

## CLINICAL RESEARCH

# Efficacy and Safety of Novel Oral Anticoagulants in Patients With Atrial Fibrillation and Heart Failure

## A Meta-Analysis

Gianluigi Savarese, MD,<sup>a,b</sup> Robert P. Giugliano, MD, SM,<sup>c</sup> Giuseppe M.C. Rosano, MD, PhD,<sup>d,e</sup> John McMurray, MD,<sup>f</sup> Giulia Magnani, MD,<sup>c</sup> Gerasimos Filippatos, MD, PhD,<sup>g</sup> Santo DelleGrottaglie, MD, PhD,<sup>h,i</sup> Lars H. Lund, MD, PhD,<sup>b</sup> Bruno Trimarco, MD, PhD,<sup>a</sup> Pasquale Perrone-Filardi, MD, PhD<sup>a</sup>



### JACC: HEART FAILURE CME

This article has been selected as the month's *JACC: Heart Failure* CME activity, available online at <http://www.acc.org/jacc-journals-cme> by selecting the CME tab on the top navigation bar.

#### Accreditation and Designation Statement

The American College of Cardiology Foundation (ACCF) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The ACCF designates this Journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit(s)*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

#### Method of Participation and Receipt of CME Certificate

To obtain credit for *JACC: Heart Failure* CME, you must:

1. Be an ACC member or *JACC* subscriber.
2. Carefully read the CME-designated article available online and in this issue of the journal.
3. Answer the post-test questions. At least 2 out of the 3 questions provided must be answered correctly to obtain CME credit.
4. Complete a brief evaluation.
5. Claim your CME credit and receive your certificate electronically by following the instructions given at the conclusion of the activity.

**CME Objective for This Article:** After reading this article, the reader should be able to discuss: 1) The epidemiology of atrial fibrillation (AF) in heart failure (HF) patients; 2) present available data regarding novel oral anticoagulant (NOAC) use in HF patients with AF; and 3) the implications of these data related to clinical practice and future research.

**CME Editor Disclosure:** Editor-in-Chief Christopher O'Connor, MD, FACC, has received consultant fees/honoraria from AbbVie, Inc., Actelion Pharmaceuticals Ltd., Bayer, Bristol Myers Squibb, Cardiorientis, Merco & Co., Inc., ResMed, and Roche Diagnostics; and ownership interest in Biscardia, LLC. Executive Editor Mona Fuizat, PharmD, FACC, has received research support from ResMed, Gilead, Critical Diagnostics, Otsuka, and Roche Diagnostics. Tariq Ahmad, MD, MPH, has received a travel scholarship from Thoratec. Robert Mentz, MD, has received a travel scholarship from Thoratec; research grants from Gilead; research support from ResMed, Otsuka, Bristol-Myers Squibb, AstraZeneca, Novartis, and GlaxoSmithKline; and travel related to investigator meetings from ResMed, Bristol-Myers Squibb, AstraZeneca, Novartis, and GlaxoSmithKline. Adam DeVore, MD, has received research support from the American Heart Association, Novartis Pharmaceuticals, Thoratec, and Amgen.

**Author Disclosures:** Daiichi-Sankyo provided support for the ENGAGE AF-TIMI 48 Trial with a grant to the Brigham and Women's Hospital. Dr. Giugliano has received honoraria for CME lectures from with Daiichi Sankyo and Merck; honoraria for consulting from the American College of Cardiology, Boehringer-Ingelheim, Pfizer, Bristol-Myers Squibb, Daiichi-Sankyo, Pfizer, and Portola. Dr. Filippatos is a member of the steering committee of trials sponsored by Bayer, Novartis, and Vifor. Dr. Lund has received speaker or consulting honoraria from St. Jude, Novartis, Bayer, Vifor Pharma, and HeartWare; and research grants to his institution from Boston Scientific, Medtronic, and AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**Medium of Participation:** Print (article only); online (article and quiz).

#### CME Term of Approval

Issue date: November 2016

Expiration date: October 31, 2017

From the <sup>a</sup>Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy; <sup>b</sup>Cardiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; <sup>c</sup>TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; <sup>d</sup>Cardiovascular and Cell Sciences Research Institute, St. George's University, London, United Kingdom; <sup>e</sup>IRCCS San Raffaele Pisana, Rome, Italy; <sup>f</sup>Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; <sup>g</sup>Athens University Hospital Attikon, Athens, Greece; <sup>h</sup>Villa dei Fiori, Acerra, Napoli, Italy; and the <sup>i</sup>Mount Sinai Medical School, New York City, New York. Daiichi-Sankyo provided support for the ENGAGE AF-TIMI 48 trial with a grant to the Brigham and Women's Hospital. Dr. Giugliano has received honoraria for CME lectures from Daiichi Sankyo and Merck; honoraria for consulting from the American College of Cardiology,

# Efficacy and Safety of Novel Oral Anticoagulants in Patients With Atrial Fibrillation and Heart Failure

## A Meta-Analysis

Gianluigi Savarese, MD,<sup>a,b</sup> Robert P. Giugliano, MD, SM,<sup>c</sup> Giuseppe M.C. Rosano, MD, PhD,<sup>d,e</sup> John McMurray, MD,<sup>f</sup> Giulia Magnani, MD,<sup>c</sup> Gerasimos Filippatos, MD, PhD,<sup>g</sup> Santo Dellegrottaglie, MD, PhD,<sup>h,i</sup> Lars H. Lund, MD, PhD,<sup>b</sup> Bruno Trimarco, MD, PhD,<sup>a</sup> Pasquale Perrone-Filardi, MD, PhD<sup>a</sup>

### ABSTRACT

**OBJECTIVES** This study investigated the efficacy and safety of novel oral anticoagulants (NOACs) in patients with atrial fibrillation (AF) and heart failure (HF) by a meta-analysis.

**BACKGROUND** AF is quite prevalent in patients with HF.

**METHODS** Four phase III clinical trials comparing NOACs to warfarin in patients with AF were included. Each patient was defined as affected by HF according to the criteria of the trial in which the patient was enrolled. Pre-specified outcomes were the composite of stroke/systemic embolism (SSE); major, intracranial, and any bleeding; and cardiovascular (CV) and all-cause death.

