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# Stroke Event Rates and the Optimal Antithrombotic Choice of Patients With Paroxysmal Atrial Fibrillation

A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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**Abstract:** The risks of stroke or systemic embolism and major bleeding are considered similar between paroxysmal and sustained atrial fibrillation (AF), and warfarin has demonstrated superior efficacy to aspirin, irrespective of the AF type. However, with the advent of novel oral anticoagulants (NOACs) and antiplatelet agents, the optimal antithrombotic prophylaxis for paroxysmal AF remains unclear.

We searched Medline, Embase, CENTRAL, and China Biology Medicine up to October week 1, 2015. Randomized controlled trials of AF patients assigned to NOACs, warfarin, or antiplatelets, with reports of outcomes stratified by the AF type, were included. A fixed-effects model was used if no statistically significant heterogeneity was indicated; otherwise, a random-effects model was used.

Six studies of 69,990 nonvalvular AF patients with  $\geq 1$  risk factor for stroke were included. Postantithrombotic treatment, paroxysmal AF patients showed lower risks of stroke (risk ratio [RR], 0.72; 95% confidence interval [CI], 0.59–0.87), stroke or systemic embolism (RR, 0.74; 95% CI, 0.63–0.86), and all-cause mortality (RR, 0.75; 95% CI, 0.67–0.83), while the major bleeding risk was comparable (RR, 0.96; 95% CI, 0.85–1.08). We were unable to detect the superiority of anticoagulation over antiplatelets for paroxysmal AF (RR, 0.72; 95% CI, 0.43–1.23), while it was more effective than antiplatelets for sustained AF (RR, 0.42; 95% CI, 0.33–0.54). NOACs showed superior

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- YC and YZ conducted the study search and quality assessment and contributed to the drafting of the manuscript. YC, YZ, and FO performed data extraction, and YC, GD, and XC conducted statistical analysis. JZ participated in study conception and design, and critically revised drafts of the manuscript. All of the authors contributed to the interpretation of data. All of the authors read and approved the final manuscript.
- Ethical approval was not needed as the data used in this systematic review was not individual patient data and there were no privacy issues to address (*J Grad Med Educ*. 2011;3(1):5-6).
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efficacy over warfarin and trended to show reduced major bleeding irrespective of the AF type.

The AF type is a predictor for thromboembolism, and might be helpful in stroke risk stratification model in combination with other risk factors. With the appearance of novel anticoagulant and antiplatelet agents, the best antithrombotic choice for paroxysmal AF needs further exploration.

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Abbreviations: AF = atrial fibrillation, CENTRAL = Central Register of Controlled Trials, CHADS<sub>2</sub> = cardiac failure, hypertension, age, diabetes, stroke (doubled), CIs = confidence intervals, non-CNS = non-central nervous system, ECG = electrocardiogram, ESUS = embolic stroke of undetermined source, MeSH = medical subject headings, NOACs = novel oral anticoagulants, PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses, RCT = randomized controlled trial, RRs = risk ratios, SE = standard error, VKA = vitamin K antagonist.

#### INTRODUCTION

trial fibrillation (AF) is associated with 2- to 7-fold increased risks of stroke $^{1-5}$  and higher occurrence of non-central nervous system (non-CNS) systemic embolism.<sup>5</sup> The correlation between AF and stroke, particularly paroxysmal AF, defined as recurrent AF that terminates spontaneously and lasts up to 7 days, has drawn much attention in recent years. Covert paroxysmal AF has been proposed as a potential cause of embolic stroke of undetermined source (ESUS),<sup>6</sup> and novel electrocardiogram (ECG) monitoring techniques with 30-day event-triggered recorders<sup>7</sup> and insertable cardiac monitors<sup>8,9</sup> have found paroxysmal AF to be associated with cryptogenic ischemic stroke.<sup>7,8</sup> The AF type is generally considered irrelevant to the stroke risk,<sup>5,10,11</sup> and the distinction between paroxysmal AF and persistent AF has not been used to guide the choice of stroke prophylaxis; however, increasing studies have suggested that paroxysmal AF carries a lower risk of stroke compared with sustained (persistent or permanent) AF.12-18 Whether thromboembolic risk varies by AF type remains uncertain.<sup>11,13,15–21</sup> The reported relative stroke risks between paroxysmal and sustained AF may be confounded by the treatment of differential anticoagulant use in patients with paroxysmal and sustained AF in some studies.<sup>18,20-23</sup> Therefore, comparing the risk of thromboembolism between different AF types by performing a pooled analysis according to antithrombotic treatment assignment is needed.

Warfarin is considered more efficacious than aspirin for stroke prevention in AF<sup>10,24,25,45</sup>; thus, anticoagulation prophylaxis is recommended for at-risk patients with paroxysmal or

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sustained AF.<sup>5,10,26</sup> However, few studies have specifically evaluated the efficacy and safety of anticoagulant versus antiplatelet agents for paroxysmal AF, and the choice of thromboembolic prophylaxis for paroxysmal AF has become more diversified with the emergence of novel antiplatelet and anticoagulant agents. Novel oral anticoagulants (NOACs) have shown a favorable risk-benefit profile for AF, with reductions in stroke or systemic embolism and similar major bleeding risk as for dose-adjusted warfarin<sup>27–29</sup>; however, whether their advantages extend to both AF types is unknown.

Accordingly, we conducted this meta-analysis to assess the differences in thromboembolism and bleeding risk between paroxysmal and sustained AF patients according to the antithrombotic therapy used, and to detect whether there was a difference in the treatment effect between anticoagulation versus antiplatelets and NOACs versus warfarin in such patients.

## **METHODS**

## **Data Sources and Searches**

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were followed. We firstly identified published studies that compared the efficacy and safety outcomes by AF type in patients randomized to antithrombotic therapies through systematically searching Medline (Ovid, 1946 to September 2014), Embase (Ovid, 1974 to September 2014), Cochrane Central Register of Controlled Trials (CENTRAL) (Ovid, September 2014), and China Biology Medicine disc (SinoMed, 1978 to September 2014). We updated the search up to October week 1, 2015 for any additional eligible studies. Medical subject headings (MeSH) and the terms "atrial fibrillation," "AF," "stroke," "brain infarction," "brain vascular accident," "cerebrovascular accident," and "embolism" were used and the randomized controlled trials (RCT) filters for Medline and Embase in Ovid Expert Search were applied (see TEXT 1, Supplemental Content, which illustrates the search strategy, http://links.lww.com/ MD/A582). No language restriction was used. Additionally, we manually reviewed the reference lists of related reviews, editorials, and studies identified after title and abstract screening for potential relevant studies. This cross-checking was repeated until no further studies were identified.

#### **Study Selection**

Two reviewers (YC and YZ) performed the study selection independently, with disagreements solved through discussion or by judgment of a third reviewer (JZ). The study inclusion criteria were: phase III RCTs comparing the efficacy and safety of NOACs, warfarin, or antiplatelet therapy in AF patients; studies including secondary analyses stratified by AF types with the endpoints of stroke, composite of stroke or non-CNS systemic embolism, all-cause mortality, or major bleeding; and  $\geq 1$ -year follow-up.

# **Data Extraction and Quality Assessment**

Data on the included studies (publication year, inclusion criteria, follow-up period, studied drugs), population characteristics (age, sex, comorbidities, medication use at entry), treatment (therapeutic indication, drug, dosage), and outcomes were extracted using a standardized data extraction form. For trials reported >1 publications, we extracted data from the most complete one and used the others to supplement the data. Outcome information was stratified by paroxysmal and sustained AF. The primary efficacy outcome was stroke or non-CNS systemic embolism. Secondary efficacy outcomes included stroke (ischemic, hemorrhagic, unspecified) and allcause mortality. The primary safety outcome was major bleeding, defined according to the International Society on Thrombosis and Hemostasis criteria as clinically overt bleeding accompanied by a fall in the hemoglobin level of  $\geq 2 \text{ g/dL}$ , transfusion of  $\geq 2$  units of whole or packed red blood cells, occurring in a critical site, or leading to death.<sup>30</sup>

Among the trials included, AF was mainly diagnosed by local investigators at the time of enrollment according to ECG and the previous medical history. Paroxysmal AF was defined as recurrent AF self-terminating within 7 days; when persisting beyond 7 days or terminated upon pharmacological therapy or electrical cardioversion, it was considered persistent. Permanent AF referred to long-standing AF with no evidence of sinus rhythm for several months prior to randomization (see TEXT 2, Supplemental Content, which illustrates the definitions and classifications of AF type, http://links.lww.com/MD/A582).<sup>10</sup> Because persistent AF has a tendency to convert into permanent AF, and since both sustain beyond 7 days, we combined these 2 groups into sustained AF.<sup>10</sup>

Study quality assessment was performed following a validated scale for RCTs recommended by the Cochrane Collaboration,<sup>31</sup> by evaluating the random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each item was evaluated as high, low, or unclear risk. A study was classified as low risk when every item was considered low risk, and as high or unclear risk if 1 or more items were evaluated as being high or unclear risk, respectively. Discrepancies about the quality assessment were resolved by consensus.

# Data Synthesis and Analysis

The population baseline characteristics according to the AF type were analyzed using Pearson's chi-squared test for categorical variables in SPSS 16.0 for windows (SPSS Inc., Chicago, IL).

Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for each outcome. Subgroup analysis was conducted according to anticoagulant (NOACs and warfarin) and antiplatelet treatment to assess the comparative risks of stroke or systemic embolism and major bleeding between paroxysmal and sustained AF. The efficacy and safety outcomes were also compared for anticoagulation versus antiplatelet treatment; and for NOACs versus warfarin. Heterogeneity was assessed by comparing the inclusion criteria and the design and conduct differences of the trials. Heterogeneity across studies was assessed by the Q test and  $I^2$  index, which measures the proportion of total variability attributable to between-studies differences rather than sampling error. We synthesized and compared outcomes by a fixed-effects model (Mantel-Haenszel method) if no statistically significant heterogeneity was indicated (P > 0.10 with  $I^2 < 50\%$ ); otherwise, a randomeffects model was used. Because the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial provided only RRs with 95% CIs rather than event numbers for each outcome by AF type,<sup>32</sup> in the comparison of NOACs and warfarin, we transformed the data into ln(RR) and standard error of ln(RR) (SE[lnRR]) and performed data synthesis using the Inverse-Variance method. SE(lnRR) was calculated as  $[\ln(95\% \text{ CI[upper limit]}) - \ln RR]/1.96$ . *P* values  $\leq 0.05$  were considered significant.

All analyses were performed with Review Manager, version 5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

### RESULTS

We identified a total of 2091 studies through database and manual searches, of which the full text of 42 were evaluated based on our inclusion criteria; eventually, 6 were eligible for inclusion (Fig. 1).<sup>13,16,17,21,22,32</sup>

#### Study Characteristics and Study Quality

Six phase III RCTs, including 69,990 participants, comparing the efficacy and safety of NOACs, warfarin, or antiplatelet therapy in nonvalvular AF patients with  $\geq 1$  risk factor for stroke, which included secondary analyses of the rates of stroke or systemic embolism and major bleeding stratified by AF type, were identified (Table 1).<sup>15,16,17,21,22,32</sup> Specifically, the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism (ROCKET-AF) trial enrolled a high risk population with  $\geq 2$  risk factors.<sup>17</sup> Four trials involved comparisons of NOACs (apixaban, rivaroxaban, dabigatran, and ximelagatran) versus warfarin.<sup>13,16,17,32</sup> One study examined the effects of apixaban and aspirin in patients who failed or were unsuitable for vitamin K antagonist (VKA) therapy,<sup>22</sup> and the remaining trial focused on combined clopidogrel (75 mg/d) and aspirin (75–100 mg/d) versus warfarin.<sup>21</sup> Patients with paroxysmal AF accounted for 11.4% to 32.8% of cases in these studies. The mean/median age ranged from 70 to 73 years, and females were less prevalent (30.8–41.5%). The mean CHADS<sub>2</sub> (cardiac failure, hypertension, age, diabetes, stroke [doubled]) scores were approximately 2.0, with the exception of in the ROCKET-AF trial, in which it was 3.5. The median/mean follow-up periods were 1.1 to 2.0 years.<sup>13,16,17,21,22,27–29,33–36</sup>

For study quality assessment, 2 studies were rated as low risk, while 3 studies were evaluated as high risk according to the quality assessments scale for RCTs recommended by the Cochrane Collaboration.<sup>31</sup> The Apixaban versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients who have Failed or are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial<sup>22</sup> did not provide information regarding

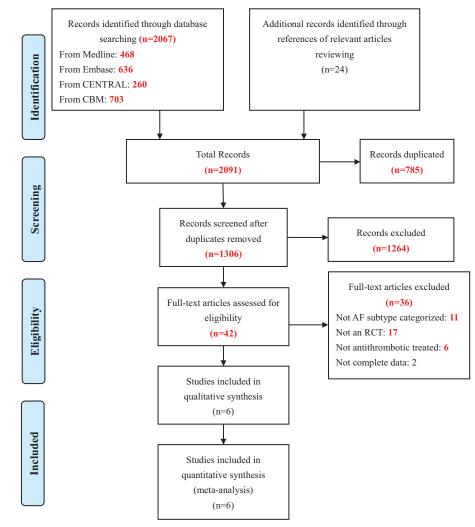


FIGURE 1. Flow diagram of study selection.

