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REVIEW

# Non-vitamin K antagonist oral anticoagulants and heart failure

## *Anticoagulants oraux directs et insuffisance cardiaque*

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*Abbreviations:* AF, atrial fibrillation; $CHADS_2$, Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled); $CHA_2DS_2$-VASc, Cardiac failure, Hypertension, Age ≥ 75 (Doubled), Diabetes, Stroke (Doubled) — Vascular disease, Age 65—74 and Sex category (Female); CI, confidence interval; HF-PEF, heart failure with preserved ejection fraction; HF-REF, heart failure with reduced ejection fraction; HF, heart failure; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; NYHA, New York Heart Association.

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**Summary** Thromboembolism contributes to morbidity and mortality in patients with heart failure (HF), and atrial fibrillation (AF) is one of the main factors promoting this complication. As they share many risk factors, HF and AF frequently coexist, and patients with both conditions are at a particularly high risk of thromboembolism. Non-vitamin K antagonist oral anticoagulants (NOACs) are direct antagonists of thrombin (dabigatran) and factor Xa (rivaroxaban, apixaban and edoxaban), and were designed to overcome the limitations of vitamin K antagonists. Compared with warfarin in non-valvular AF, NOACs demonstrated non-inferiority with better safety, most particularly for intracranial haemorrhages. Therefore, the European Society of Cardiology guidelines recommend NOACs for most patients with non-valvular AF. Subgroups of patients with both AF and HF from the pivotal studies investigating the safety and efficacy of NOACs have been analysed and, for each NOAC, results were similar to those of the total analysis population. A recent meta-analysis of these subgroups has confirmed the better efficacy and safety of NOACs in patients with AF and HF — particularly the 41% decrease in the incidence of intracranial haemorrhages. The prothrombotic state associated with HF suggests that patients with HF in sinus rhythm could also benefit from treatment with NOACs. However, in the absence of clinical trial data supporting this indication, current guidelines do not recommend anticoagulant treatment of patients with HF in sinus rhythm. In conclusion, recent analyses of pivotal studies support the use of NOACs in accordance with their indications in HF patients with non-valvular AF.


**MOTS CLÉS**
Antivitamine K ;
Fibrillation atriale ;
Insuffisance cardiaque ;
Accident vasculaire cérébral

**Résumé** Les complications thromboemboliques contribuent à la morbidité et à la mortalité des patients insuffisants cardiaques (IC) et la fibrillation atriale (FA) en est un des principaux facteurs. Partageant de nombreux facteurs de risque, l'IC et la FA sont fréquemment associées et les patients ayant les deux maladies ont un risque thromboembolique particulièrement élevé. Les anticoagulants oraux directs (AOD) sont des antagonistes directs de la thrombine (dabigatran) et du facteur Xa (rivaroxaban, apixaban et edoxaban) ; ils ont été développés dans le but de pallier les inconvénients des antivitamine K. Comparés à la warfarine, les AOD ont démontré leur non-infériorité en cas de FA non valvulaire ainsi que leur meilleure tolérance, en particulier en diminuant significativement les hémorragies intracrâniennes. Les recommandations de la Société européenne de cardiologie les préconisent en première intention chez la plupart des patients avec une FA non valvulaire. Les sous-groupes de patients avec FA et IC issus des études pivots des AOD ont été analysés et, pour chaque AOD, les résultats sont comparables à ceux observés pour l'ensemble de la population analysée. Une méta-analyse récente de ces sous-groupes confirme la meilleure efficacité et tolérance des AOD chez les patients avec FA non valvulaire et IC, avec en particulier une réduction de 41 % des hémorragies intracrâniennes. L'état prothrombotique associé à l'IC suggère que les patients IC en rythme sinusal pourraient également bénéficier d'un traitement par AOD. Cependant en l'absence de résultats d'études cliniques en faveur de cette indication, les recommandations actuelles ne conseillent pas l'utilisation d'un traitement anticoagulant chez les patients IC en rythme sinusal. En conclusion, des analyses récentes des études pivots sont en faveur de l'utilisation des AOD, en accord avec leurs indications, chez les patients IC avec une FA non valvulaire.