**RESULTS** A total of 55,011 patients were enrolled, 26,384 (48%) with HF, and 28,627 (52%) without HF; 27,518 receiving NOACs and 27,493 receiving warfarin (median, 70 years of age; 36% females; follow-up: 1.5 to 2.8 years). Rates of SSE (relative risk [RR]: 0.98; 95% confidence interval [CI]: 0.90 to 1.07;  $p = 0.68$ ) and major bleeding (RR: 0.95; 95% CI: 0.88 to 1.03;  $p = 0.21$ ) were comparable in patients with and without HF. HF patients had reduced rates of any (RR: 0.86; 95% CI: 0.81 to 0.91;  $p < 0.01$ ) and intracranial (RR: 0.74 95% CI: 0.63 to 0.88;  $p < 0.01$ ) bleeding but increased rates of all-cause (RR: 1.70 95% CI: 1.31 to 2.19;  $p < 0.01$ ) and CV death (RR: 2.05 95% CI: 1.66 to 2.55;  $p < 0.01$ ). NOACs, compared with warfarin significantly reduced SSE and major, intracranial, and any bleeding, regardless of the presence or absence of HF ( $p_{\text{interaction}} > 0.05$  for each).

**CONCLUSIONS** Patients with AF and HF had increased mortality but reduced rates of intracranial and any bleeding compared with the no-HF patients, with no differences in rates of SSE and major bleeding. NOACs significantly reduced SSE, major bleeding, and intracranial hemorrhage in HF patients. No interactions in efficacy and safety of NOACs were observed between AF patients with and without HF. (J Am Coll Cardiol HF 2016;4:870-80) © 2016 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) is highly prevalent (up to 41%) in patients with heart failure (HF) (1), and the combination of HF and AF is steadily increasing (2).

HF is considered a major risk factor for thromboembolic (3,4) and bleeding risk (5,6) in patients with AF and is included in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (7). In addition, HF is widely recognized as a risk factor for reduced time in therapeutic range (TTR) in AF

patients taking warfarin-based anticoagulation therapy (8,9), which may contribute to excess thromboembolic and bleeding risk in AF patients with HF.

Novel oral anticoagulants (NOACs), due to their more predictable therapeutic effect and more favorable hemorrhagic risk profile, represent a particularly attractive therapeutic option in AF patients with concomitant HF. However, currently, no randomized clinical trials assessing the efficacy and safety of

Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Pfizer, and Portola. Dr. Filippatos is a member of the steering committee of trials sponsored by Bayer, Novartis, and Vifor. Dr. Lund has received speaker or consulting honoraria from St Jude, Novartis, Bayer, ViforPharma, and HeartWare; and research grants to his institution from Boston Scientific, Medtronic and AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 21, 2016; revised manuscript received June 3, 2016, accepted July 7, 2016.

## ABBREVIATIONS AND ACRONYMS

**AF** = atrial fibrillation  
**CI** = confidence interval  
**CV** = cardiovascular  
**HF** = heart failure  
**NOACs** = novel oral anticoagulants  
**NYHA** = New York Heart Association  
**RR** = relative risk  
**SSE** = stroke and systemic embolism  
**TTR** = time in therapeutic range

NOACs in HF patients with AF have been conducted, and only subgroup analyses from the 4 major NOAC phase III clinical trials reporting data for HF patients that have not enough statistical power to investigate less frequent events (i.e., intracranial bleeding) are available (10-13). Notably, Ruff et al. (14), in a recent meta-analysis, evaluated the relative efficacy and safety of NOACs across clinically relevant patient subgroups, but no data for patients with AF and concomitant HF were reported. Xiong et al. (15) reported in another meta-analysis a significant reduction of thromboembolic events and major bleeding with high-dose NOACs compared with warfarin in HF patients.

SEE PAGE 881

There was a similar incidence of both major bleeding and thromboembolic events in AF patients with and without HF treated with NOACs, but in this study, data from the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial (13) were not available for most of the outcomes and subanalyses.

Thus, the aim of the present analysis was to assess the efficacy and safety of NOACs in patients with AF and HF enrolled in all phase III NOACs clinical trials and to detect whether the efficacy and safety of NOACs differed between AF patients with and without HF.

## METHODS

**STUDY SELECTION.** The current analysis included the 4 major phase III randomized clinical trials comparing NOACs to warfarin in patients with AF: ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, comparing apixaban, a direct factor Xa inhibitor, with warfarin (10); the RE-LY (Randomized Evaluation of Long Term Anticoagulation Therapy) trial, comparing dabigatran, a direct inhibitor of thrombin, with warfarin (11); the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial (12); and the ENGAGE AF-TIMI 48 study, comparing edoxaban, a direct factor Xa inhibitor, with warfarin (13).

**DATA EXTRACTION AND QUALITY ASSESSMENT.** Two reviewers (G.S. and P.P.F.) independently selected

potentially eligible trials. Discrepancies were resolved by consensus. From each study, information about the inclusion criteria, year of publication, number of patients in treatment and control arms, duration of follow-up, age, sex, cardiovascular (CV) risk factors, prior myocardial infarction or coronary artery disease, CHADS<sub>2</sub> score, New York Heart Association (NYHA) functional class and baseline medications were abstracted by one author (G.S.) and checked by another author (P.P.F.). Pre-specified outcomes for the current analysis were the composite of stroke and systemic embolism (SSE), major bleeding, intracranial bleeding, any bleeding, CV mortality, and all-cause death. These data were abstracted for subgroups of patients with and without HF and randomized to NOACs or warfarin and were available in published articles for apixaban (10), dabigatran (11), and rivaroxaban (12), whereas they were obtained directly from authors for edoxaban, as the analyses of patients stratified by HF in ENGAGE AF-TIMI 48 were still not published at the time of the current meta-analysis. Patients were reported to be affected or not by HF according to the different definitions used by the trials in which they were enrolled (Table 1).

In 2 of 4 trials, 2 different dosages of NOACs (dabigatran, 110 and 150 mg twice daily, in RE-LY; and edoxaban, 30 or 60 mg once daily, in ENGAGE AF-TIMI 48) were compared to those of warfarin (11,13). In order not to merge the effects of different doses, we performed a meta-analysis including the higher dose arms of the RE-LY (11) and ENGAGE AF-TIMI 48 (13) studies together with the single-dosage arms of the ARISTOTLE (apixaban, 5 mg twice daily) (10) and ROCKET AF (rivaroxaban, 20 mg once daily) (12) trials.

