing thromboembolism associated with a reduction in major bleeding when compared with warfarin suggest that in patients without contraindications, apixaban is preferable to warfarin. The indirect comparisons of apixaban with the other oral anticoagulants dabigatran, edoxaban, and rivaroxaban, show that efficacy of apixaban in preventing thromboembolism is not statistically different from the others. A numerically higher risk of thromboembolism was seen for apixaban in comparison with high-dose dabigatran (OR = 1.17), high-dose edoxaban (OR = 3.70) and low-dose edoxaban (OR = 1.43), but for all these cases the confidence interval largely crossed the unity meaning that the difference was not statistically credible, for which the superiority of these agents in comparison with apixaban could not be proven (nor negated). In terms of safety, apixaban was associated with significantly fewer major bleeding episodes when compared with

warfarin, high-dose dabigatran and rivaroxaban (ORs between 0.66 and 0.73) and no significant differences compared with low-dose dabigatran or edoxaban with all ORs crossing the unity.

Dabigatran, on the other hand, is a coagulation factor IIa (thrombin) inhibitor (15, 28). Dabigatran etexilate is orally bioavailable and rapidly converted in dabigatran under the effects of plasma and hepatic esterases. Dabigatran is cleared by the kidney, and the dose recommended by the Food and Drug Administration is 150 mg twice daily for creatinine clearance >30 ml/min*m^2, with the dose reduced to 75 mg twice daily for creatinine clearance ≤ 30 ml/min*m^2, whereas its use it not recommended for lower creatinine clearance (i.e. ≤ 15 ml/min*m^2). At odds with apixaban, dabigatran is not metabolized by the liver and it has no drug-to-drug interaction with CYP3A4 inhibitors or inducers, whereas it still interacts with P-glycoprotein inhibitors or inducers. Dabigatran affects both activated partial thromboblastin and ecarin clotting times, but routine monitoring of efficacy is not indicated. Like apixaban, no specific antidote to reverse the effects of dabigatran is known.

The RELY trial appraised also the 110 mg twice daily dose (low-dose) of dabigatran which is not approved for clinical use in the US but only in Europe (9). In this study, in which randomization to dabigatran (one of two doses) or warfarin was open label, high-dose dabigatran showed greater efficacy in prevention of thromboembolism and a similar effect on major bleeding. These effects were associated with an important reduction by dabigatran in intracranial bleeding and a significant increase in gastrointestinal bleeding with dabigatran when compared with warfarin. Moreover, dabigatran was associated with a higher discontinuation rate than warfarin. In the indirect analyses, when compared with apixaban, dabigatran showed a similar efficacy in the prevention of thromboembolism (OR 1.17 [0.85-1.63] favoring dabigatran) but a credibly higher rate of major bleeding or discontinuation. Considering these factors, in the absence of contraindications, apixaban may appear superior to dabigatran. Special conditions such as the presence of liver impairment or concomitant use of CYP34A inhibitors or inducers may however prevent the use of apixaban and not of dabigatran. Additional head-to-head studies sufficiently powered to directly compare efficacy of the 2 drugs are needed, but unlikely to be available in the next 4-6 years. Notably, apixaban and dabigatran are both approved for the use in patients with non-valvular atrial fibrillation in the USA, whereas edoxaban and rivaroxaban are not. The European Medicines Agency has already approved both 110 mg and 150 mg twice daily regimens of dabigatran, but has not yet approved other novel oral anticoagulants for the treatment of atrial fibrillation.

Edoxaban is an additional factor Xa inhibitor that has been studied in a smaller number of patients (14, 15). It is also orally bioavailable, it has renal clearance and minor hepatic metabolism. Data on efficacy and safety are however limited, awaiting the pertinent phase III pivotal trial (ENGAGE-TIMI 48) (14).