## Background

Heart failure (HF) is a frequent and severe condition with poor outcome [1]. In developed countries, 1—2% of the adult population has HF, and prevalence increases with age [2]. Thus, in an European study, the prevalence of HF was 1% in the group aged 55—64 years, 3% for 65—74 years, 7% for 75—84 years and > 10% in patients aged > 85 years [3]; similar findings were reported in the USA [4]. The 5-year survival rate is approximately 50%, and is much lower for the oldest patients [5]. Among the complications of HF, it is well-recognized that patients have an increased risk of thromboembolic events; both systemic and venous thromboembolism may occur. Currently, European and American guidelines recommend the prescription of anticoagulation only in patients with HF and atrial fibrillation (AF), in patients with a previous thromboembolism and in patients with cardiac thrombi [1,6]. Non-vitamin K antagonist oral anticoagulants (NOACs) have been extensively studied in non-valvular AF in four pivotal trials, but not specifically in HF. However, a substantial proportion of patients included in these trials have both conditions. In this review, we will successively address the issues of the extent of thromboembolism in HF, the relationship between HF and AF, the use of NOACs in HF with non-valvular AF and, finally, we will also discuss the use of anticoagulants in HF patients in sinus rhythm, and the potential place of NOACs in the prevention of venous thromboembolism.

## Thromboembolism in HF

In patients with HF, the risk of thromboembolism is multifactorial. Low cardiac output through dilated cavities of poor contractility, regional wall motion abnormalities, abnormal endocardial surface after myocardial infarction and AF are the main factors inducing blood stasis and formation of clots [7]. Thromboembolism contributes to the morbidity and mortality of patients with HF. The incidence of thromboembolism has been extensively studied in both single-centre studies and large-scale therapeutic trials, and is about 2% per year taking into account only peripheral and pulmonary embolism [8]; these figures do not include coronary atherothrombotic events in ischaemic HF. In the Rotterdam study, the risk of ischaemic stroke was increased more than 5-fold (age- and sex-adjusted hazard ratio [HR]: 5.79) in the first month after diagnosis of HF, but returned to normal within 6 months after the onset of HF [9]. The reported risks of stroke have a high degree of variability between studies. In a meta-analysis of studies in chronic HF, the risk of stroke was reported to be 18 per 1000 patients during the first year after the diagnosis of HF; this risk increased to 47 per 1000 after 5 years [10]. Comparing these rates with the annual ischaemic stroke rate of the Rochester Minnesota experience, the authors concluded that among patients with HF the rate of ischaemic stroke is markedly higher than in the general population, and is slightly higher than in patients with AF who are receiving anticoagulation. Melgaard et al., using data from a Danish cohort, recently reported that the risk of ischaemic stroke in HF patients without AF who were not on anticoagulant therapy rose from 1.5% for a $CHA_2DS_2$-VASc (Cardiac failure, Hypertension, Age $\geq$ 75 [Doubled], Diabetes, Stroke [Doubled] — Vascular disease, Age 65—74 and Sex category [Female]) score of 1 to 7% for a score of 6 [11].

HF also predisposes to venous thromboembolism, and is an important risk factor for in-hospital death. Without thromboprophylaxis, venous thromboembolism proven by venography occurred in 10—22% of hospitalized patients with HF [12]. Pulmonary embolism may be the primary cause of death in 3—10% of patients with HF [13]. HF is also a strong independent predictor of death within 30 days in patients with venous thromboembolism [12]. In practice, the European guidelines on acute HF state that thromboembolism prophylaxis (e.g. with low-molecular-weight heparin) is recommended in patients not already anticoagulated and with no contraindication to anticoagulation, in order to reduce the risk of deep vein thrombosis and pulmonary embolism [1].

## HF and AF: a dangerous combination

AF is the most common heart rhythm disorder in the elderly, and has important consequences in terms of morbidity, mortality and healthcare costs. As with HF, the prevalence of AF rises exponentially with age: 0.12—0.16% in subjects aged < 49 years; 3.7—4.2% in those aged 60—70 years; and 10—17% in subjects aged > 80 years [14]. As a consequence, AF and HF frequently coexist, and the burden of AF and HF is expected to increase with population ageing. Indeed, both conditions share common risk factors: older age, hypertension, diabetes mellitus, valvular heart disease and ischaemic heart disease [15]. Moreover, from a pathophysiological point of view, it is also well known that HF and AF beget one another: HF is associated with increased left ventricular filling pressures contributing to left atrial dilatation and AF. On the other hand, the loss of atrial systole associated or not with tachycardia impairs left ventricular filling and contributes to HF [16].