Some outcome data were not available for the secondary analyses: all-cause and CV mortality were not reported in the ARISTOTLE and RE-LY HF subgroups (10,11), respectively. In the ROCKET AF HF substudy, major bleeding was not reported, and major or nonmajor clinically relevant bleeding was used instead of any bleeding (12).

Methodological quality of trials was assessed by the Detsky method, scoring the following items: method of randomization: 1 point; adequate description of method of randomization: 2 points; blindness: 2 points; adequate description of outcome: 1 point, and of outcome assessment: 2 points; inclusion/exclusion criteria: 2 points; number of patients excluded and reasons: 2 points; description of therapy in treatment and control groups: 4 points; and appropriateness of statistical analysis: up to 5 points (16).

**TABLE 1** Baseline Characteristics of Trials Included in the Analysis

	ARISTOTLE		ENGAGE AF		RE-LY		ROCKET AF		TOTAL		HF vs. No HF
	HF	No HF	HF	No HF	HF	No HF	HF	No HF	HF	No HF	p Value
Year	2013		2015		2013		2013				
Treatment	Apixaban 5 mg twice daily		Edoxaban 60 mg once daily		Dabigatran 150 mg twice daily		Rivaroxaban 20 mg once daily				
FUP, yrs	1.5		2.8		2.0		1.94		NA		NA
Patients, %	5,943	8,728	8,145	5,926	3,263	8,835	9,033	5,138	26,384	28,627	NA
Females, %	33	35	38	38	34	39	39	40	36	38	<0.01
Age, yrs	69	71	70	75	68	73	72	74	70	73	0.03
CHADS <sub>2</sub>	2.46	1.88	3.00	2.60	2.65	2.00	3.70	3.15	2.95	2.41	0.22
Hypertension, %	83	90	94	93	75	80	93	86	86	87	<0.01
Diabetes, %	26	25	31	44	27	22	42	35	31	31	1.00
Prior MI/CAD, %	22	11	15	8	32	26	22	10	23	14	<0.01
NYHA functional classes I-II, %	57	NA	78	NA	NA	NA	69	NA	68	NA	NA
NYHA functional classes III-IV, %	23	NA	22	NA	NA	NA	31	NA	25	NA	NA
Aspirin, %	33	30	31	29	NA	NA	31	25	32	28	<0.01
Detsky quality score	100%		100%		95%		100%		100%		NA
Definition of HF	Symptomatic congestive HF within 3 months with reduced or preserved ejection fraction		Current presence or history of HF class C or D according to the AHA/ACC definition*		Presence of NYHA class II or higher HF symptoms within 6 months in patients with history of previous admission for HF		Left ventricular ejection <40%		NA	NA	NA

\*ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2005;112:154-235.

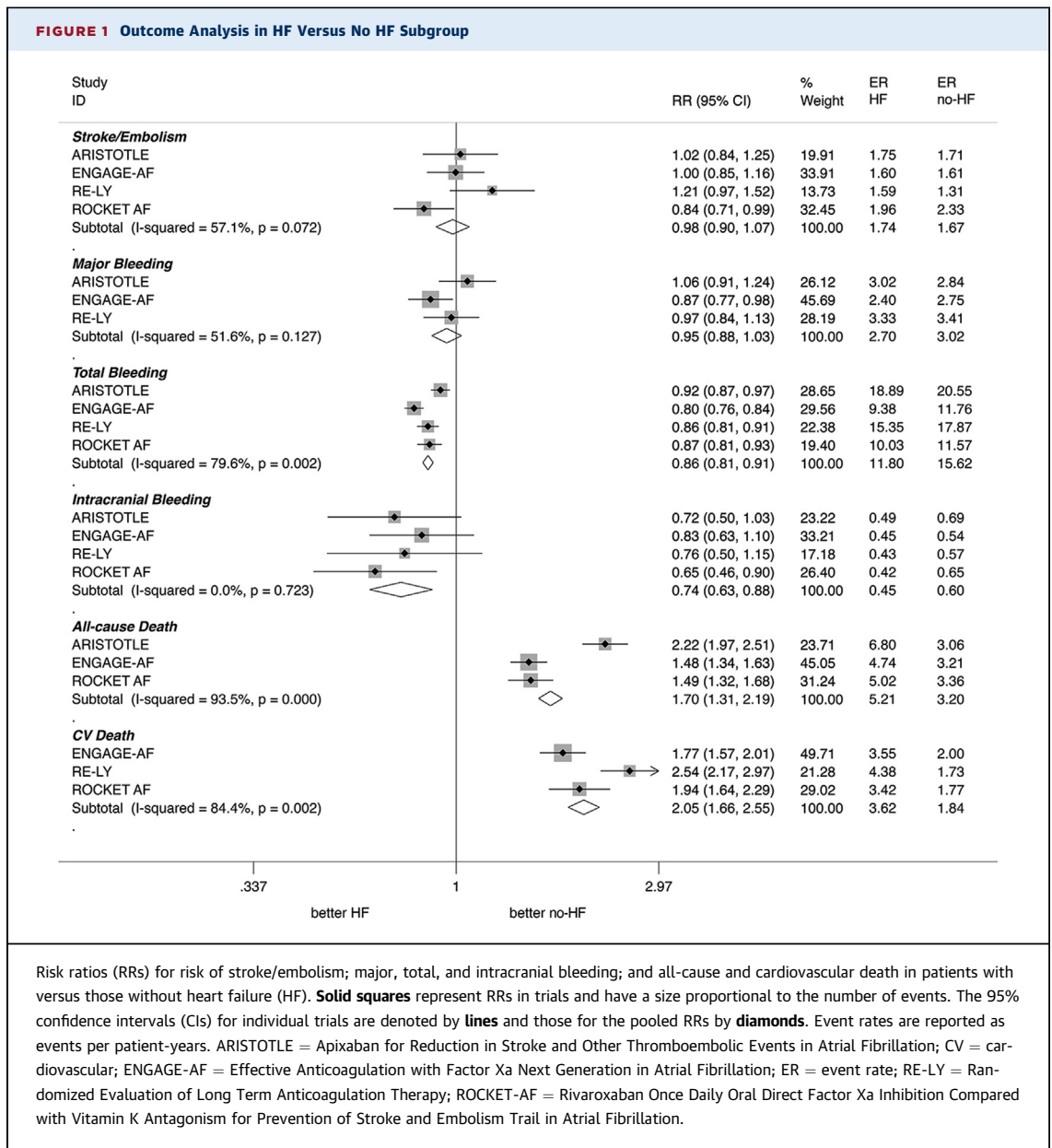
ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CAD = coronary artery disease; ENGAGE-AF = Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation; FUP = follow-up; HF = heart failure; MI = myocardial infarction; NA = not available; NYHA = New York Heart Association; 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 Trial in Atrial Fibrillation.