Rivaroxaban is another factor Xa inhibitor which is orally bioavailable, metabolized by liver and kidney (15, 29).The dose used in the large ROCKET-AF study was 20 mg daily (to be reduced to 15 mg if creatinine clearance between 30-49 ml/min*m^2). Like apixaban, it interacts with CYP3A4 or P-glycoprotein inhibitors and inducers, and should not be used in patients with advanced liver disease. As for all factor Xa inhibitors routine monitoring of efficacy is not available, as anti-Xa activity may be determined but it is uncom-

monly used. In the ROCKET-AF trial, rivaroxaban was shown to be non-inferior to warfarin in terms of thromboembolism or stroke. In this indirect comparison, rivaroxaban appeared to have similar efficacy in preventing thromboembolism when compared with the apixaban and dabigatran but was associated with significantly greater bleeding compared with apixaban. The once daily administration schedule may appear favorable to patient compliance as compared with apixaban and dabigatran, but the superior efficacy of apixaban and dabigatran, and greater safety of apixaban make rivaroxaban a less favorable choice. There is no specific antidote for rivaroxaban, however, a recent report described full reversibility of rivaroxaban effects (but not of dabigatran effects) with protrombin complex concentrate (30).

If confirmed in additional studies which would need to include also a determination of the effects of prothrombin complex concentrate on apixaban, this may support the use of rivaroxaban in settings in which need for rapid reversal may be anticipated.

The lack of requirement for monitoring with these agents has been viewed mostly as an advantage, but it can clearly represent a disadvantage when non-compliance with therapy or overdose is suspected. The wide-spread availability of INR monitoring for warfarin use has been advocated as a reason to prefer warfarin to these new anticoagulants, however, the lack of reduced bleeding with warfarin and INR monitoring in comparison with the use of these agents without monitoring argues that the availability of INR monitoring is not a sufficient reason to advocate for warfarin.

The lack of an antidote for the new agents has also been viewed as a limitation, and it certainly is. However the same holds true for warfarin considering that vitamin K is a slow acting antidote and is likely to reverse the effects of warfarin in the same time needed for any of these new agents to revert their effects without antidote.

In addition, direct costs will be much higher with these new agents than with warfarin. Whereas a cost-benefit or cost-utility analysis was of course beyond our scope, we can provide some informed speculations. First, warfarin costs are very low if we focus only on the cost of the pill itself, but if we add the indirect yet remarkable costs of dedicated INR monitoring centers, days off work to get blood draws, and, most importantly, the cost of recurrent thromboses and bleeding complications, then a warfarin regimen does not appear as economically appealing as it initially seemed. Moreover, taking for granted the reduction in the risk of death with novel oral anticoagulants, which is a rather uncommon finding in the realm of thromboembolism management, we should ask ourselves whether it is ethically sound to deny this drugs to any patient suitable for such life-saving therapy. More practically, we may anticipate that uptake of these new drugs will be slow, yet progressively increase. It can also be conceived that these drugs might be cost-saving (thus proving cheaper than warfarin) in those intolerant to warfarin or failing warfarin (i.e. experiencing a thromboembolic events despite adequate INR). Conversely, we might expect novel oral anticoagulants to be reasonable cost-effective (thus associated with a socially acceptable premium price), in patients at moderate to high thromboembolic risk and concomitantly at moderate to high bleeding risk with warfarin. It is unclear what cost analyses will show in other patient subsets. Thus, further detailed analyses, including also real-world patients (typically excluded from pivotal randomized trials) are warranted.

Finally, the unprecedented reduction in mortality with novel oral anticoagulants might appear surprising. Awaiting for further sub-analyses of the included trials, we

may suggest a number of explanations for this finding. First, novel oral anticoagulant might prove life-saving because they maintain more often the patient in the correct therapeutic window. This means fewer thromboembolic episodes as well as fewer bleedings, both of which might be fatal if very severe or occurring in very sensible organs or systems. In addition, novel oral anticoagulants might be suitable for more patients than warfarin alone, and thus treat adequately a subset of patient who otherwise discontinue or are never treated with warfarin. Finally, we cannot exclude pleiotropic effects, such as those provided, in a very different context, by statins. However, much more clinical and pathophysiologic studies are required before considering the life-saving properties of novel oral anticoagulants as a given fact.