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TABLE 1. Study	TABLE 1. Study Characteristics								
Study, Year*	Inclusion Criteria	Intervention Drug	Comparison Drug	Follow-Up, Median, y	Age, Mean, y	Female, n, %	CHADS <sub>2</sub> , Mean	Paroxysmal AF, n (%)	Sustained AF, n (%)
ACTIVE-W, 2007 <sup>21</sup>	NVAF and $\geq 1$ risk (age $\geq 75$ y, HT, prior stroke or T1A or SE, LVEF <45%, PVD, aLVEF <45%, PVD, age $55-74$ y + DM or MI or $C$ AD)	Clopidogrel 75 mg/ d + aspirin 75–100 mg/d	Warfarin (INR = 2.0- 3.0)	1 :	70	2274 (34.0)	2.0	1202 (17.9)	5495 (82.1)
ARISTOTLE, 2013 <sup>16</sup>	NVAF and 21 risk (age 275 y, prior stroke or TIA or SE, HF/LVEF <40%, DM, HT)	Apixaban 5 mg bid or 2.5 mg bid (if $\geq 2$ criteria: age $\geq 80$ y, body weight $\leq 60$ kg, serum creatinine $\geq 1.5$	Warfarin (INR = 2.0- 3.0)	1.8	70 (median) 6415 (35.3)	6415 (35.3)	2.1	2786 (15.3)	15,412 (84.7)
AVERROES, 2013 <sup>22</sup>	NVAF, age ≥50 y, failed or unsuitable for VKA and ≥1 risk (prior stroke or TIA, age ≥75 y, HT, DM, HF/LVEF ≤35%,	Apixaban 5 mg bid or 2.5 mg bid (if $\geq 2$ criteria: age $\geq 80$ y, body weight $\leq 60$ kg, serum creatinine $\geq 1.5$ mg/dL)	Aspirin 81–324 mg/d	1.1 (mean)	70	2322 (41.5)	2.0	1512 (27.0)	4085 (73.0)
RE-LY, 2012 <sup>32</sup>	NVAF and $\geq 1$ risk (prior stroke or TIA or SE, LVEF <40%, HF, age $\geq 75$ y, age $\geq 65$ y + DM or CAD or y + DM.	Dabigatran etexilate 150 or 110 mg bid	Warfarin (INR = 2.0- 3.0)	2.0	72	6599 (36.4)	2.1	5943 (32.8)	12,164 (67.2)
ROCKET-AF, 2014 <sup>17</sup>	NULL NVAFF and prior stroke/ TIA/SE or 22 risk (age 275 y, HF/LVEF (350, DM HF/LVEF	Rivaroxaban 20 mg od	Warfarin (INR = 2.0- 3.0)	1.9	73 (median) 5580 (39.7)	5580 (39.7)	3.5	2514 (17.9)	11,548 (82.1)
SPORTIF III–V, 2007 <sup>13</sup>	NVAF and $\geq 10^{-0.04}$ , LM, LM, HT, NVAF and $\geq 175$ y, prior age $\geq 75$ y, prior stroke or TIA or SE, HF/LVEF <40%, age $\geq 65$ y + CAD or DM)	Ximelagatran 36 mg bid	Warfarin (INR = 2.0- 3.0)	1.6	71	2257 (30.8)	NA	836 (11.4)	6493 (88.6)
ACTIVE-W = <i>i</i> embolic Events in Treatment, Bid = t INR = internations peripheral arterial. Inhibition Compan Fibrillation, TIA = * The published	ACTIVE-W = Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events, AF = atrial fibrillation, ARISTOTLE = Apixaban for Reduction in Stroke and Other Thrombo- embolic Events in Atrial Fibrillation, AVERROES = Apixaban vs Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or are Unsuitable for Vitamin K Antagonist Treatment, Bid = twice daily, CAD = coronary artery disease, CHADS <sub>2</sub> = cardiac failure, hypertension, age, diabetes, stroke [doubled], DM = diabetes mellitus, HF = heart failure, HT = hypertension, INR = international normalized ratio, LVEF = left ventricular ejection fraction, MI = myocardial infarction, NA = not available, NVAF = non-valvular atrial fibrillation, od = once daily, PAD = peripheral arterial disease, PVD = peripheral vascular disease, RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy, ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism, SFORTIF = Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation, TIA = transient ischemic attack, VKA = vitamin K antagonist. * The published year of post-hoc analysis outcomes according to atrial fibrillation type of the trials.	Frial with Irbesartan for Preve ES = Apixaban vs Acetylsalic trery disease, CHADS <sub>2</sub> = card eft ventricular ejection fractio ular disease, RE-LY = Randou sm for Prevention of Stroke CA = vitamin K antagonist. comes according to atrial fib	ntion of Vascular Events, A ylic Acid to Prevent Stroke iac failure, hypertension, ag on, MI = myocardial infarc mized Evaluation of Long-T and Embolism, SE = syste illation type of the trials.	F = atrial fibrill in Atrial Fibrill ge, diabetes, stro tion, NA = not term Anticoagul mic embolism,	ation, ARISTO ation Patients V ke [doubled], D available, NVA ation Therapy, F SPORTIF = Sti	$\Gamma LE = Apixaba$ Who Have Faile M = diabetes m F = non-valvulCCKET-AF = oke Prevention	n for Reductio d or are Unsu ellitus, HF = H ar atrial fibrill Rivaroxaban C Using an Or	n in Stroke and C itable for Vitami neart failure, HT lation, od = once Duce Daily Oral I al Thrombin Inh	ther Thrombo- n K Antagonist = hypertension, daily, PAD = birect Factor Xa ibitor in Atrial

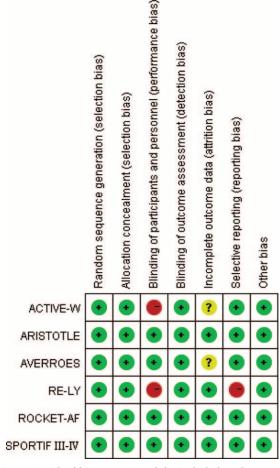


FIGURE 2. Risk of bias summary of the included studies.

dropouts (incomplete outcome data) and was thus rated as unclear risk (Fig. 2).

# **Patient Characteristics**

The baseline patient characteristics, stratified by AF type, are summarized in Table 2. A total of 69,990 AF patients with >1 risk factor for stroke were included; 14,793 (21.1%) had paroxysmal and 55,197 (78.9%) had sustained AF. The treatment assignment of anticoagulation (NOACs or warfarin) and antiplatelet agents were evenly distributed between patients with paroxysmal and sustained AF (P = 0.290). Compared to sustained AF, patients with paroxysmal AF were younger (≥75 years: 30.9% vs 37.7%; P < 0.001), more frequently female (41.3% vs 34.7%; P < 0.001), and less likely to have diabetes (27.4% vs 30.5%; P < 0.001) and cardiac dysfunction (34.6% vs 42.4%; P < 0.001). Higher rates of hypertension (88.1% vs 85.4%; P < 0.001) and previous stroke, transient ischemic attack, or systemic embolism (33.0% vs 29.6%; P < 0.001) were observed in paroxysmal AF. However, the CHADS<sub>2</sub> score was balanced between patients with paroxysmal and sustained AF (score >2: 55.5% vs 54.8%; P = 0.340). Prior use of antithrombotic medications also differed, with lower VKA (69.0% vs 79.4%; P < 0.001) and higher aspirin (33.9% vs 26.6%; P < 0.001) use in paroxysmal AF patients.

# Outcomes

# **Outcomes by Atrial Fibrillation Type**

The outcomes stratified by AF type are shown in Figure 3. In patients receiving antithrombotic therapies, paroxysmal AF was associated with significantly lower risks of stroke (RR, 0.72; 95% CI, 0.59–0.87; P=0.001), stroke or non-CNS systemic embolism (RR, 0.74; 95% CI, 0.63–0.86; P<0.001), and all-cause mortality (RR, 0.75; 95% CI, 0.67–0.83; P<0.001) as compared to sustained AF. The

### TABLE 2. Baseline Characteristics of Patients With Paroxysmal and Sustained Atrial Fibrillation

Characteristics	Paroxysmal AF, % (n/total)	Sustained AF, % (n/total)	P Value
Randomized to studied drugs			Anticoagulation vs antiplatelet 0.290
NOACs	52.2 (7728/14,793)	48.9 (26,978/55,197)	antiplatelet 0.270
Warfarin	38.6 (5705/14,793)	42.5 (23,459/55,197)	
Antiplatelet*	9.2 (1360/14,793)	8.6 (4760/55,197)	
Age $\geq 75$ y	30.9 (629/2038)	37.7 (4517/11,988)	< 0.001
Female	41.3 (3030/7338)	34.7 (13,496/38,948)	< 0.001
CHADS <sub>2</sub> score			$\leq 2 \text{ vs} > 2, 0.340$
1	20.2 (1070/5300)	19.0 (5115/26,960)	
2	23.8 (1262/5300)	26.3 (70,97/26,960)	
3-6	56.0 (2968/5300)	54.7 (14,748/26,960)	0.083
Hypertension	88.1 (6465/7338)	85.4 (33,256/38,948)	< 0.001
Diabetes	27.4 (2009/7338)	30.5 (11,892/38,948)	< 0.001
Previous stroke/TIA/systemic embolism	33.0 (2420/7338)	29.6 (11,522/38,948)	< 0.001
Heart failure/LV dysfunction	34.6 (2538/7338)	42.4 (16,512/38,948)	< 0.001
Peripheral arterial disease	4.9 (183/3716)	4.9 (839/17,043)	0.996
Medications at baseline			
VKA used	69.0 (1407/2038)	79.4 (9518/11,988)	< 0.001
Aspirin used	33.9 (1637/4824)	26.6 (7301/27,400)	< 0.001
Clopedogrel used	3.1 (124/3988)	1.8 (378/20,907)	< 0.001

 $AF = atrial fibrillation, CHADS_2 = cardiac failure, hypertension, age, diabetes, stroke [doubled], LV dysfunction = left ventricular dysfunction, NOACs = novel oral anticoagulants, TIA = transient ischemic attack, VKA = vitamin K antagonist.$ 

\* Clopedogrel plus aspirin or aspirin alone.