**STATISTICAL ANALYSIS.** Relative risks (RR) of the outcomes in HF versus no-HF patients and of effects of randomized treatments were calculated using the metan routine (version 12.0 software, StataCorp LLC, College Station, Texas) to account for the probability of events occurring in the treatment group versus the control group (17). RR and 95% confidence interval (CI) for each outcome were separately calculated for each trial, with grouped data, using the intention-to-treat principle (18). Pooled RRs were logarithmically transformed and weighted for the inverse of variance. Overall estimates of effect were calculated with a fixed-effects model or with a random effects model when heterogeneity could not be explained. The assumption of homogeneity between the treatment effects in different trials was tested using Q statistic and further quantified by I<sup>2</sup> statistic. A significant heterogeneity was defined by a p value of <0.05 at Q statistic; i<sup>2</sup> values ranging from 0% to 40% indicated unimportant heterogeneity, 30% to 60% represented moderate heterogeneity, 50% to 90% indicated substantial heterogeneity, and 75% to 100% represented considerable heterogeneity (19). The significance

level for all outcome and heterogeneity analyses was set at a p value ≤0.05.

**SENSITIVITY ANALYSIS.** To explore the influence of potential effect modifiers on outcomes, weighted random effects metaregression analysis was performed with the metareg command (version 12.0, Statacorp) to test demographic characteristics of the study population, duration of follow-up, CV risk factors, New York Heart Association (NYHA) functional class, CHADS<sub>2</sub> score, and concomitant medications (20). For all metaregression analyses, the weight used for each trial was the inverse of the sum of the within-trial variance and the residual between trial variance. Additionally, the residual maximum likelihood methods were used to explain residual heterogeneity not explained by potential effect modifiers, including an additive between-study variance component Tau<sup>2</sup> (21).

Because the main analysis was performed by pooling the trials with a single-dose arm (ARISTOTLE and ROCKET AF) together with the higher dose arm of the trials assessing 2 different doses of the same drug (RE-LY and ENGAGE AF-TIMI 48), further analysis



was performed in HF patients, also including the lower dose arms.

## RESULTS

**CHARACTERISTICS OF INCLUDED TRIALS.** The 4 trials included in analyses of 55,011 subjects, 26,384 with HF, of whom 13,251 were treated with NOACs and 13,133 with warfarin, and 28,627 without HF, of whom 14,267 were treated with NOACs and 14,360 with warfarin (Figure 1). The median follow-up ranged

from 1.5 to 2.8 years across the 4 trials. Characteristics of patients with and without HF are reported in Table 1. Patients with HF on average were younger and less likely to be female and hypertensive but had higher rates of diabetes and prior myocardial infarction or coronary artery disease.

**METHODOLOGICAL QUALITY.** The median Detsky score was 100%, meaning that the quality of the trials included in the meta-analysis was very high. All trials satisfied all Detsky method items, except for RE-LY, which was not double-blinded.

**Outcome analysis: HF versus no HF subgroup.** A total of 1.74 SSEs per 100 patient-years were reported in HF patients compared with 1.67 in subjects without HF; thus, the rates of SSE in patients with HF were comparable to those in patients without HF ( $p = 0.68$ ) (Figure 1). Similarly, 2.70 major bleedings per 100 patient-years occurred in HF patients and 3.02 in subjects without HF, with no differences between the subgroups ( $p = 0.21$ ).

Both the rates of intracranial bleeding (0.45 vs. 0.60 per 100 patient-years;  $p < 0.01$ ) and any bleeding (11.80 versus 15.62 per 100 patient-years;  $p < 0.01$ ) were significantly lower in patients with HF than in patients without HF. Rates of CV death (3.62 vs. 1.84 per 100 patient-years;  $p < 0.01$ ) and all-cause death (5.21 vs. 3.20 per 100 patient-years;  $p < 0.01$ ) were approximately 2-fold significantly higher in HF patients than in patients without HF.

**TREATMENT ANALYSIS: EFFECTS OF NOACs IN HF VERSUS NO HF SUBGROUPS.** No differences in treatment effect were detected between HF and no-HF patients for SSE ( $p = 0.23$ ), major bleeding ( $p = 0.09$ ), intracranial bleeding ( $p = 0.32$ ), any bleeding ( $p = 0.99$ ), CV death ( $p = 0.11$ ), and all-cause mortality ( $p = 0.13$ ) (Figure 2).

**Effects of NOACs in HF patients.** In patients with HF, NOACs significantly reduced the rate of SSE by 14.4% ( $p = 0.01$ ), major bleeding by 23.2% ( $p < 0.01$ ), intracranial bleeding by 57.3% ( $p < 0.01$ ), and any bleeding by 11.6% ( $p = 0.02$ ) compared with warfarin. CV and all-cause death rates were not significantly different between NOAC- and warfarin-treated patients ( $p = 0.11$  and  $p = 0.08$ , respectively) (Figures 2 and 3).

**Effects of NOACs in patients without HF.** NOACs significantly reduced the rate of SSE by 23.1% ( $p < 0.01$ ), major bleeding by 12.2% ( $p = 0.01$ ), and intracranial bleeding by 49.0% ( $p < 0.01$ ) compared with warfarin. Rates of any bleeding were numerically lower with NOACs, but this did not meet statistical significance ( $p = 0.054$ ). NOACs significantly reduced both CV and all-cause death by 19.2% ( $p = 0.02$ ) and 14.7% ( $p = 0.04$ ), respectively, compared with warfarin (Figures 2 and 4).