Limitations

Drawbacks of meta-analyses in general are well known, and additional limitations of network meta-analyses can be envisioned (31-33). Nonetheless, we emphasize that clinical decision making is often based on incomplete evidence, and large head-to-head randomized trials of novel oral anticoagulants for atrial fibrillation do not exist and are not foreseeable for the next 4-6 years, at least. Indeed, we remain positive that network meta-analyses based on indirect comparisons are exquisitely scientific, as they inform on what will be the outcomes of future randomized clinical trials, and thus are uniquely falsifiable, in keeping with Popper's theories (34). In addition, we decided a priori to exclude studies, remote or recent, enrolling patients unsuitable for warfarin therapy such as those candidates to low-dose aspirin (35), clopidogrel (36), or left atrial appendage closure (37), under the assumption that these subjectes were unlikely to have a risk-benefit profile similar to those suitable for long-term warfarin therapy. Yet, this focus on warfarin-eligibile patients limited the scope of the present network meta-analysis. In addition, data on edoxaban were limited, and thus results on this specific agent should be mainly considered hypothesis-generating. Other drawbacks of our work include the focus on 4 end-points only. Specifically, we did not explore in detail reasons for drug discontinuation (e.g. dyspepsia for dabigatran) nor causes for death (e.g. myocardial infarction) or type of bleeding (e.g. intracranial versus gastrointestinal). Further confirmatory analyses, beyond indirect comparisons (38-43), are warranted for these important details, but are beyond the scope of the this review.

CONCLUSION

Novel oral anticoagulants represent a paradigm shift in the management of non-valvular atrial fibrillation. This study shows that both apixaban and dabigatran (150 mg) are superior to warfarin for the prevention of thromboembolism with a similar efficacy, and that apixaban appears to be better tolerated and associated with reduced bleeding when compared with dabigatran. Considering that 'one size' may not fit all patients, apixaban may represent the preferred agent for the majority of patients with non-valvular atrial fibrillation. Dabigatran may be considered for patients who are not candidates for apixaban. Rivaroxaban may be a less favorable choice in comparison to apixaban or dabigatran whereas it remains a valid alternative to warfarin. The data on edoxaban is to date inconclusive. Given the superiority in one or more aspects (efficacy, safety, ease-of-use), warfarin should not remain first choice of anticoagulation in patients with non-valvular atrial fibrillation and at least moderate thromboembolic risk.