Stroke	Paroxysn		Sustain			Risk Ratio	Risk Ratio
Study or Subgroup Anticoagulation	Events	Total	Events	Total	Weight	M-H. Fixed. 95% CI	M-H. Fixed. 95% Cl
AVERROES <sup>22</sup>	11	760	30	2047	6.3%	0.99 [0.50, 1.96]	
ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>13</sup>	78 12	2514 836	446 172	11548 6493	62.2% 15.3%	0.80 [0.63, 1.02] 0.54 [0.30, 0.97]	
Subtotal (95% CI)		4110		20088	83.8%	0.77 [0.62, 0.95]	◆
Total events Heterogeneity: Chi <sup>2</sup> = 3	101 2 04 df = 2	(P = 0.36	648 ): 1 <sup>2</sup> = 2%				
Test for overall effect:			,,				
Antiplatelet							
AVERROES <sup>22</sup>	13	752	77	2038	16.2%	0.46 [0.26, 0.82]	
Subtotal (95% CI) Total events	13	752	77	2038	16.2%	0.46 [0.26, 0.82]	
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 2.63 (P	= 0.008)					
Total (95% CI)		4862		22126	100.0%	0.72 [0.59, 0.87]	•
Total events Heterogeneity: Chi <sup>2</sup> = 4	114 4.90. df = 3	(P = 0.18	725 ): I <sup>2</sup> = 39%	6			— <u>,                                    </u>
Test for overall effect:	Z = 3.30 (P	= 0.0010	)				0.2 0.5 1 2 5 Favours [Paroxysmal AF] Favours [Sustained AF]
A Test for subgroup diffe	rences: Chr	<sup>2</sup> = 2.72, 0	at = 1 (P =	= 0.10), I	* = 63.2%		
Stroke or non-CNS s							
Study or Subgroup	Paroxysr Events		Sustain Events		Weight	Risk Ratio M-H. Fixed, 95% C	Risk Ratio I M-H. Fixed. 95% Cl
Anticoagulation							
ACTIVE-W <sup>21</sup> ARISTOTLE <sup>16</sup>	11 51	594 2786	51 426	2773 15412	4.3% 30.9%	1.01 [0.53, 1.92] 0.66 [0.50, 0.88]	
AVERROES <sup>11</sup>	12	760	31	2047	4.0%	1.04 [0.54, 2.02]	<del></del> <del></del>
ROCKET-AF <sup>17</sup> Subtotal (95% CI)	85	2514 6654	480	11548 31780	40.6% 79.8%	0.81 [0.65, 1.02] 0.78 [0.66, 0.92]	•
Total events	159		988		. 0.0 /0		-
Heterogeneity: Chi <sup>2</sup> = Test for overall effect:			l); l² = 0%	, ,			
	_ 2.35 (P	0.000)					
Antiplatelet ACTIVE-W <sup>21</sup>	18	608	104	2722	9.0%	0.77 [0.47, 1.27]	<b>_</b> _
AVERROES <sup>22</sup>	14	752	88	2038	11.2%	0.43 [0.25, 0.75]	
Subtotal (95% CI) Total events	32	1360	192	4760	20.2%	0.58 [0.40, 0.84]	-
Heterogeneity: Chi <sup>2</sup> =	2.40, df = 1		2); 12 = 58	%			
Test for overall effect:	Z = 2.87 (P	= 0.004)					
Total (95% CI)		8014		36540	100.0%	0.74 [0.63, 0.86]	•
Total events Heterogeneity: Chi <sup>2</sup> =	191 6 90 df - 5	(D = 0.2)	1180	D.C.			
Test for overall effect:	Z = 3.95 (P	< 0.0001	)				0.2 0.5 1 2 5 Favours [Paroxysmal AF] Favours [Sustained AF]
B Test for subgroup diffe	erences: Ch	i² = 1.93,	df = 1 (P	= 0.16),	l² = 48.1%		
All-cause mortality							
	Paroxysn Events		Sustain Events		Weight	Risk Ratio M-H. Fixed. 95% Cl	Risk Ratio M-H. Fixed, 95% Cl
Study or Subgroup	Events	Total	Events	Total		M-H. Fixed, 95% Cl	
Study or Subgroup Anticoagulation ARISTOTLE <sup>16</sup> ROCKET-AF <sup>17</sup>	Events 149		Events 1123		Weight 43.3% 46.3%	M-H. Fixed. 95% Cl	
Study or Subgroup Anticoagulation ARISTOTLE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>13</sup>	Events	Total 2786 2514 836	Events	Total 15412 11548 6493	43.3% 46.3% 10.4%	M-H. Fixed. 95% Cl 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03]	
Study or Subgroup Anticoagulation ARISTOTLE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>13</sup> Subtotal (95% CI)	Events 149 170 34	Total 2786 2514	1123 1029 362	Total 15412 11548	43.3% 46.3% 10.4%	M-H. Fixed. 95% Cl 0.73 [0.62, 0.87] 0.76 [0.65, 0.89]	
Study or Subgroup Anticoagulation ARISTOTLE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>13</sup> Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1	Events 149 170 34 353 0.10, df = 2	Total 2786 2514 836 6136 (P = 0.95	Events 1123 1029 362 2514 ); I <sup>2</sup> = 0%	Total 15412 11548 6493	43.3% 46.3% 10.4%	M-H. Fixed. 95% Cl 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03]	
Study or Subgroup Anticoagulation ARISTOTLE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>13</sup> Subtotal (95% CI) Total events	Events 149 170 34 353 0.10, df = 2	Total 2786 2514 836 6136 (P = 0.95	Events 1123 1029 362 2514 ); I <sup>2</sup> = 0%	Total 15412 11548 6493	43.3% 46.3% 10.4%	M-H. Fixed. 95% Cl 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03]	
Study or Subgroup           Anticoagulation           ARISTOTLE <sup>16</sup> RCCKET-AF <sup>17</sup> SPORTIF II-V <sup>13</sup> Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 1           Test for overall effect:           Antiplatelet	Events 149 170 34 353 0.10, df = 2	Total 2786 2514 836 6136 (P = 0.95 < 0.0000	Events 1123 1029 362 2514 ); I <sup>2</sup> = 0%	Total 15412 11548 6493 33453	43.3% 46.3% 10.4%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83]	
Study or Subgroup Anticoagulation ARISTOTLE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF IIL-V <sup>33</sup> Subtotal (95% CI) Total events Heterogeneity: Ch <sup>2</sup> = I Test for overall effect: Antiplatelet Subtotal (95% CI)	Events           149           170           34           353           0.10, df = 2           Z = 5.34 (P	Total 2786 2514 836 6136 (P = 0.95	Events 1123 1029 362 2514 ); I <sup>2</sup> = 0% 1)	Total 15412 11548 6493	43.3% 46.3% 10.4%	M-H. Fixed. 95% Cl 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03]	
Study of Subgroup Anticoaguiation ARISTOTE <sup>L®</sup> ROCKET-AF <sup>77</sup> SPORTIF III-V <sup>13</sup> Subtotal (95% CI) Total events Heterogeneity: Ch <sup>2</sup> = 1 Test for overall effect: Antiplatelet Subtotal (95% CI) Total events Heterogeneity: Not apl	Events 149 170 34 353 0.10, df = 2 Z = 5.34 (P 0 plicable	Total 2786 2514 836 6136 (P = 0.95 < 0.0000 0	Events 1123 1029 362 2514 ); I <sup>2</sup> = 0%	Total 15412 11548 6493 33453	43.3% 46.3% 10.4%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83]	
Study of Subgroup Anticoagulation ARISTOTE <sup>12</sup> NOCKET-AF <sup>71</sup> SPORTIF III-V <sup>13</sup> Subtotal (95% CI) Total events Heterogenetis ChiP = 1 Test for overall effect: Antiplatelet Subtotal (95% CI) Total events	Events 149 170 34 353 0.10, df = 2 Z = 5.34 (P 0 plicable	Total 2786 2514 836 6136 (P = 0.95 < 0.0000 0	Events 1123 1029 362 2514 ); I <sup>2</sup> = 0% 1)	Total 15412 11548 6493 33453	43.3% 46.3% 10.4%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83]	
Study or Subaroun Anticoagulation ARISTOTE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect:	Events           149           170           34           353           0.10, df = 2           Z = 5.34 (P           0           plicable           Not applicate	Total 2786 2514 836 6136 (P = 0.95 < 0.0000 0	Events 1123 1029 362 2514 ); I <sup>2</sup> = 0% 1) 0	Total 15412 11548 6493 33453 0	43.3% 46.3% 10.4%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83]	
Study of Subgroup           Anticoaguiation           ARISTOTE <sup>(2)</sup> ROCKET-AF <sup>(2)</sup> SPORTIF III-V <sup>13</sup> Subtati (95% c1)           Total events           Heterogeneity: Ch <sup>2</sup> = 1           Total events           Hottotal (95% c1)           Total events           Hottotal (95% c1)           Total events           Heterogeneity: Not ap           Test for overall effect:	Events           149           170           34           353           0.10, df = 2 ·           Z = 5.34 (P           0           0           plicable           Not applicat           353	Total 2786 2514 836 6136 (P = 0.95 < 0.0000 0 0 ble 6136	Events 1123 1029 362 2514 ); I <sup>2</sup> = 0% 1) 0 2514	Total 15412 11548 6493 33453 0	43.3% 46.3% 10.4% 100.0%	M-H. Fixed, 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] Not estimable	M.H. Fixed. 95% Cl
Study of Subgroup Anticoagulation ARISTOTE <sup>21</sup> ROCKET-AF <sup>71</sup> SPORTIF III-V <sup>13</sup> SPORTIF III-V <sup>13</sup> Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Total events Heterogeneity: Not ap Total events Heterogeneity: Not ap Total events Heterogeneity: Ch <sup>2</sup> = 1 Total events Heterogeneity: Ch <sup>2</sup> = 1 Total events	Events           149           170           34           353           0.10, df = 2           Z = 5.34 (P           plicable           Not applicate           353           0.10, df = 2.           2 = 5.34 (P	Total 2786 2514 836 6136 (P = 0.95 < 0.0000 0 6136 (P = 0.95 < 0.95 < 0.0000	Events 1123 1029 362 2514 1); I <sup>2</sup> = 0% 1) 0 2514 ); I <sup>2</sup> = 0% 1)	Total 15412 11548 6493 33453 0	43.3% 46.3% 10.4% 100.0%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.74 [0.55, 0.89] 0.73 [0.52, 103] 0.75 [0.67, 0.83] Not estimable 0.75 [0.67, 0.83]	
Study or Subaroun Anticoagulation ARISTOTLE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Total (95% CI) Total events Heterogeneity: Not ap Total events Heterogeneity: Chi <sup>2</sup> = 1	Events           149           170           34           353           0.10, df = 2           Z = 5.34 (P           plicable           Not applicate           353           0.10, df = 2.           2 = 5.34 (P	Total 2786 2514 836 6136 (P = 0.95 < 0.0000 0 6136 (P = 0.95 < 0.95 < 0.0000	Events 1123 1029 362 2514 1); I <sup>2</sup> = 0% 1) 0 2514 ); I <sup>2</sup> = 0% 1)	Total 15412 11548 6493 33453 0	43.3% 46.3% 10.4% 100.0%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.74 [0.55, 0.89] 0.73 [0.52, 103] 0.75 [0.67, 0.83] Not estimable 0.75 [0.67, 0.83]	MH.Fixed.95%.Cl
Study of Subgroup Anticoagulation ARISTOTE <sup>21</sup> ROCKET-AF <sup>71</sup> SPORTIF III-V <sup>13</sup> SPORTIF III-V <sup>13</sup> Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Total events Heterogeneity: Not ap Total events Heterogeneity: Not ap Total events Heterogeneity: Ch <sup>2</sup> = 1 Total events Heterogeneity: Ch <sup>2</sup> = 1 Total events	Events           149           170           34           353           0.10, df = 2.           Z = 5.34 (P           Not applicate           363           0.10, df = 2.           2 = 5.34 (P	Total 2786 2514 836 6136 (P = 0.95 < 0.0000 0 6136 (P = 0.95 < 0.0000 applicab	Events 1123 1029 362 2514 ); I <sup>2</sup> = 0% 1) 0 2514 ); I <sup>2</sup> = 0% 1) le	Total 15412 11548 6493 33453 0 33453	43.3% 46.3% 10.4% 100.0%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.74 [0.52, 103] 0.75 [0.67, 0.83] Not estimable	M-H. Fixed. 95% Cl
Study of Subgroup Anticoagulation ARISTOTE <sup>21</sup> ROCKET-AF <sup>71</sup> SPORTIF III-V <sup>13</sup> SPORTIF III-V <sup>13</sup> SPORTIF III-V <sup>13</sup> Subtotal (95% c1) Total events Heterogeneity: Not ag Test for overall effect: Total (95% c1) Total events Heterogeneity: Not ag Test for overall effect: C Test for subgroup diffe Major bleeding Study or Subgroup	Events           149           170           34           353           0.10, df = 2           Z = 5.34 (P           plicable           Not applicate           353           0.10, df = 2.           2 = 5.34 (P	Total 2786 2514 836 6136 (P = 0.95 < 0.0000 0 6136 (P = 0.95 < 0.0000 applicab	Events 1123 1029 362 2514 1); I <sup>2</sup> = 0% 1) 0 2514 ); I <sup>2</sup> = 0% 1)	Total 15412 11548 6493 33453 0 0 33453	43.3% 46.3% 10.4% 100.0%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.74 [0.55, 0.89] 0.73 [0.52, 103] 0.75 [0.67, 0.83] Not estimable 0.75 [0.67, 0.83]	MH. Fixed. 95% Cl
Study or Subaroup Anticoagulation ARISTOTLE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> Subtat (95% Ct) Total events Heterogeneity: Not ap Test for overall effect: Total (95% Ct) Total events Heterogeneity: Not ap Test for overall effect: C Test for subgroup diffe Major bleeding Study or Subgroup	Events           149           170           34           353           0.10, df = 2 :           Z = 5.34 (P           Not applicable           0.10, df = 2 :           2 = 5.34 (P           2 = 5.32 (P)           rences: Not           Paroxysm           Events	Total 2786 2514 836 6136 (P = 0.95 < 0.0000 0 6136 (P = 0.95 < 0.0000 applicab hal AF Total	Events 1123 1029 362 2514 ); l <sup>2</sup> = 0% 1) 0 2514 1) 0 2514 Sustain Events	Total 15412 11548 6493 33453 0 0 33453 0 33453	43.3% 46.3% 10.4% 100.0%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.80] 0.73 [0.52, 80] 0.75 [0.67, 0.83] Not estimable 0.75 [0.67, 0.83] Risk Ratio M-H. Fixed. 95% CI	MH. Fixed. 95% Cl