**Sensitivity analysis.** In ROCKET AF (12), major or nonmajor clinical relevant bleeding was used instead of any bleeding, as the latter was not available. For this reason, we also excluded data from ROCKET AF in a sensitivity analyses of the outcome of any bleeding, and results were confirmed in HF versus no-HF analysis and within the HF subgroup. Within the no-HF subgroup, after the removal of data from ROCKET AF, NOACs significantly reduced the risk of

any bleeding by 14.1% (RR: 0.86; 95% confidence interval [CI]: 0.77 to 0.96; comparison  $p = 0.01$ ; heterogeneity  $p < 0.01$ ;  $i^2 = 88.3\%$ ).

In a metaregression analysis, no relevant effect modifiers were identified that influenced the findings of the meta-analysis (Online Table 1).

When lower dose arms of RE-LY and ENGAGE AF-TIMI 48 trials were also included in the analyses assessing the effects of NOACs on outcomes in HF population (3,979 patients in edoxaban, 30 mg once daily, arm of ENGAGE AF-TIMI 48 trial and 1,641 patients in dabigatran, 110 mg twice daily, arm of RE-LY trial), NOACs significantly reduced the risk of major bleeding by 27.3% (RR: 0.73; 95% CI: 0.62 to 0.85); comparison  $p < 0.01$ ; heterogeneity  $p = 0.04$ ;  $i^2 = 61.1\%$ ), total bleeding by 12.8% (RR: 0.87; 95% CI: 0.80 to 0.95; comparison  $p < 0.01$ ; heterogeneity  $p < 0.01$ ;  $i^2 = 78.3\%$ ), and intracranial bleeding by 58.1% (RR: 0.42; 95% CI: 0.32 to 0.54; comparison  $p < 0.01$ ; heterogeneity  $p = 0.257$ ;  $i^2 = 24.7\%$ ), without any effect on risk of SSE (RR: 0.94; 95% CI: 0.85 to 1.04;  $p$  comparison = 0.241;  $p$  heterogeneity = 0.120;  $i^2 = 42.8\%$ ) and CV death (RR: 0.94; 95% CI: 0.86 to 1.02;  $p$  comparison = 0.123;  $p$  heterogeneity = 0.824;  $i^2 = 0.0\%$  [data for edoxaban, 30 mg once daily, were missing]). Data for all-cause mortality in RE-LY and for edoxaban, 30 mg once daily, were not available; therefore, this outcome analysis could not be performed.

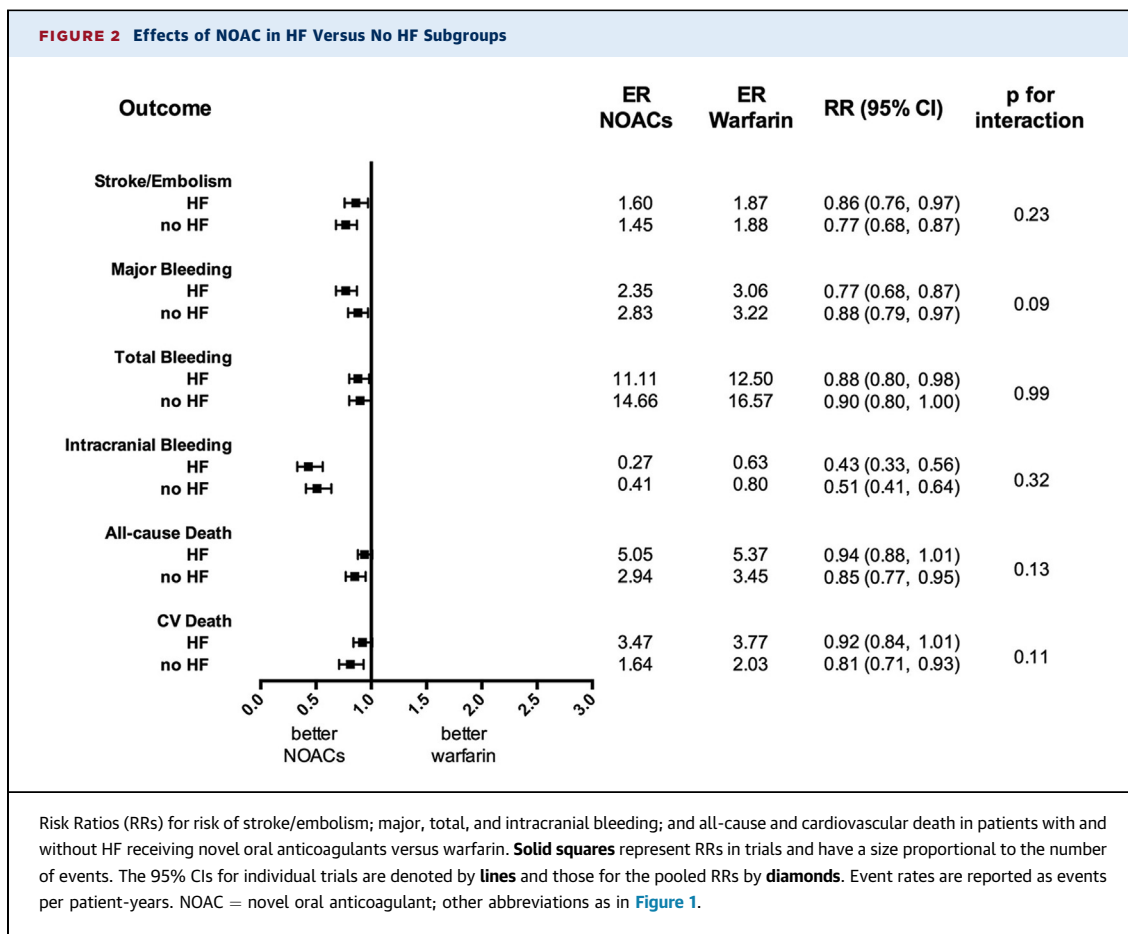
## DISCUSSION

The findings of the present study indicate that NOACs, compared with warfarin, significantly reduce the risk of SSE as well as the risk of major, intracranial, and any bleeding in AF patients regardless of the presence or absence of HF.