REFERENCES

1. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010; 31: 2369-429.
2. Testa L, Biondi-Zoccai GG, Dello Russo A, et al. Rate-control vs. rhythm-control in patients with atrial fibrillation: a meta-analysis. Eur Heart J 2005; 26: 2000-6.
3. Andersen LV, Vestergaard P, Deichgraeber P, et al. Warfarin for the prevention of systemic embolism in patients with non-valvular atrial fibrillation: a meta-analysis. Heart 2008; 94: 1607-13.
4. Rietbrock S, Heeley E, Plumb J, van Staa T. Chronic atrial fibrillation: Incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age > 75, Diabetes mellitus, and prior Stroke or transient ischemic attack (CHADS2) risk stratification scheme. Am Heart J 2008; 156: 57-64.
5. International Warfarin Pharmacogenetics Consortium, Klein TE, Altman RB, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med 2009; 360: 753-64.
6. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med 2005; 165: 1095-106.
7. Ogilvie IM, Newton N, Welner SA, et al. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med 2010; 123: 638-45.
8. Wieloch M, Själander A, Frykman V, et al. Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. Eur Heart J 2011; 32: 2282-9.
9. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-51.
10. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981-92.
11. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883-91.
12. Weitz JI, Connolly SJ, Patel I, et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Thromb Haemost 2010; 104: 633-41.
13. Chung N, Jeon HK, Lien LM, et al. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. Thromb Haemost 2011; 105: 535-44.
14. Ruff CT, Giugliano RP, Antman EM, et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). Am Heart J 2010; 160: 635-41.
15. Steffel J, Braunwald E. Novel oral anticoagulants: focus on stroke prevention and treatment of venous thrombo-embolism. Eur Heart J 2011; 32: 1968-76.
16. Song F, Harvey I, Lilford R. Adjusted indirect comparison may be less biased than direct comparison for evaluating new pharmaceutical interventions. J Clin Epidemiol 2008; 61: 455-63.
17. Roskell NS, Lip GY, Noack H, et al. Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparisons versus dabigatran etexilate. Thromb Haemost 2010; 104: 1106-15.
18. Owen A. Antithrombotic treatment for the primary prevention of stroke in patients with non valvular atrial fibrillation: a reappraisal of the evidence and network meta analysis. Int J Cardiol 2010; 142: 218-23.
19. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org last accessed on 2 October 2011.
20. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339: 2700.
21. Biondi-Zoccai GG, Agostoni P, Abbate A, et al. A simple hint to improve Robinson and Dickersin's highly sensitive PubMed search strategy for controlled clinical trials. Int J Epidemiol. 2005; 34: 224-5.
22. Testa L, Andreotti F, Biondi Zoccai GG, et al. Ximelagatran/melagatran against conventional anticoagulation: a meta-analysis based on 22,639 patients. Int J Cardiol 2007; 122: 117-24.
23. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org (last accessed on November 23, 2012).
24. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-58.
25. Ogawa S, Shinohara Y, Kanmuri K. Safety and efficacy of the oral direct factor xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation. -The ARISTOTLE-J study-. Circ J 2011; 75: 1852-9.
26. Ezekowitz MD, Reilly PA, Nehmiz G, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol 2007; 100: 1419-26.
27. Lopes RD, Alexander JH, Al-Khatib SM, et al. Apixaban for reduction in stroke and other ThromboembоLic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. Am Heart J 2010; 159: 331-9.
28. Ezekowitz MD, Connolly S, Parekh A, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 2009; 157: 805-10.
29. ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. Am Heart J 2010; 159: 340-347.
30. Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011; 124: 1573-9.
31. Song F, Xiong T, Parekh-Bhurke S, et al. Inconsistency between direct and indirect comparisons of competing interventions: meta-epidemiological study. BMJ 2011; 343: 4909.
32. Biondi-Zoccai G, Lotrionte M, Landoni G, Modena MG. The rough guide to systematic reviews and meta-analyses. HSR Proceedings in Intensive Care and Cardiovascular Anesthesia 2011; 3: 161-173.
33. Biondi-Zoccai G, Landoni G, Modena MG. A journey into clinical evidence: from case reports to mixed treatment comparisons. HSR Proceedings in Intensive Care and Cardiovascular Anesthesia 2011; 3: 93-96.

34. Popper KR. The logic of scientific discovery. Routledge, London: 2002.
35. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011; 364: 806-17.
36. ACTIVE Investigators, Connolly SJ, Pogue J, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009; 360: 2066-78.
37. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet 2009; 374: 534-42.
38. Rasmussen LH, Larsen TB, Graungaard T, et al. Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis. BMJ 2012; 345: 7097.
39. Baker WL, Phung OJ. Systematic review and adjusted indirect comparison meta-analysis of oral anticoagulants in atrial fibrillation. Circ Cardiovasc Qual Outcomes 2012; 5: 711-9.
40. Schneeweiss S, Gagne JJ, Patrick AR, et al. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes 2012; 5: 480-6.
41. Testa L, Agnifili M, Latini RA, et al. Adjusted indirect comparison of new oral anticoagulants for stroke prevention in atrial fibrillation. QJM 2012; 105: 949-57.
42. Lip GY, Larsen TB, Skjøth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. J Am Coll Cardiol 2012; 60: 738-46.
43. Mantha S, Ansell J. An indirect comparison of dabigatran, rivaroxaban and apixaban for atrial fibrillation. Thromb Haemost 2012; 108: 476-84.

Cite this article as: Biondi-Zoccai G, Malavasi V, D'Ascenzo F, Abbate A, Agostoni P, Lotrionte M, Castagno D, Van Tassell B, Casali E, Marietta M, Modena MG, Ellenbogen KA, Frati G. Comparative effectiveness of novel oral anticoagulants for atrial fibrillation: evidence from pair-wise and warfarin-controlled network meta-analyses. HSR Proc Intensive Care Cardiovasc Anesth. 2013; 5 (1): 40-54.

Source of Support: Nil. **Disclosures:** Dr. Biondi-Zoccai has consulted/lectured for AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly/Daiichi Sankyo, and Johnson & Johnson.