Study or Subaroun           Anticoagulation           Anticoagulation           ARISTOTE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>33</sup> Subtati (95% C1)           Total events           Heterogeneity: Not ap           Test for overall effect:           Total events           Heterogeneity: Ch <sup>2</sup> = 1           Test for overall effect:           C           Test for subgroup diffe           Major bleeding           Study or Subgroup           Anticoagulation           ACTVE-W <sup>21</sup>	Events           149           170           34           353           0.10, df = 2.           2 = 5.34 (P           0           plicable           Not applicat           353           0.10, df = 2.           2 = 5.34 (P           Prences: Not           Paroxysm           Events           23           104	Total           2786           2514           836           6136           (P = 0.95           6136           6136           (P = 0.95           6136           (P = 0.95           9           6136           (P = 0.95           9           6136           (P = 0.95           9           9           9           10           11           12           12           13           14           15           15           16           17           18           19           10           11           12           13           14           15           15           16           17           18           17           18           17           18           17           18           17           18           18      <	Events           1123           1029           362           2514           1); P = 0%           1)           0           2514           1); P = 0%           1)           0           2514           1); P = 0%           1)           0           2514           1); P = 0%           Sustain           69           685           685	Total 15412 11548 6493 33453 0 0 33453 33453 0 0 33453	43.3% 46.3% 10.4% 100.0% 100.0% Weight 4.5% 38.6%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.74 [0.52, 1.03] 0.75 [0.67, 0.83] Not estimable 0.75 [0.67, 0.83] Risk Ratio M-H. Fixed. 95% CI 1.56 [0.98, 2.47] 0.84 [0.69, 1.03]	MH. Fixed. 95% Cl
Study of Subgroup Anticoagulation Antisoagulation Antisoagulation Antisoagulation Research and a subscription RockET-AF <sup>77</sup> SPORTIF III-V <sup>37</sup> SPORTIF III-V <sup>37</sup> Subtotal (95% C1) Total events Heterogeneity: Not ap Test for overall effect: Total (95% C1) Total events Heterogeneity: ChP <sup>2</sup> = 1 Total (95% C1) Total events Heterogeneity: ChP <sup>2</sup> = 1 Test for overall effect: Total (95% C1) Total events Heterogeneity: ChP <sup>2</sup> = 1 Test for subgroup diffe Major bleeding Study of Subgroup Anticoagulation ACTIVE-W <sup>21</sup> ARISTOTLE <sup>10</sup>	Events           149           170           34           363           0.10, df = 2:           z = 5.34 (P           0           plicable           Not applicat           353           0.10, df = 2:           2 = 5.34 (P           Prences: Not           Paroxysm           23           104           5	Total           2786           2514           2514           8136           6136           6136           6136           6136           6136           6136           6136           918           6136           7594           2776           770	Events 1123 1029 362 2514 ); I <sup>2</sup> = 0% 0 2514 1) 0 2514 2514 1) 0 Sustain Events 69 685 7	Total 15412 11548 6493 33453 33453 0 0 33453 33453 23453 23453	43.3% 46.3% 10.4% 100.0% 100.0% 100.0%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] Not estimable 0.75 [0.67, 0.83] Risk Ratio M-H. Fixed. 95% CI 1.56 [0.98, 2.47] 0.84 [0.69, 1.03]	MH. Fixed. 95% Cl
Study or Subaroun Anticoagulation ARISTOTLE <sup>16</sup> NOCKET-AF <sup>17</sup> SPORTIF III-V <sup>33</sup> Subtotal (95% CI) Total events Heterogeneity: Chi# =1 Total (95% CI) Total events Heterogeneity: Not app Test for overall effect: Total (95% CI) Total events Heterogeneity: Not app Test for overall effect: Total (95% CI) Total events Heterogeneity: Chi# =1 Test for subgroup diffe Major bleeding Study or Subgroup and Anticoagulation ACTIVE-W <sup>21</sup> AVERROES <sup>22</sup> ROCKET-AF <sup>27</sup> SPORTIF III-V <sup>35</sup>	Events           149           170           34           353           0.10, df = 2.           2 = 5.34 (P           0           plicable           Not applicat           353           0.10, df = 2.           2 = 5.34 (P           Prences: Not           Paroxysm           Events           23           104	Total           2786           2514           2514           836           6136           (P = 0.95           < 0.0000	Events           1123           1029           362           2514           1); P = 0%           1)           0           2514           1); P = 0%           1)           0           2514           1)           0           2514           1)           0           2514           10           0           2514           10           0           2514           9           685           689           685	Total 15412 11548 6493 33453 33453 33453 33453 33453 2047 115361 2047 115361 2047	43.3% 46.3% 10.4% 100.0% 100.0% **********************************	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] Not estimable 0.75 [0.67, 0.83] Risk Ratio M-H. Fixed. 95% CI 1.56 [0.98, 2.47] 0.84 [0.69, 1.03] 1.92 [0.61, 6.04] 0.94 [0.71, 1.13]	MH. Fixed. 95% Cl
Study or Subaroun           Anticoaguitation           ARISTOTLE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIFII-II-V <sup>33</sup> Subtotal (95% CI)           Total events           Heterogeneity: Not ap           Test for overall effect:           Total (95% CI)           Total events           Heterogeneity: Coll <sup>2</sup> Test for subgroup diffe           Major blecking           Study or Subaroun           ACTIVE-W <sup>471</sup> ARISTOTLE <sup>16</sup> AVERROES <sup>22</sup> SPORTIFII-II-V <sup>13</sup> SPORTIFII-II-V <sup>13</sup> Subtotal (95% CI)	Events           149           353           0.10, df = 2.           Z = 5.34 (P           0           plicable           Not applicat           2 = 5.34 (P           2 = 5.34 (P           2 = 5.34 (P           2 = 5.34 (P           Paroxysn           Events           23           104           5           131           26	Total           2786           2514           336           6136           (P = 0.95           < 0.0000	Events 1123 1029 362 2514 2514 1) 0 2514 1) 0 2514 1) 0 <b>Sustain</b> Events 69 685 7 638 191	Total 15412 11548 6493 33453 0 0 33453 33453 2047 15361 2047 11548	43,3% 46,3% 10,4% 100,0% 100,0% 4,5% 38,6% 0,7% 4,20%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.74 [0.52, 0.03] 0.75 [0.67, 0.83] Not estimable 0.75 [0.67, 0.83] M-H. Fixed. 95% CI 1.56 [0.98, 2.47] 0.84 [0.68, 1.03] 1.92 [0.61, 6.04] 0.94 [0.79, 1.13]	MH. Fixed. 95% Cl
Study or Subaroun           Anticoaguitation           ARISTOTLE <sup>16</sup> ROCKET-AF <sup>17</sup> ROCKET-AF <sup>17</sup> SPORTIFII-II-V <sup>13</sup> SPORTIFII-II-V <sup>13</sup> Subtotal (95% CI)           Total events           Heterogeneity: ChiP = I           Subtotal (95% CI)           Total events           Heterogeneity: Not ap           Test for overall effect:           Total events           Heterogeneity: Not ap           Test for overall effect:           Total events           Heterogeneity: ChiP = I           Test for overall effect:           Test for overall effect:           Test for overall effect:           Certs for subgroup diffe           Major bleeding           Study or Subgroup           AVERROES <sup>22</sup> ROCKET-AF <sup>17</sup> SPORTIFIL-II-V <sup>13</sup> Subtotal (95% CI)           Total events           Heterogeneity: ChiP = I	Events           149           353           0.10, df = 2           2 = 5.34 (P           0           plicable           353           0.10, df = 2           2 = 5.34 (P           2 = 5.34 (P           Paroxysn           2 = 5.34           2 = 5.34           104           5           131           26           289           7.52, df = 4	Total           2786           2514           836           6136           (P = 0.95           6136           6137           6138           6139           760           7480           (P = 0.11	Events 1123 1029 2514 1); I <sup>2</sup> = 0% 1) 2514 1) 0 2514 1) 0 Sustain Events 69 685 7 638 8191 1590	Total 15412 11548 6493 33453 0 0 33453 33453 33453 2047 2047 2047 15361 2047 11548 6493 38222	43.3% 46.3% 10.4% 100.0% 100.0% **********************************	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] Not estimable 0.75 [0.67, 0.83] Risk Ratio M-H. Fixed. 95% CI 1.56 [0.98, 2.47] 0.84 [0.69, 1.03] 1.92 [0.61, 6.04] 0.94 [0.71, 1.13]	MH. Fixed. 95% Cl
Study or Subaroun Anticoagulation ARISTOTE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>33</sup> Subtotal (95% C1) Total events Heterogeneity: Ant ap Test for overall effect: Total (95% C1) Total events Heterogeneity: Not ap Test for overall effect: Total (95% C1) Total events Heterogeneity: ChP = 1 Test for overall effect: Test for subaroup diffe Major bleeding Study or Subaroup diffe Anticoagulation ACTIVE-W <sup>31</sup> ARISTOTE <sup>16</sup> AVERNOES <sup>22</sup> AVERNOES <sup>23</sup> Subtotal (95% C1)	Events           149           353           0.10, df = 2           2 = 5.34 (P           0           plicable           353           0.10, df = 2           2 = 5.34 (P           2 = 5.34 (P           Paroxysn           2 = 5.34           2 = 5.34           104           5           131           26           289           7.52, df = 4	Total           2786           2514           836           6136           (P = 0.95           6136           6137           6138           6139           760           7480           (P = 0.11	Events 1123 1029 2514 1); I <sup>2</sup> = 0% 1) 2514 1) 0 2514 1) 0 Sustain Events 69 685 7 638 8191 1590	Total 15412 11548 6493 33453 0 0 33453 33453 33453 2047 2047 2047 15361 2047 11548 6493 38222	43.3% 46.3% 10.4% 100.0% 100.0% **********************************	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] Not estimable 0.75 [0.67, 0.83] Risk Ratio M-H. Fixed. 95% CI 1.56 [0.98, 2.47] 0.84 [0.69, 1.03] 1.92 [0.61, 6.04] 0.94 [0.71, 1.13]	MH. Fixed. 95% Cl
Study or Subaroup Anticoagulation ARISTOTE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> Subtat (95% C1) Total events Heterogeneity: Not ap Test for overall effect: Total (95% C1) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for subgroup diffe Major bleeding Study or Subaroup Anticoagulation ACTIVE-W <sup>31</sup> ROCKET-AF <sup>17</sup> Subtatal (95% C1) Total events Heterogeneity: Chi <sup>2</sup> = 1 Study or Subaroup ARISTOTE <sup>16</sup> AVERROES <sup>22</sup> ROCKET-AF <sup>17</sup> Subtatal (95% C1) Total events Heterogeneity: Chi <sup>2</sup> = 1 Set for ovents Heterogeneity: Chi <sup>2</sup> = 1 Set for subgroup diffe	Events           149           353           0.10, df = 2           2 = 5.34 (P           0           plicable           Not application           363           0.10, df = 2, 2           2 = 5.34 (P           9           0.10, df = 2, 2           2 = 5.34 (P           9           10, df = 2, 2           2 = 5.34 (P           9           10, df = 2, 2           2 = 5.34 (P           23           103           5           131           26           7.52, df = 4, 2           2 = 0.87 (P	Total           2786           2514           836           636           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           700           814           776           760           72776           760           7480           (P = 0.39)		Total 15412 11548 33453 0 0 33453 0 33453 2047 11548 6493 38222	43.3% 46.3% 10.4% 100.0% 100.0% 100.0% 8.6% 8.0% 8.0% 8.3%	M-H. Fixed. 95% CI 0.73 [0.62, 0.63, 0.73 0.76 [0.65, 0.83] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 1.56 [0.98, 24] 0.45 [0.94, 1.07] 0.84 [0.69, 0.41] 0.94 [0.79, 1.43] 1.06 [0.74, 1.45] 0.85 [0.84, 1.07]	MH. Fixed. 95% Cl