### THROMBOEMBOLIC AND BLEEDING RISK IN PATIENTS WITH AF AND HF.

Current guidelines include HF among the factors to be summed in the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc risk scores (7), even though the evidence that HF is associated with a higher thromboembolic risk in patients with AF is reported in some studies (3,4) but not in others (6,22,23). In fact, this apparent discrepancy needs to be interpreted with caution, taking into account the different enrollment criteria adopted in the studies. In ARISTOTLE and ROCKET AF, no differences in cardioembolic or bleeding risk were observed between patients with and without HF, although a higher mortality was reported (10,12). In addition, in both of those trials (10,12), no interaction was observed between ejection fraction and SSE risk. However, patients enrolled in



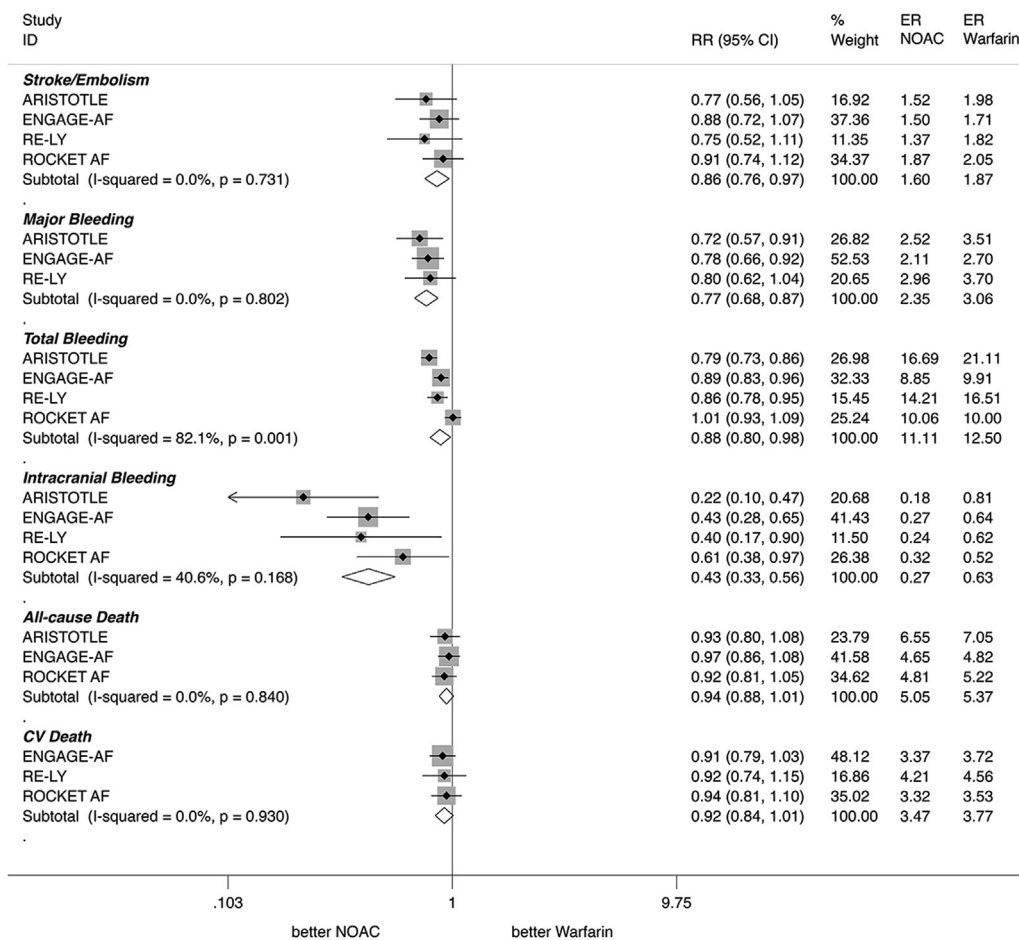


the ROCKET AF trial were at substantially higher stroke risk than patients in the other NOAC trials, which might have diluted the prognostic impact of HF (12). In the RE-LY trial, although the rate of SSE was numerically higher in patients with HF than in those without HF, after multivariate adjustment for baseline characteristics, the risk of SSE was similar among patients with and without HF, whereas in the same analysis, HF was an independent risk factor for CV death (11). In contrast to other NOAC phase III trials, in ENGAGE AF-TIMI 48, significantly higher SSE and bleeding risks were observed in patients with HF, after adjustment for other confounders (13). In our analysis summarizing all the data from the 4 major NOAC clinical trials, we found no differences in the risk of either thromboembolic or major bleeding events between patients with versus those without a history of HF, but an increased mortality was present in patients with HF.

It is important to recognize that HF is associated with an increased likelihood of a suboptimal TTR in AF patients treated with vitamin K antagonists (8,9). Because inadequate control of the level of

anticoagulation increases the risk of thromboembolic events, bleeding, and death, this might by itself contribute to increased risk in HF patients with AF (9,13). In fact, a recent meta-analysis of all 4 major NOAC versus warfarin trials reported a greater reduction in bleeding risk with NOACs in patients enrolled at centers with a median TTR <66% (14). In RE-LY, patients with HF, compared with those without HF, showed a significantly lower rate of any bleeding, whereas no significantly reduced rate of intracranial bleeding in patients with HF was observed in RE-LY, ARISTOTLE, and ROCKET AF (10-12). In our analysis, the rates of intracranial and of any bleeding were significantly lower in patients with HF than in patients without. This counterintuitive finding might be explained in part by the enrollment criteria of NOAC clinical trials, in which patients with HF, compared with those without HF, were younger, had a lower prevalence of hypertension, and, consequently, had lower blood pressure values that might explain in particular the reduced rates of intracranial bleeding in these patients.

**FIGURE 3** Effects of NOACs in HF Subgroup



Risk Ratios (RRs) for risk of stroke/embolism; major, total, and intracranial bleeding; and all-cause and cardiovascular death in patients with HF receiving novel oral anticoagulants versus warfarin. **Solid squares** represent RRs in trials and have a size proportional to the number of events. The 95% CIs for individual trials are denoted by **lines** and those for the pooled RRs by **diamonds**. Event rates are reported as events per patient-years. Abbreviations as in [Figures 1 and 2](#).

Finally, the absence of differences in the risk of either thromboembolic or bleeding events shown in our meta-analysis between patients with and those without a history of HF does not deny the unfavorable impact of HF and could be explained by the enrollment criteria used in the 4 NOAC trials. In fact, to be enrolled in these trials, patients needed to have AF plus only 1 additional risk factor, including HF. This resulted in a selection bias among patients without HF, as other major risk factors for SSE were needed for participation in the trials, which might have obscured the impact of HF on SSE and bleeding risk. In addition, all patients in these trials received anticoagulation therapy, whether they had HF or not, and that might have attenuated any difference

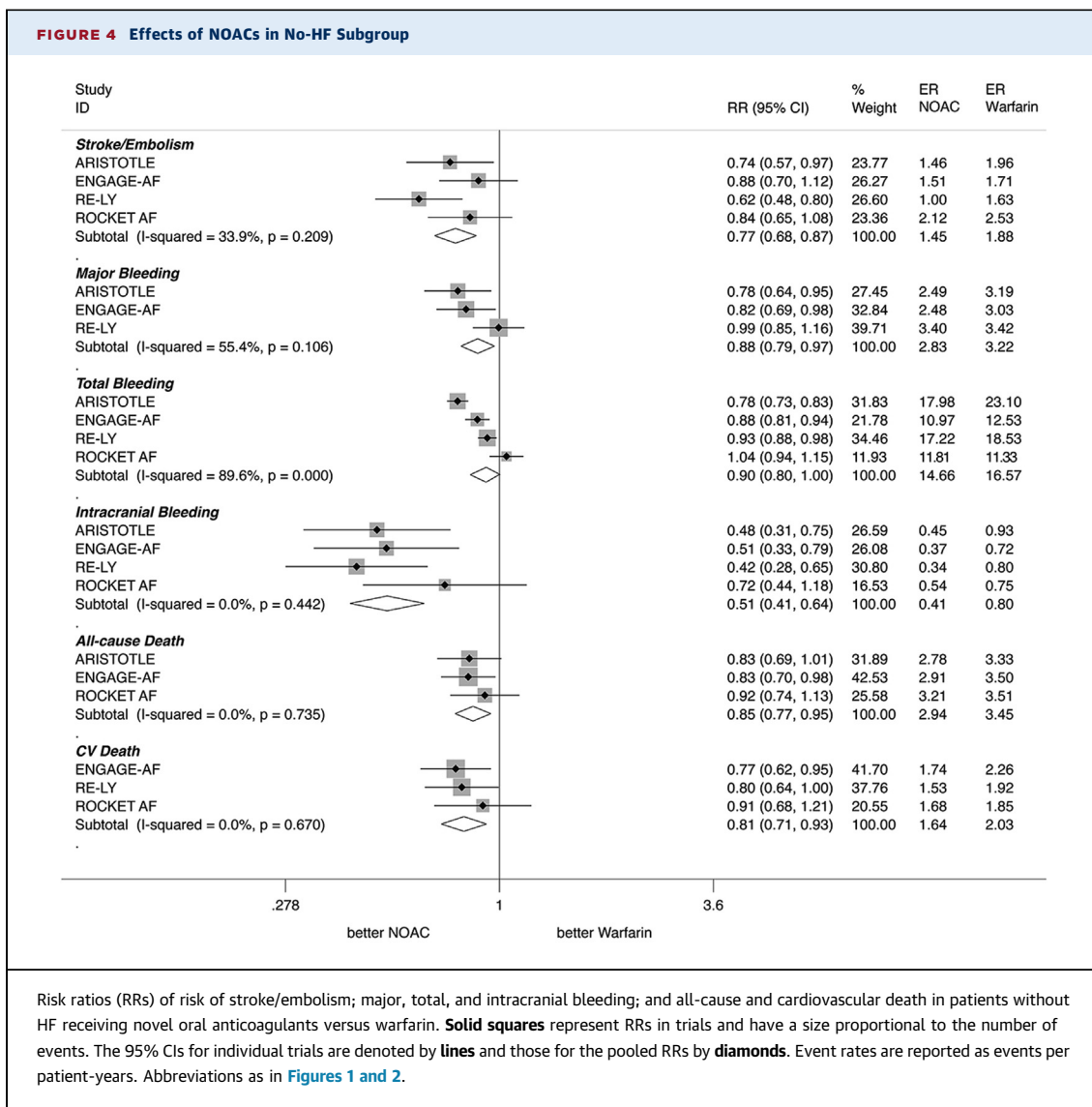
in thromboembolic and bleeding related to HF status.

**EFFICACY AND SAFETY OF NOACs IN HF VERSUS NO-HF PATIENTS.** This meta-analysis of HF patients enrolled in the 4 major trials on NOACs allowed us to investigate the overall effects of these drugs on major efficacy and safety end points.

In these 4 trials, NOACs achieved efficacy and safety outcomes that were at least as good as warfarin in patients with HF.

In the main ARISTOTLE trial, apixaban significantly reduced the risk of SSE compared with warfarin, and the subgroup analysis comparing patients with HF with reduced ejection fraction to





patients without HF demonstrated no significant interaction between treatments and subgroups (10). Risks of intracranial, major, and total bleeding were significantly reduced by apixaban compared with warfarin in the main trial and to a similar degree in subgroups stratified by HF, with no evidence of subgroup by treatment interaction for these safety endpoints (10).

In RE-LY, no differences in treatment efficacy were reported between HF and no-HF subgroups (11). In both the patients with and those without HF, intracranial and any bleeding were significantly reduced by dabigatran, 150 mg twice daily, whereas no differences were observed between dabigatran and warfarin for major bleeding (11).

In ROCKET AF, rivaroxaban compared with warfarin did not significantly reduce the risks of SSE, bleeding, CV death, or overall mortality in patients with or in patients without HF (12).

In ENGAGE AF-TIMI 48, edoxaban, 60 mg, was similar to warfarin for the prevention of thromboembolism, regardless of the presence or absence of prior HF. In addition, edoxaban significantly reduced CV death and CV hospitalization even in patients with severe HF. Regardless of HF severity, edoxaban significantly reduced the risk of major bleeding and intracranial hemorrhage compared with warfarin (13).

Our analysis shows that NOACs, compared with warfarin, significantly reduced the risks of SSE, major

and intracranial bleeding, and any bleeding in patients with HF, with no significant interactions with patients without HF. Furthermore, when the lower dosage arms of RE-LY (11) and ENGAGE AF-TIMI 48 (13) were also included in the analysis, NOACs were still shown not to be inferior to warfarin in reducing the risk of SSE but superior in reducing the risk of bleeding in AF patients with HF. Thus, NOACs represent a valuable and preferable alternative to warfarin in this clinical setting. The current meta-analysis confirms and expands the previous study performed by Xiong et al. (15). The inclusion of data from ENGAGE AF-TIMI 48 and the evaluation of other outcome data not reported in the previous meta-analysis complement the previous analysis and further strengthen the efficacy and safety of NOACs in HF patients.