Study or Subaroup           Anticoaguitation           ARISTOTLE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIFII-II-V <sup>33</sup> SPORTIFII-II-V <sup>33</sup> SPORTIFII-II-V <sup>33</sup> SPORTIFII-II-V <sup>33</sup> Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 1           Test for overall effect:           Subtotal (95% CI)           Total events           Heterogeneity: Not ap           Test for overall effect:           Cotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> = 1           Cest for subgroup diffe           Major bleeding           Study or Subgroup           ACTIVE-W <sup>21</sup> ACTROES <sup>22</sup> AVERROES <sup>22</sup> Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> =           Subtotal (95% CI)           Total events           Heterogeneity: Chi <sup>2</sup> =           Test for overall effect:           Antiptatelet           ACTIVE-W <sup>21</sup>	Events           149           353           0.10, df = 2,           2 = 5.34 (P           0           0           0           0           0           0           0           149           0           1           1           1           26           28           29           752, df = 4           21	Total           2786           2514           836           6136           (P = 0.95           6136           (P = 0.95           6136           (P = 0.95           (P = 0.95           9           6136           (P = 0.95           9           10           9           10           11           12           12           13           13           14           14           15           14           15           14           14           14           15           16           16           17           18           18           19           10           10           10           11           12           13           14           14           15           14           15           16           12 <t< td=""><td>Events 1123 1029 2514 1; P = 0% 0 2514 1; P = 0% 0 2514 1; P = 0% 0 Sustains 69 685 7 638 191 1590 1590 777</td><td>Total 15412 11548 6493 33453 0 0 33453 33453 33453 33453 33453 2077 11548 2277 38222 6</td><td>43.3% 46.3% 10.4% 100.0% 100.0% 100.0% 100.0% 8.6% 38.6% 93.8% 93.8% 5.2%</td><td>M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 1.56 [0.98, 2.47] 0.84 [0.69, 1.03] 1.92 [0.61, 6.04] 0.95 [0.84, 1.07] 1.22 [0.76, 1.96]</td><td>MH. Fixed. 95% Cl</td></t<>	Events 1123 1029 2514 1; P = 0% 0 2514 1; P = 0% 0 2514 1; P = 0% 0 Sustains 69 685 7 638 191 1590 1590 777	Total 15412 11548 6493 33453 0 0 33453 33453 33453 33453 33453 2077 11548 2277 38222 6	43.3% 46.3% 10.4% 100.0% 100.0% 100.0% 100.0% 8.6% 38.6% 93.8% 93.8% 5.2%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 1.56 [0.98, 2.47] 0.84 [0.69, 1.03] 1.92 [0.61, 6.04] 0.95 [0.84, 1.07] 1.22 [0.76, 1.96]	MH. Fixed. 95% Cl
Study of Subarous Anticoagulation ARISTOTLE <sup>16</sup> NOCKET-AF <sup>17</sup> SPORTIF III-V <sup>13</sup> SPORTIF III-V <sup>13</sup> SPORTIF III-V <sup>13</sup> Subtat (95% C1) Total events Heterogeneity: Ant ap Test for overall effect: Total (95% C1) Total events Heterogeneity: Chi# =1 Test for overall effect: Test for subgroup diffe Major bleeding Study of Subarous Anticoagulation Anticoagulation Anticoagulation Anticoagulation Anticoagulation Anticoagulation Anticoagulation Heterogeneity: Chi# =1 Test for overall effect: Subtatal (95% C1) Total events Heterogeneity: Chi# =1 Test for overall effect: Antipatelet Active=W <sup>21</sup> Active=W <sup>21</sup> Active=W <sup>21</sup> Active=W <sup>21</sup> Active=W <sup>21</sup> AverRoges <sup>22</sup> Active=W <sup>21</sup> Active=W <sup>21</sup> AverRoges <sup>22</sup> Active=W <sup>21</sup> AverRoges <sup>22</sup> Active=W <sup>21</sup> AverRoges <sup>22</sup> Active=W <sup>21</sup> AverRoges <sup>22</sup> Active=W <sup>21</sup> AverRoges <sup>22</sup> AverRoges <sup>2</sup>	Events           149           133           353           0.10, df = 2, $Z = 5.34$ (P           Not applicate           353           0.10, df = 2,           2 = 5.34 (P           Prences: Not           2 = 5.34           2 = 5.34           0.10, df = 2,           2 = 5.34           1.10, df = 2,           2.2           2.3           1.04           5           1.26           2.28,           7.52, df = 4,           2.29,           7.52, df = 4,           2.21,           3	Total           2786           2514           836           636           6136           6136           6136           6136           6136           6136           9           6136           6136           6136           6136           6136           6136           700           9	Events 1123 1029 362 2514 1); P = 0% 0 2514 1) 0 2514 1) 0 2514 1) 0 2514 1) 1) 0 2514 10 10 10 10 10 10 10 10 10 10	Total 15412 11548 33453 0 0 33453 0 33453 2047 11548 6493 38222	43.3% 46.3% 10.4% 100.0% 100.0% 100.0% 8.6% 8.0% 8.0% 8.3%	M-H. Fixed. 95% CI 0.73 [0.62, 0.63, 0.73 0.76 [0.65, 0.83] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 1.56 [0.98, 24] 0.45 [0.98, 24] 0.45 [0.98, 24] 0.45 [0.98, 24] 0.45 [0.98, 1.17] 0.45 [0.84, 1.07]	MH. Fixed. 95% Cl
Study of Subaroup           Anticoagulation           Anticoagulation           Anticoagulation           ARISTOTE <sup>16</sup> NOCKET-AF <sup>17</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> Subtotal (95% C1)           Total events           Heterogeneity: ChiP = 1           Test for overall effect:           Total events           Heterogeneity: Not app Test for overall effect:           C Test for subgroup diffe           Major bleeding           Study or Subgroup           Anticoagulation           ACTIVE-W <sup>21</sup> ARISTOTE <sup>4</sup> AVERROES <sup>22</sup> ROCKET-AF <sup>12</sup> SPORTIF III-V <sup>13</sup> Subtotal (95% C1)           Total events           Heterogeneity: ChiP = 1           Test for overs <sup>23</sup> Subtotal (95% C1)           Total events	Events           149           353           0.10, df = 2           2 = 5.34 (P           0           plicable           Not applicat           353           0.10, df = 2           2 = 5.34 (P           9           9           2 = 5.34 (P           9           9           104           5           131           26           97.52, df = 4           Z = 0.87 (P           21           3           24	Total           2786           2514           836           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           514           2776           760           760           7480           (P = 0.39)           608           752           1360	Events 1123 1029 362 2514 (; ) <sup>2</sup> = 0% 0 2514 (; ) <sup>2</sup> = 0% 0 2514 (; ) <sup>2</sup> = 0% 0 <b>Sustainn</b> 69 685 73 69 685 73 191 1590 77 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 77 10 77 10 77 77 77 77 77 77 77 77 77 7	Total 15412 11548 33453 0 0 33453 0 0 33453 0 0 33453 0 0 0 33453 0 0 0 0 0 0 0 0 0 0 0 0 0	43.3% 46.3% 10.4% 100.0% 100.0% 100.0% 4.5% 8.8.6% 0.7% 8.0% 8.0% 8.38.6% 93.8%	M-H. Fixed. 95% CI 0.73 [0.62, 0.83] 0.78 [0.65, 0.83] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 1.56 [0.98, 247] 0.84 [0.69, 0.41] 0.84 [0.69, 0.41] 0.94 [0.79, 1.158] 0.85 [0.84, 1.07] 1.22 [0.76, 1.96] 0.81 [0.22, 2.95]	MH. Fixed. 95% Cl
Study of Subarous Anticoagulation ARISTOTLE <sup>16</sup> NOCKET-AF <sup>17</sup> SPORTIF III-V <sup>13</sup> SPORTIF III-V <sup>13</sup> SPORTIF III-V <sup>13</sup> Subtat (95% C1) Total events Heterogeneity: Ant ap Test for overall effect: Total (95% C1) Total events Heterogeneity: Chi# =1 Test for overall effect: Test for subgroup diffe Major bleeding Study of Subarous Anticoagulation Anticoagulation Anticoagulation Anticoagulation Anticoagulation Anticoagulation Anticoagulation Heterogeneity: Chi# =1 Test for overall effect: Subtatal (95% C1) Total events Heterogeneity: Chi# =1 Test for overall effect: Antipatelet Active=W <sup>21</sup> Active=W <sup>21</sup> Active=W <sup>21</sup> Active=W <sup>21</sup> Active=W <sup>21</sup> AverRoges <sup>22</sup> Active=W <sup>21</sup> Active=W <sup>21</sup> AverRoges <sup>22</sup> Active=W <sup>21</sup> AverRoges <sup>22</sup> Active=W <sup>21</sup> AverRoges <sup>22</sup> Active=W <sup>21</sup> AverRoges <sup>22</sup> Active=W <sup>21</sup> AverRoges <sup>22</sup> AverRoges <sup>2</sup>	Events           149           353           0.10, df = 2,           2 = 5.34 (P           0           0           0           0           0           0           0           149           0           0           0           0           0           0           0           0           0           0           0           0           0           0           10           23           104           26           289           7.52, df = 4           224, df = 4           21           3           24           0.34, df = 1	Total           2786           2514           236           6136           6136           6136           6136           6136           6136           6136           6136           6136           760           2176           760           2594           7760           760           218           638           760           214           836           760           214           836           760           214           836           760           2130           608           71360	Events 1123 1029 362 2514 (; ) <sup>2</sup> = 0% 0 2514 (; ) <sup>2</sup> = 0% 0 2514 (; ) <sup>2</sup> = 0% 0 <b>Sustainn</b> 69 685 73 69 685 73 191 1590 77 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 77 10 77 10 77 77 77 77 77 77 77 77 77 7	Total 15412 11548 33453 0 0 33453 0 0 33453 0 0 33453 0 0 0 33453 0 0 0 0 0 0 0 0 0 0 0 0 0	43.3% 46.3% 10.4% 100.0% 100.0% 100.0% 4.5% 8.8.6% 0.7% 8.0% 8.0% 8.38.6% 93.8%	M-H. Fixed. 95% CI 0.73 [0.62, 0.83] 0.78 [0.65, 0.83] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 1.56 [0.98, 247] 0.84 [0.69, 0.41] 0.84 [0.69, 0.41] 0.94 [0.79, 1.158] 0.85 [0.84, 1.07] 1.22 [0.76, 1.96] 0.81 [0.22, 2.95]	MH. Fixed. 95% Cl
Study or Subarous         Anticoagulation         ARISTOTLE <sup>16</sup> ARISTOTLE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>33</sup> Subtotal (95% C1)         Total events         Heterogeneity: Not api Test for overall effect:         Total events         Heterogeneity: Not api Test for overall effect:         Total events         Heterogeneity: Not api Test for overall effect:         Total events         Heterogeneity: ChP = 1         Test for subgroup diffe         Major bleeding         Study or Subgroup diffe         Anticoagulation         ACTVE-W <sup>21</sup> AVERROES <sup>22</sup> ROCKET-AF <sup>17</sup> Subtotal (95% C1)         Total events         Heterogeneity: ChP = 1         Test for overall effect:         Articoagulation         ACTVE-W <sup>21</sup> AVEROES <sup>22</sup> Subtotal (95% C1)         Total events         Heterogeneity: ChP = 1         Test for overall effect:	Events           149           353           0.10, df = 2,           2 = 5.34 (P           0           0           0           0           0           0           0           149           0           0           0           0           0           0           0           0           0           0           0           0           0           0           10           23           104           26           289           7.52, df = 4           224, df = 4           21           3           24           0.34, df = 1	Total           2786           22814           836           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           760           2176           760           2594           7760           218           636           7480           (P = 0.11)           608           752           1380           (P = 0.58)	Events 1123 1029 362 2514 (; ) <sup>2</sup> = 0% 0 2514 (; ) <sup>2</sup> = 0% 0 2514 (; ) <sup>2</sup> = 0% 0 <b>Sustainn</b> 69 685 73 69 685 73 191 1590 77 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 87 77 10 77 10 77 10 77 77 77 77 77 77 77 77 77 7	Total 1541 6493 33453 0 0 33453 0 0 33453 2047 11548 4493 38222 2047 11548 4493 38222 6	43.3% 46.3% 10.4% 100.0% 100.0% 100.0% 45.% 0.7% 93.86% 0.7% 93.8% 5.2% 6.2%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 1.56 [0.98, 2.47] 0.84 (0.89, 1.03] 1.92 [0.61, 6.04] 0.95 [0.84, 1.07] 1.92 [0.76, 1.96] 0.81 [0.22, 2.95] 1.16 [0.74, 1.80]	MH. Fixed. 95% Cl
Study or Subaroup         Anticoagulation         ARISTOTLE <sup>16</sup> ARISTOTLE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>33</sup> Subtotal (95% C1)         Total events         Heterogeneity: Not ap         Test for overall effect:         Total events         Heterogeneity: Not ap         Test for overall effect:         Total events         Heterogeneity: Not ap         Test for overall effect:         Total events         Heterogeneity: Ch <sup>2</sup> = 1         Test for overall effect:         Total events         Heterogeneity: Ch <sup>2</sup> = 1         Test for overall effect:         Anticoagulation         ACTIVE-W <sup>21</sup> ARISTOTLE <sup>16</sup> AVERROES <sup>22</sup> Subtotal (95% C1)         Total events         Heterogeneity: Ch <sup>2</sup> = 1         Test for overall effect:         Antiplatelet         ACTIVE-W <sup>21</sup> AVERROES <sup>23</sup> Subtotal (95% C1)         Total events         Heterogeneity: Ch <sup>2</sup> = 1         Test for overall effect:         Total events         Heterogeneity: Ch <sup>2</sup> = 1     <	Events           149           133           353           0.10, df = 2,           2 = 5.34 (P           0           plicable           Not application           353           0.00, df = 2,           2 = 5.34 (P           Paroxysm           23           104           25           126           289           7.52, df = 4,           2 = 0.87 (P           21           3           0.34, df = 1,           Z = 0.64 (P           313	Total           2786           2787           836           6136           6136           (P = 0.95)           6136           (P = 0.95)           6136           (P = 0.95)           760           2514           836           760           2514           836           760           2514           608           752           7480           (P = 0.111           608           752           1360           (P = 0.52)           8840	Events           1123         362           2514         (): (P = 0%)           1): (P = 0%)         (): (P = 0%)           0         0           2514         (): (P = 0%)           100         (): (P = 0%)           0         (): (P = 0%)           10         (): (P = 0%)           11         (): (P = 47%)           77         (): (P = 0%)           10         (): (P = 0%)           10: (P = 0%)         (): (P = 0%)           10: (P = 0%)         (): (P = 0%)	Total 1541 6493 33453 0 0 33453 33453 0 0 33453 15361 2047 11548 38222 2047 11548 38222 2047 11548 4760 42982	43.3% 46.3% 10.4% 100.0% 100.0% 100.0% 4.5% 8.8.6% 0.7% 8.0% 8.0% 8.38.6% 93.8%	M-H. Fixed. 95% CI 0.73 [0.62, 0.83] 0.78 [0.65, 0.83] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 1.56 [0.98, 247] 0.84 [0.69, 0.41] 0.84 [0.69, 0.41] 0.94 [0.79, 1.158] 0.85 [0.84, 1.07] 1.22 [0.76, 1.96] 0.81 [0.22, 2.95]	MH. Fixed. 95% Cl
Study or Subaroup Anticoagulation ARISTOTLE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: C Test for subgroup diffe <b>Major blecding</b> <b>Study or Subaroup</b> Anticoagulation ACTIVE-W <sup>21</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>13</sup> SPORTIF III-V <sup>13</sup> SPORTIF III-V <sup>13</sup> SPORTIF III-V <sup>13</sup> SPORTIF III-V <sup>13</sup> SPORTIF III-V <sup>13</sup> Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect:	Events           149           363           0.10, df = 2           2 = 5.34 (P           0           plicable           Not applicate           353           0.10, df = 2           2 = 5.34 (P           Paroxysn           Events           23           104           5           131           26           7.52, df = 4           2           0.34 (P           21           3           0.34 (P           24           0.34 (P           313           8.57, df = 6	Total           2786           2814           336           436           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           6136           700           594           2776           760           2594           7480           (P = 0.39)           608           7520           760           2514           594           2776           608           7480           (P = 0.351           840           (P = 0.52)	Events           1123         362           2514         (): (P = 0%)           1): (P = 0%)         (): (P = 0%)           0         0           2514         (): (P = 0%)           100         (): (P = 0%)           0         (): (P = 0%)           10         (): (P = 0%)           11         (): (P = 47%)           77         (): (P = 0%)           10; (P = 0%)         (): (P = 0%)           10; (P = 0%)         (): (P = 0%)           10; (P = 0%)         (): (P = 0%)	Total 1541 6493 33453 0 0 33453 33453 0 0 33453 15361 2047 11548 38222 2047 11548 38222 2047 11548 4760 42982	43.3% 46.3% 10.4% 100.0% 100.0% 100.0% 45.% 0.7% 93.86% 0.7% 93.8% 5.2% 6.2%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 1.56 [0.98, 2.47] 0.84 [0.69, 1.03] 1.92 [0.61, 6.04] 0.95 [0.84, 1.07] 1.22 [0.76, 1.96] 0.81 [0.22, 2.95] 1.16 [0.74, 1.80] 0.96 [0.85, 1.08]	MH. Fixed. 95% Cl
Study or Subaroun         Anticoaguitation         ARISTOTLE <sup>16</sup> ROCKET-AF <sup>27</sup> SPORTIF III-V <sup>33</sup> Subtotal (95% CI)         Total events         Heterogeneity: Chi <sup>2</sup> = 1         Cest for avenal effect:         Total sevents         Heterogeneity: Chi <sup>2</sup> = 1         Cest for avenal effect:         Total events         Autocaguitation         ACTIVE-W <sup>21</sup> AVEROES <sup>22</sup> ROCKET-AF <sup>27</sup> SUBtotal (95% CI)         Total events         Heterogeneity: Chi <sup>2</sup> = 1         Test for overall effect:         ACTIVE-W <sup>21</sup> AVERROES <sup>22</sup> Subtotal (95% CI)         Total events         Heterogeneity: Chi <sup>2</sup> = 1         Test for overall effect:         Total events         Heterogeneity: Chi <sup>2</sup> = 1 </td <td>Events           149           130           34           353           0.10, df = 2           2 = 5.34 (P           Not applicable           Not applicable           363           0.010, df = 2, Z = 5.34 (P           Paroxysm           23           104           5           23           104           5           23           104           5           2289           7.52, df = 4, Z           21           24           0.34, df = 1, Z           24.034, df = 1, Z           313           8.57, df = 6, Z           313           8.57, df = 6, Z           313</td> <td>Total           2786         2614           286         6136           6136         6136           (P = 0.95         0           ole         6136           6136         (P = 0.95           (P = 0.95         0           applicab         applicab           hal AF         Total           594         2776           780         2276           780         780           608         752           1360         (P = 0.52)           8840         (P = 0.52)</td> <td>Events 1123 1029 362 2514 (); P = 0% (); P = 0%</td> <td>Total 1541 6493 33453 0 0 33453 33453 0 0 33453 2047 15381 2247 15381 2247 15382 2047 15382 2047 15381 2047 15381 2047 15381 2047 1548 8493 36222 6 4 22722 2038 4760 6 42932 6 6</td> <td>43.3% 46.3% 10.4% 100.0% 100.0% 4.5% 8.6% 0.7% 4.5% 8.0% 8.0% 8.0% 8.0% 8.0% 6.2% 100.0%</td> <td>M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 1.56 [0.98, 2.47] 0.84 [0.69, 1.03] 1.92 [0.61, 6.04] 0.95 [0.84, 1.07] 1.22 [0.76, 1.96] 0.81 [0.22, 2.95] 1.16 [0.74, 1.80] 0.96 [0.85, 1.08]</td> <td>MH. Fixed. 95% Cl</td>	Events           149           130           34           353           0.10, df = 2           2 = 5.34 (P           Not applicable           Not applicable           363           0.010, df = 2, Z = 5.34 (P           Paroxysm           23           104           5           23           104           5           23           104           5           2289           7.52, df = 4, Z           21           24           0.34, df = 1, Z           24.034, df = 1, Z           313           8.57, df = 6, Z           313           8.57, df = 6, Z           313	Total           2786         2614           286         6136           6136         6136           (P = 0.95         0           ole         6136           6136         (P = 0.95           (P = 0.95         0           applicab         applicab           hal AF         Total           594         2776           780         2276           780         780           608         752           1360         (P = 0.52)           8840         (P = 0.52)	Events 1123 1029 362 2514 (); P = 0% (); P = 0%	Total 1541 6493 33453 0 0 33453 33453 0 0 33453 2047 15381 2247 15381 2247 15382 2047 15382 2047 15381 2047 15381 2047 15381 2047 1548 8493 36222 6 4 22722 2038 4760 6 42932 6 6	43.3% 46.3% 10.4% 100.0% 100.0% 4.5% 8.6% 0.7% 4.5% 8.0% 8.0% 8.0% 8.0% 8.0% 6.2% 100.0%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 1.56 [0.98, 2.47] 0.84 [0.69, 1.03] 1.92 [0.61, 6.04] 0.95 [0.84, 1.07] 1.22 [0.76, 1.96] 0.81 [0.22, 2.95] 1.16 [0.74, 1.80] 0.96 [0.85, 1.08]	MH. Fixed. 95% Cl
Study or Subaroup Anticoagulation ARISTOTE <sup>16</sup> ROCKET-AF <sup>17</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> SPORTIF III-V <sup>33</sup> Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Test for overall effect: Test for overall effect: Test for overall effect: C Test for subgroup diffe Major bleeding Study or Subaroup Anticoagulation ACTIVE-W <sup>31</sup> Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Antiplatelet ACTIVE-W <sup>31</sup> Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Total (95% CI)	Events           149           130           34           353           0.10, df = 2           2 = 5.34 (P           Not applicable           Not applicable           363           0.010, df = 2, Z = 5.34 (P           Paroxysm           23           104           5           23           104           5           23           104           5           2289           7.52, df = 4, Z           21           24           0.34, df = 1, Z           24.034, df = 1, Z           313           8.57, df = 6, Z           313           8.57, df = 6, Z           313	Total           2786         2614           286         6136           6136         6136           (P = 0.95         0           ole         6136           6136         (P = 0.95           (P = 0.95         0           applicab         applicab           hal AF         Total           594         2776           780         2276           780         780           608         752           1360         (P = 0.52)           8840         (P = 0.52)	Events 1123 1029 362 2514 (); P = 0% (); P = 0%	Total 1541 6493 33453 0 0 33453 33453 0 0 33453 2047 15381 2247 15381 2247 15382 2047 15382 2047 15381 2047 15381 2047 15381 2047 1548 8493 36222 6 4 22722 2038 4760 6 42932 6 6	43.3% 46.3% 10.4% 100.0% 100.0% 4.5% 8.6% 0.7% 4.5% 8.0% 8.0% 8.0% 8.0% 8.0% 6.2% 100.0%	M-H. Fixed. 95% CI 0.73 [0.62, 0.87] 0.76 [0.65, 0.89] 0.73 [0.52, 1.03] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 0.75 [0.67, 0.83] 1.56 [0.98, 2.47] 0.84 [0.69, 1.03] 1.92 [0.61, 6.04] 0.95 [0.84, 1.07] 1.22 [0.76, 1.96] 0.81 [0.22, 2.95] 1.16 [0.74, 1.80] 0.96 [0.85, 1.08]	MH. Fixed. 95% Cl