**STUDY LIMITATIONS.** The current meta-analysis has some limitations to acknowledge. First, the studies included in the analysis were not prospectively designed to assess the efficacy and safety of NOACs in patients with HF versus without HF. Consequently, the definitions of HF varied across trials, and this could have led to consider patients with similar characteristics as affected by HF in some trials but not in others, with the possibility of introducing a bias in the analysis. Additionally, our analyses were based on aggregate trial-level data and not on patient-level data. However, we performed meta-regression to assess for potential confounding by differences in baseline characteristics in patients with versus without HF, and the results were similar. Because we did not have patient-level data, we could not perform subgroup analyses to assess the impact of treatment in relation to relevant clinical characteristics, including TTR, level of left ventricular dysfunction, renal impairment, or other comorbid conditions commonly observed in HF patients. It is also important to acknowledge that our results cannot be

generalized to the overall AF population with HF but may be applied only to patients showing similar characteristics to those enrolled in NOACs randomized clinical trials. Finally, the J-ROCKET study (24), even if it was a phase III trial randomizing AF patients to NOAC (rivaroxaban) versus warfarin, was not included in the analysis because it would have been the only trial with a smaller sample size and enrolling patients in just 1 country, leading to the possibility of including a bias and generating heterogeneity in our analysis.

## CONCLUSIONS

In HF patients NOACs significantly reduced the risks of SSE and bleeding events, including major bleeding and intracranial hemorrhage, compared with warfarin. No interaction in the efficacy or safety profile of NOACs compared with warfarin was present in patients with versus those without HF.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Pasquale Perrone-Filardi, Department of Advanced Biomedical Sciences, Federico II University, Via Pansini, 5-I-80131-Naples, Italy. E-mail: [fperron@unina.it](mailto:fperron@unina.it).

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** AF patients with HF enrolled in NOAC clinical trials have reduced rates of any and intracranial bleeding, but increased rates of all-cause and CV death. NOACs, compared with warfarin, significantly reduce SSE and major, intracranial, and any bleeding in AF patients regardless of the presence or absence of HF.

**TRANSLATIONAL OUTLOOK:** NOACs represent a valuable and preferable alternative to warfarin in HF clinical setting.

## REFERENCES

1. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol* 2003;91:2D-8D.
2. Ling LH, Kistler PM, Kalman JM, Schilling RJ, Hunter RJ. Comorbidity of atrial fibrillation and heart failure. *Nat Rev Cardiol* 2016;13:131-47.
3. Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation. II. Echocardiographic features of patients at risk. *Ann Intern Med* 1992;116:6-12.
4. Agarwal M, Apostolakis S, Lane DA, Lip GY. The impact of heart failure and left ventricular dysfunction in predicting stroke, thromboembolism, and mortality in atrial fibrillation patients: a systematic review. *Clin Ther* 2014;36:1135-44.
5. DiMarco JP, Flaker G, Waldo AL, et al. Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 2005;149:650-6.
6. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J* 2012;33:1500-10.
7. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;33:2719-47.
8. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR. Patient characteristics associated with oral anticoagulation control: results of the Veterans Affairs Study to Improve

Anticoagulation (VARIA). *J Thromb Haemost* 2010;8:2182-91.

9. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAME-TT<sub>2</sub>R<sub>2</sub> score. *Chest* 2013;144:1555-63.

10. McMurray JJ, Ezekowitz JA, Lewis BS, et al. Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Circ Heart Fail* 2013;6:451-60.

11. Ferreira J, Ezekowitz MD, Connolly SJ, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and symptomatic heart failure: a subgroup analysis of the RE-LY trial. *Eur J Heart Fail* 2013;15:1053-61.

12. van Diepen S, Hellkamp AS, Patel MR, et al. Efficacy and safety of rivaroxaban in patients with heart failure and nonvalvular atrial fibrillation: insights from ROCKET AF. *Circ Heart Fail* 2013;6:740-7.

13. Magnani G, Giugliano RP, Ruff CT, et al. Efficacy and safety of edoxaban compared with warfarin in patients with atrial fibrillation and heart failure: insights from ENGAGE AF-TIMI 48. *Eur J Heart Fail* 2016 Jun 28 [Epub ahead of print].

14. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral

anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955-62.

15. Xiong Q, Lau YC, Senoo K, Lane DA, Hong K, Lip GY. Non-vitamin K antagonist oral anticoagulants (NOACs) in patients with concomitant atrial fibrillation and heart failure: a systemic review and meta-analysis of randomized trials. *Eur J Heart Fail* 2015;17:1192-200.

16. Detsky AS, Naylor CD, O'Rourke K, McGeer AJ, L'Abbé KA. Incorporating variations in the quality of individual randomized trials into meta-analysis. *J Clin Epidemiol* 1992;45:255-65.

17. Sharp S, Sterne J. Meta-analysis. *Stata Technical Bulletin Reprints* 1998;7:100-108. Available at: <http://www.stata.com/products/stb/journals/stb16.pdf>. Accessed August 11, 2016.

18. Whitehead A. *Meta-Analysis of Controlled Clinical Trials*. Chichester, England: John Wiley & Sons Inc; 2002.

19. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. Identifying and measuring heterogeneity. Available at: <http://handbook.cochrane.org/>. Accessed March 11, 2016.

20. Sharp SJ. Meta-analysis regression. *Stata Technical Bulletin* 1998;42:16-22. Available at: <http://www.stata.com/products/stb/journals/stb42.pdf>. Accessed August 11, 2016.

21. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999;18:2693-708.

22. Olesen JB, Lip GY, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011;342:d124.

23. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007;69:546-54.

24. Hori M, Matsumoto M, Tanahashi N, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation—the J-ROCKET AF study. *Circ J* 2012;76:2104-11.

---

**KEY WORDS** atrial fibrillation, heart failure, meta-analysis, novel oral anticoagulants, trials

---

**APPENDIX** For a supplemental table, please see the online version of this article.

---



Go to <http://www.acc.org/jacc-journals-cme> to take the CME quiz for this article.