**FIGURE 3.** Efficacy (A–C) and safety (D) outcomes of paroxysmal versus sustained AF according to treatment of anticoagulation and antiplatelet.  $AF = atrial \ fibrillation, \ df = degrees \ of \ freedom, \ M-H = Mantel-Haenszel, \ non-CNS = non-central \ nervous \ system.$ 

incidence of major bleeding was comparable between the 2 groups (RR, 0.96; 95% CI, 0.85–1.08; P = 0.50).

In the subgroup analysis, irrespective of anticoagulation or antiplatelet administration, paroxysmal AF patients consistently showed reduced stroke and stroke or non-CNS systemic embolism risks and similar major bleeding risk compared with sustained AF patients (Fig. 3). Likewise, in the anticoagulation treatment group, independent of whether NOACs or warfarin was administered, patients with paroxysmal AF showed favorable outcomes (see Figure 1, Supplemental Content, which illustrates the outcomes by AF type according to treatment with NOACs and warfarin, http://links.lww.com/MD/A582). Specifically, despite statistical nonsignificance, patients with paroxysmal AF receiving NOACs tended to have reduced

#### Sustained AF

risks of stroke or systemic embolism (RR, 0.79; 95% CI, 0.62– 1.01; P = 0.06).

# **Outcomes by Treatment**

The efficacy and safety of anticoagulation versus antiplatelet according to the AF type are shown in Figure 4. Anticoagulation treatment significantly reduced the risk of stroke or non-CNS systemic embolism in sustained AF patients (RR, 0.42; 95% CI, 0.33–0.54; P < 0.001), with no risk increase in major bleeding observed (RR, 0.86; 95% CI, 0.63–1.16; P = 0.33). For paroxysmal AF patients, we were not able to detect a significant difference between anticoagulation and antiplatelet treatment both for stroke or systemic embolism prevention (RR, 0.72; 95% CI, 0.43–1.23; P = 0.23)

	Anticoagu	lation	Antiplat	elet		Risk Ratio	Risk	Ratio
Study or Subgroup	Events		Events		Weight	M-H, Fixed, 95% Cl		ed, 95% Cl
ACTIVE-W <sup>21</sup>	51	2773	104	2722	54.3%	0.48 [0.35, 0.67]	— <b>—</b>	
AVERROES <sup>22</sup>	31	2047	88	2038	45.7%	0.35 [0.23, 0.53]	<b>—</b>	
/WEIWOLD	01	2011	00	2000	10.770	0.00 [0.20, 0.00]		
Total (95% CI)		4820		4760	100.0%	0.42 [0.33, 0.54]	•	
Total events	82		192					
Heterogeneity: Chi <sup>2</sup> = <sup>2</sup>	1.41, df = 1 (F	P = 0.23)	; l² = 29%			-		
Test for overall effect:	Z = 6.62 (P <	: 0.0000 <sup>2</sup>	)			Fou	0.2 0.5 ours [Anticoagulation]	1 2 5
b. Major bleeding						Fdv	ours [Anticoaguiation]	Favours [Antipiateiet
b. Major biccung	Anticoagu	lation	Antiplat	elet		Risk Ratio	Risk	Ratio
Study or Subgroup	Events				Weight			ed, 95% Cl
ACTIVE-W <sup>21</sup>	<u>69</u>	2773	77	2722	88.6%	0.88 [0.64, 1.21]		-
AVERROES <sup>22</sup>	7	2047	10	2038	11.4%	0.70 [0.27, 1.83]		
AVEINIOLO	'	2047	10	2000	11.470	0.70 [0.27, 1.00]		
Total (95% CI)		4820		4760	100.0%	0.86 [0.63, 1.16]		
Total events	76		87					
Heterogeneity: Chi <sup>2</sup> = (		P = 0.65				-	+ +	<u> </u>
Test for overall effect:		,	,			_	0.2 0.5	1 2 5
						Iav	ours [Anticoagulation]	i avouis [Antiplatelet
	INS system	nic emb	olism					
Paroxysmal AF a. Stroke or non-C	Anticoagu	lation	Antipla			Risk Ratio		Ratio
a. Stroke or non-C Study or Subgroup	Anticoagu Events	lation Total	Antiplat Events	Total		M-H, Fixed, 95% Cl		Ratio ed, 95% Cl
a. Stroke or non-C Study or Subgroup ACTIVE-W <sup>21</sup>	Anticoagu Events 11	l <b>ation</b> Total 594	Antiplat Events 18	<b>Total</b> 608	55.8%	M-H, Fixed, 95% Cl 0.63 [0.30, 1.31]		
a. Stroke or non-C Study or Subgroup	Anticoagu Events	lation Total	Antiplat Events	Total		M-H, Fixed, 95% Cl		
a. Stroke or non-C Study or Subgroup ACTIVE-W <sup>21</sup> AVERROES <sup>22</sup>	Anticoagu Events 11	l <b>ation</b> <u>Total</u> 594 760	Antiplat Events 18	Total 608 752	55.8% 44.2%	M-H, Fixed, 95% Cl 0.63 [0.30, 1.31] 0.85 [0.39, 1.82]		
a. Štroke or non-C <u>Study or Subgroup</u> ACTIVE-W <sup>21</sup> AVERROES <sup>22</sup> Total (95% CI)	Anticoagu Events 11 12	l <b>ation</b> Total 594	Antiplat Events 18 14	Total 608 752	55.8%	M-H, Fixed, 95% Cl 0.63 [0.30, 1.31]		
a. Štroke or non-C <u>Study or Subgroup</u> ACTIVE-W <sup>21</sup> AVERROES <sup>22</sup> Total (95% CI) Total events	Anticoagu Events 11 12 23	lation Total 594 760 1354	Antiplat Events 18 14 32	Total 608 752	55.8% 44.2%	M-H, Fixed, 95% Cl 0.63 [0.30, 1.31] 0.85 [0.39, 1.82]	M-H. Fixe	ed, 95% Cl
a. Stroke or non-C <u>Study or Subgroup</u> ACTIVE-W <sup>21</sup> AVERROES <sup>22</sup> Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0	Anticoagu Events 11 12 23 0.31, df = 1 (f	<b>Total</b> 594 760 <b>1354</b> P = 0.58)	Antiplat Events 18 14 32	Total 608 752	55.8% 44.2%	<u>M-H, Fixed, 95% Cl</u> 0.63 [0.30, 1.31] 0.85 [0.39, 1.82] <b>0.72 [0.43, 1.23]</b>	M-H, Fixe	ed, 95% Cl
a. Stroke or non-C Study or Subgroup ACTIVE-W <sup>21</sup> AVERROES <sup>22</sup> Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0 Test for overall effect:	Anticoagu Events 11 12 23 0.31, df = 1 (f Z = 1.19 (P =	<b>Total</b> 594 760 <b>1354</b> P = 0.58)	Antiplat Events 18 14 32	Total 608 752	55.8% 44.2%	<u>M-H, Fixed, 95% Cl</u> 0.63 [0.30, 1.31] 0.85 [0.39, 1.82] <b>0.72 [0.43, 1.23]</b>	M-H. Fixe	ed, 95% Cl
a. Stroke or non-C <u>Study or Subgroup</u> ACTIVE-W <sup>21</sup> AVERROES <sup>22</sup> Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0	Anticoagu Events 11 12 23 0.31, df = 1 (f Z = 1.19 (P =	<b>Total</b> 594 760 <b>1354</b> P = 0.58) 0.23)	Antiplat <u>Events</u> 18 14 32 ; I <sup>2</sup> = 0%	Total 608 752 1360	55.8% 44.2%	<u>M-H, Fixed, 95% Cl</u> 0.63 [0.30, 1.31] 0.85 [0.39, 1.82] 0.72 [0.43, 1.23] - Fav	M-H, Fixe	ed, 95% Cl
a. Stroke or non-C Study or Subgroup ACTIVE-W <sup>21</sup> AVERROES <sup>22</sup> Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: b. Major bleeding	Anticoagu <u>Events</u> 11 12 23 0.31, df = 1 (f Z = 1.19 (P = Anticoagu	lation <u>Total</u> 594 760 <b>1354</b> P = 0.58 0.23) lation	Antiplat <u>Events</u> 18 14 32 ;   <sup>2</sup> = 0% Antiplat	Total 608 752 1360	55.8% 44.2% <b>100.0%</b>	<u>M-H, Fixed, 95% Cl</u> 0.63 [0.30, 1.31] 0.85 [0.39, 1.82] 0.72 [0.43, 1.23] Fav Risk Ratio	M-H, Fixe 0.2 0.5 ours [Anticoagulation] Risk	ed, 95% Cl
<ul> <li>a. Stroke or non-C</li> <li><u>Study or Subgroup</u></li> <li>ACTIVE-W<sup>21</sup></li> <li>AVERROES<sup>22</sup></li> <li>Total (95% CI)</li> <li>Total events</li> <li>Heterogeneity: Chi<sup>2</sup> = 0</li> <li>Test for overall effect:</li> <li>b. Major bleeding</li> <li><u>Study or Subgroup</u></li> </ul>	Anticoagu <u>Events</u> 11 12 23 0.31, df = 1 (f Z = 1.19 (P = Anticoagu <u>Events</u>	lation <u>Total</u> 594 760 <b>1354</b> P = 0.58 0.23) lation <u>Total</u>	Antiplas Events 18 14 32 ;   <sup>2</sup> = 0% Antiplas Events	Total 608 752 1360 telet Total	55.8% 44.2% 100.0% Weight	<u>M-H, Fixed, 95% Cl</u> 0.63 [0.30, 1.31] 0.85 [0.39, 1.82] 0.72 [0.43, 1.23] Fav Risk Ratio <u>M-H, Fixed, 95% Cl</u>	M-H, Fixe 0.2 0.5 ours [Anticoagulation] Risk	ed, 95% Cl
a. Stroke or non-C Study or Subgroup ACTIVE-W <sup>21</sup> AVERROES <sup>22</sup> Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: b. Major bleeding Study or Subgroup ACTIVE-W <sup>21</sup>	Anticoagu <u>Events</u> 11 12 23 0.31, df = 1 (f Z = 1.19 (P = <u>Anticoagu</u> <u>Events</u> 23	Itation           Total           594           760           1354           P = 0.58)           = 0.23)           Ilation           Total           594	Antiplas Events 18 14 ;   <sup>2</sup> = 0% Antiplas Events 21	Total 608 752 1360 telet Total 608	55.8% 44.2% 100.0% <u>Weight</u> 87.3%	<u>M-H, Fixed, 95% Cl</u> 0.63 [0.30, 1.31] 0.85 [0.39, 1.82] 0.72 [0.43, 1.23] 	M-H, Fixe 0.2 0.5 ours [Anticoagulation] Risk	ed, 95% Cl
<ul> <li>a. Stroke or non-C</li> <li><u>Study or Subgroup</u></li> <li>ACTIVE-W<sup>21</sup></li> <li>AVERROES<sup>22</sup></li> <li>Total (95% CI)</li> <li>Total events</li> <li>Heterogeneity: Chi<sup>2</sup> = 0</li> <li>Test for overall effect:</li> <li>b. Major bleeding</li> <li><u>Study or Subgroup</u></li> </ul>	Anticoagu <u>Events</u> 11 12 23 0.31, df = 1 (f Z = 1.19 (P = Anticoagu <u>Events</u>	lation <u>Total</u> 594 760 <b>1354</b> P = 0.58 0.23) lation <u>Total</u>	Antiplas Events 18 14 32 ;   <sup>2</sup> = 0% Antiplas Events	Total 608 752 1360 telet Total	55.8% 44.2% 100.0% Weight	<u>M-H, Fixed, 95% Cl</u> 0.63 [0.30, 1.31] 0.85 [0.39, 1.82] 0.72 [0.43, 1.23] Fav Risk Ratio <u>M-H, Fixed, 95% Cl</u>	M-H, Fixe 0.2 0.5 ours [Anticoagulation] Risk	ed, 95% Cl
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FIGURE 4. Efficacy (a) and safety (b) of anticoagulation versus antiplatelet according to AF type (A, B). AF = atrial fibrillation, df = degrees of freedom, M-H = Mantel-Haenszel, non-CNS = non-central nervous system.

Sustained AF

and major bleeding reduction (RR, 1.19; 95% CI, 0.69–2.03; P = 0.53).

For anticoagulation (Fig. 5), NOACs (dabigatran etexilate 150 mg bid included) were more effective than warfarin for prevention of stroke or systemic embolism (sustained and paroxysmal: RR, 0.81; 95% CI, 0.72–0.91 and RR, 0.75; 95% CI, 0.58–0.97; respectively) and tended to show a lower risk of major bleeding (RR, 0.88; 95% CI, 0.67–1.15 and RR, 0.93; 95% CI, 0.79–1.11, respectively) irrespective of the AF type. Pooled analysis with another dose of dabigatran etexilate

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(110 mg bid) in the RE-LY trial as compared to warfarin showed similar results (see Figure 2, Supplemental Content, which illustrates the efficacy and safety of NOACs vs warfarin according to AF type, http://links.lww.com/MD/A582).

# DISCUSSION

Our meta-analysis based on RCTs, incorporating 69,990 nonvalvular AF patients with  $\geq 1$  risk factor for stroke, has two main findings. First, post-antithrombotic therapy, paroxysmal

	a. Stroke or non-CNS sy	stemic embolism				
					Risk Ratio	Risk Ratio
_	Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
	ARISTOTLE <sup>16</sup>	-0.2231	0.0982	37.8%	0.80 [0.66, 0.97]	-#-
	RE-LY(150) <sup>32*</sup>	-0.4005	0.1392	18.8%	0.67 [0.51, 0.88]	
	ROCKET-AF <sup>17</sup>	-0.1278	0.0917	43.4%	0.88 [0.74, 1.05]	-884
	Total (95% CI)			100.0%	0.81 [0.72, 0.91]	•
	Heterogeneity: Chi <sup>2</sup> = 2	2.69, df = 2 (P = 0	.26); l² =	26%	-	
	Test for overall effect:	Z = 3.56 (P = 0.00	04)			Favours[NOAC] Favours[Warfarin]
	b. Major bleeding					
					Risk Ratio	Risk Ratio
_	Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
	ARISTOTLE <sup>16</sup>	-0.3857	0.0777	33.7%	0.68 [0.58, 0.79]	
	RE-LY(150) <sup>32*</sup>	-0.0834	0.0877	32.8%	0.92 [0.77, 1.09]	
	ROCKET-AF <sup>17</sup>	0.077	0.0802	33.5%	1.08 [0.92, 1.26]	<b>†</b>
	Total (95% CI)			100.0%	0.88 [0.67, 1.15]	•
	Heterogeneity: Tau <sup>2</sup> = 0	0.05; Chi² = 17.74,	df = 2 (P	9 = 0.0001	); I² = 89%	
						0.2 0.5 1 2 5
А	Test for overall effect: Z	. = 0.94 (P = 0.35)				Favours[NOAC] Favours[Warfarin]

## **Paroxysmal AF**

				Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
ARISTOTLE <sup>16</sup>	-0.3285	0.2844	20.7%	0.72 [0.41, 1.26]	
RE-LY(150) <sup>32*</sup>	-0.4943	0.1944	44.3%	0.61 [0.42, 0.89]	
ROCKET-AF <sup>17</sup>	0	0.2184	35.1%	1.00 [0.65, 1.53]	
Total (95% Cl)			100.0%	0.75 [0.58, 0.97]	•
Heterogeneity: Chi <sup>2</sup> = 2	2.89, df = 2 (P = 0.	24); l² =	31%		-++++++
Test for overall effect: 2	Z = 2.22 (P = 0.03	)			0.2 0.5 1 2 5 Favours[NOAC] Favours[Warfarin]
b. Major bleeding					

				Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
ARISTOTLE	-0.3147 0	0.2016	18.6%	0.73 [0.49, 1.08]	- <b>-</b> +
RE-LY(150) <sup>32*</sup>	-0.0408 0	0.1153	56.8%	0.96 [0.77, 1.20]	
ROCKET-AF <sup>17</sup>	0.0583 0	0.1751	24.6%	1.06 [0.75, 1.49]	
Total (95% CI)			100.0%	0.93 [0.79, 1.11]	•
Heterogeneity: Chi <sup>2</sup> = 2 Test for overall effect:	•	5); l² = 4	4%		0.2 0.5 1 2 5 Favours[NOAC] Favours[Warfarin]

**FIGURE 5.** Efficacy (a) and safety (b) of NOACs versus warfarin according to AF type (A, B). AF = atrial fibrillation, df = degrees of freedom, IV = inverse variance, NAOCs = novel oral anticoagulants, SE = standard error. \*Dabigatran 150 mg twice daily.

В

AF patients had lower risks of stroke and composite of stroke or systemic embolism, better survival, and a comparable risk of major bleeding compared with sustained AF patients. Risk reductions of thromboembolic events in paroxysmal AF were consistently seen in patients receiving either anticoagulation (NOACs or warfarin) or antiplatelet agents. Second, compared with antiplatelets, anticoagulation therapy showed superior efficacy for prevention of stroke or systemic embolism in sustained AF, but we did not detect this superior efficacy or safety in paroxysmal AF.

Despite the serious consequences of embolic complications, it has not been well established whether the risk of embolization varies according to the type of AF. Several prior studies have revealed no difference in the outcomes between patients with paroxysmal and sustained AF.<sup>11,19-21,23</sup> However, some studies exploring the problem under the setting of non-anticoagulation came to a different conclusion.<sup>12,15</sup> A prospective cohort study showed that among paroxysmal AF patients not taking anticoagulants, the incidence of embolic complications increased from 2.0% to 5.1% per year after transition to chronic AF.<sup>12</sup> The Loire Valley Atrial Fibrillation Project, a retrospective cohort study, also demonstrated that, in nonanticoagulated patients, the rate of stroke or thromboembolism was significantly higher in permanent AF.15 Our pooled data extended to show a greater thromboembolic risk in patients with more advanced forms of AF undergoing nonanticoagulation therapy in RCTs (the antiplatelet subgroup). However, pooled analysis of the Stroke Prevention in Atrial Fibrillation (SPAF) I-III trials, enrolling patients administered aspirin, suggested a comparable annual event rate between patients with intermittent (3.2%) and sustained AF (3.3%).<sup>19</sup> Actually, the SPAF trials included AF patients not only assigned to aspirin but also a combination of aspirin plus inefficacious fixed-dose warfarin (international normalized ratio < 1.5), because the authors believed this would offer minimal additional protection against ischemic stroke.37 Moreover, unlike our population including only AF patients with  $\geq 1$  risk factor for stroke, 37.9% patients enrolled in the SPAF trials had no stroke risk factors.19

Besides those receiving antiplatelet, our study also consistently demonstrated thromboembolic risk reduction in patients with paroxysmal AF receiving anticoagulation. The differential intensity of anticoagulation use in patients with different AF types may have potentially contributed to the conflicting results. In the AVERROES trial, risk reduction of stroke or systemic embolism in paroxysmal AF patients, as compared to sustained AF, was found in aspirin-treated, but not apixaban-treated patients.<sup>22</sup> Besides, the GISSI-AF trial and Euro Heart Survey did not reveal significant differences in the thromboembolic event rates between AF types; however, a substantially lower rate of anticoagulation was observed in patients with paroxysmal AF compared with sustained AF (26.5% vs 91.2% in GISSI-AF and 49.4% vs 77.9% in the Euro Heart Survey; P < 0.001).<sup>20,23</sup> The confounding influence of anticoagulation may be attributable to its efficacy in thromboembolism prevention, especially for sustained AF, thus diminishing the power to distinguish risk differences between different AF forms.<sup>18</sup> For this reason, we evaluated the outcomes separately in patients with paroxysmal and sustained AF in this meta-analysis. Although the ACTIVE W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) trial showed a similar risk of thromboembolic events for both types of arrhythmia irrespective of treatment with anticoagulation or antiplatelets, it enrolled quite a limited number of AF patients (n = 6697) compared with our study (n = 69,990).

Previous studies have observed different risk factor profiles according to the type of AF, and concluded that the different outcomes were due to these different risk factors, such as increasing age.<sup>19,21,38</sup> The ROCKET-AF trial, including consistently anticoagulated patients, with well-balanced CHADS<sub>2</sub> scores at baseline and treatment assignment between paroxysmal and sustained AF patients, still demonstrated lower embolic events and better survival in paroxysmal AF patients.<sup>17</sup> In our analysis, paroxysmal AF patients were younger and had less heart dysfunction, which indicated that this subgroup was at an early stage of arrhythmia; however, they were associated with higher rates of hypertension and previous thromboembolic events, and the rates of  $CHADS_2$  score >2 were equivalent between the AF types (55.5% vs 54.8%; P = 0.340). Moreover, antithrombotic prophylactic VKA use before entry was less frequent in patients with paroxysmal AF (69.0% vs 79.4%; P < 0.001). Our data provide support for a greater risk related to the more advanced form of AF and suggest that the worse outcomes in advanced AF could be attributed not only to stroke risk factors but may also be associated with the hemodynamic disorders resulting from electromechanical disturbances of the rhythm.

The current guidelines, based mainly on the results of the SPAF trials, which showed no difference in stroke risk between intermittent and sustained AF,<sup>19</sup> recommend similar antithrombotic strategies for AF patients based on risk stratification of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, without considering the AF type.<sup>5</sup> However, our pooled result of RCTs demonstrated that the AF type is a significant predictor for thromboembolism, and it might hence be helpful in risk stratification or for improvement of risk prediction if combined with other risk factors in the current risk prediction models.

Paroxysmal AF has not received as much attention as sustained AF, mainly due to its lack of symptoms and difficulty of detection.<sup>7</sup> Recent efforts have been made to improve its detection, including advances in prolonged Holter (24 hours to 7 days) monitoring, automatic or patient-activated event loop recorders, and insertable cardiac monitors.<sup>7–9,40–44</sup> Nonetheless, despite these diagnostic improvements, few studies have specifically focused on the comparison of antithrombotic therapy for paroxysmal AF. Although dose-adjusted warfarin, compared with aspirin, has been demonstrated to significantly decrease stroke and cardiovascular events independent of the AF type in a prior meta-analysis in 2002,<sup>45</sup> the appearance of novel antiplatelet agents (eg, clopidogrel) and NOACs have resulted in the choice of antithrombotic prophylaxis for paroxysmal AF patients becoming more complicated. Herein, we were unable to detect significant difference in the efficacy or safety between anticoagulation and antiplatelet therapy for paroxysmal AF, although anticoagulation showed favorable efficacy for sustained AF. Of note, our pooled data of the anticoagulation and antiplatelet comparison included only 2 trials (ACTIVE W and AVERROES)<sup>21,22</sup> with 2714 patients having paroxysmal AF, in which 1 used warfarin and 1 used a NOAC (apixaban) for anticoagulation, and 1 used a combination of aspirin plus clopidogrel and 1 used aspirin alone for antiplatelet treatment. The combination of apixaban with warfarin, and aspirin plus clopidogrel with aspirin alone in our analysis might be considered unreasonable, but post-hoc analysis of the ARISTOTLE trial<sup>16</sup> suggested that for the paroxysmal AF patients, apixaban was not superior to warfarin either for stroke prevention or major bleeding reduction and also

the ACTIVE A trial<sup>46</sup> showed a similar effect of aspirin with clopidogrel and aspirin alone for stroke prevention in this AF group. Besides our pooled result showing no difference, sensitive analysis of the ACTIVE  $W^{21}$  or the AVERROES trial<sup>22</sup> 1 consistently did not reveal the superiority of warfarin or apixaban over aspirin plus clopidogrel or aspirin for paroxysmal AF (both 95% CIs crossed 1). The low event rate of the study outcome may have been due to appropriate management of the associated stroke risk factors under supervision in these large clinical trials. Paroxysmal AF is at significant risk of stroke, relative to patients without AF,<sup>39</sup> and our data do not support withholding anticoagulation in these patients. Further, our result of the nonsignificant difference between anticoagulation and antiplatelet agents in paroxysmal AF may be controversial, but we consider that the optimal antithrombotic strategy for this AF form awaits investigation. We call for the ongoing or coming trials of the antithrombotic drugs for AF to further compare their effect and safety with regard to AF type.

As paroxysmal AF has been suggested to be a potential cause for patients with cryptogenic ischemic stroke<sup>7,8</sup> or ESUS,<sup>6</sup> implementing optimal antithrombotic prophylaxis is essential for secondary stroke prevention. Our study mainly showed the treatment effect for primary, rather than secondary stroke prevention, since only 33.3% and 29.6% of paroxysmal and sustained AF patients, respectively, had a previous history of stroke or transient ischemic attack or systemic embolism. Thus, the optimal treatment choice for secondary stroke prevention in patients with paroxysmal AF remains unknown. The outcomes of 2 ongoing large trials (Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source [RE-SPECT ESUS, NCT02239120] and Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source [NAVIGATE ESUS, NCT02313909]), investigating the efficacy and safety of dabigatran etexilate and rivaroxaban with aspirin in patients recently diagnosed as having ESUS, may help provide insight into the effects of anticoagulation (NOACs) and antiplatelet (aspirin) therapy for paroxysmal AF and provide guidance in the antithrombotic choice.

## LIMITATIONS

There are several limitations to the present study. We could not provide clear conclusion of the superiority of anticoagulation or antiplatelets for paroxysmal AF, as there were far few patients with paroxysmal AF in the 2 included studies, and the event rate was low. Moreover, because we did not have access to the individual patient data for the included trials, our statistical analysis was performed at the study level, resulting in some incompleteness in the baseline characteristics and outcome assessment data. Several baseline characteristics were significantly different between the paroxysmal and sustained AF patients, despite the CHADS<sub>2</sub> score being evenly distributed; however, multivariate analysis of the associations between risk factors and outcomes and sub-analysis of paroxysmal AF according to risk score cannot be performed in study-level analyses. The CHA2DS2-VASc score is preferred to the CHADS<sub>2</sub> score for stroke risk stratification of AF, but the difference of CHADS<sub>2</sub> score rather than the CHA<sub>2</sub>DS<sub>2</sub>-VASc was assessed herein, as the CHA2DS2-VASc score was not widely used during the ongoing period of these RCTs. Besides, there were 4 agents of NOACs and 2 different antiplatelet regimens (Aspirin 81-324 mg/d; Clopidogrel 75 mg/d + aspirin aspirin 75-100 mg/d) among the included trials, so that clinical heterogeneity should be taken into consideration for the pooled result. Lastly, while the type of AF was determined at the time of enrollment by the local investigators according to at least 2 documented ECGs and previous medical history, the burden of paroxysmal AF is heterogeneous and it may progress to persistent or permanent AF during follow-up. The incidence of embolic complications has been reported to greatly rise (from 2.7% to 13.3%) during the first year after paroxysmal transition to sustained  $AF^{12}$ ; however, in an intention-to-treat analysis, this would only strengthen our finding that paroxysmal AF patients carry a lower thromboembolic risk compared with sustained AF patients, as the increased events were calculated in the paroxysmal AF group.

#### CONCLUSIONS

In conclusion, among non-valvular AF patients with  $\geq 1$  risk factor for stroke receiving either anticoagulation (NOACs or warfarin) or antiplatelet agents, paroxysmal AF patients consistently showed a reduced risk of stroke or systemic embolism and comparable risk of major bleeding as compared with sustained AF patients. The AF type might be helpful in risk stratification for antithrombotic prophylaxis determination. Anticoagulation, especially NOACs, may represent the optimal antithrombotic choice for sustained AF. However, for those with paroxysmal AF, the best therapeutic strategy between diversified anticoagulant or antiplatelet agents awaits further confirmation.

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