The reported prevalence of AF in various HF series ranges from 13% to 27% [17], and increases with rising severity of HF; thus, patients with New York Heart Association (NYHA) functional class I symptoms have an AF prevalence of $\leq$ 4% versus $\sim$ 40% in patients with class IV symptoms [6]. In a French study, 24.1% of patients hospitalized in 2005—2008 for AF (as the principal or associated diagnosis) also had HF [18].

The Framingham study showed that patients with AF or HF who subsequently develop the other condition have a poor prognosis, regardless of which condition came first [17]. In this study, AF preceded HF about as often as HF preceded AF. In a French observational survey constituting a single-day snapshot of all unplanned hospitalizations because of acute HF in 1658 patients (72% with history of chronic HF), AF was one of the main precipitating factors (24%), along with infection (27%) [19].

HF increases the risk of stroke and systemic embolism in AF, and this appears to be largely independent of the type and severity of HF [20]. In a systematic literature review to assess the effect of HF in patients with AF, Agarwal et al. [21] recently reported that in studies in which HF was based on a clinical diagnosis, HF independently increased stroke/systemic embolism in five of 13 studies, conferring a

1.6-fold to 3.1-fold increase in risk. When HF was defined as impaired left ventricular function, the additive risk was evident in four of six studies, with a 1.7-fold to 2.6-fold increase in the risk of stroke/systemic embolism.

Before the development of persistent or permanent AF, multiple episodes of paroxysmal AF can occur in patients with HF. Often these AF episodes are asymptomatic, making detection of the arrhythmia unreliable via conventional detection methods. The interrogation of cardiac implanted devices has shown in several trials that more than 20—27% and up to 42% of patients with severe congestive HF thought to be persistently in sinus rhythm were having episodes of asymptomatic paroxysmal AF [22—24]. As paroxysmal AF is more prevalent than persistent AF in patients with acute stroke or transient ischaemic attack [25], these results raise the question of the need for a more extensive diagnostic effort to detect these episodes, in order to prevent the occurrence of ischaemic stroke more efficiently. The AF burden threshold that confers an increased risk of thromboembolism is not precisely defined. In a pooled analysis of five prospective studies including > 10,000 relatively unselected patients with an implanted cardiac device and no history of permanent AF, daily AF burden is associated with an increased risk of ischaemic stroke and transient ischaemic attack; among the evaluated thresholds, 1 hour was associated with the highest HR for ischaemic stroke [26]. Although there was no information in this analysis on the proportion of patients with HF, patients with silent AF could merit consideration for anticoagulation.

**Table 1** Meta-analysis of randomized trials: comparison of the efficacy and safety of non-vitamin K antagonist oral anticoagulants with warfarin in patients with atrial fibrillation [35].

| | Relative risk: NOAC versus warfarin | *P* |
|---|---|---|
| Stroke or embolic events | | |
| RE-LY [31][a] | 0.66 | 0.0001 |
| ROCKET-AF [34][b] | 0.88 | 0.12 |
| ARISTOTLE [33][c] | 0.80 | 0.012 |
| ENGAGE-AF [32][d] | 0.88 | 0.10 |
| Combined | 0.81 | < 0.0001 |
| Efficacy | | |
| Ischaemic stroke | 0.92 | 0.10 |
| Haemorrhagic stroke | 0.49 | < 0.0001 |
| Myocardial infarction | 0.97 | 0.77 |
| All-cause mortality | 0.90 | 0.0003 |
| Safety | | |
| Intracranial haemorrhage | 0.48 | < 0.0001 |
| Gastrointestinal bleeding | 1.25 | 0.043 |

NOAC: non-vitamin K antagonist oral anticoagulant.
[a] Dabigatran 150 mg twice daily.
[b] Rivaroxaban 20 mg once daily.
[c] Apixaban 5 mg twice daily.
[d] Edoxaban 60 mg once daily.

## Prevention of thromboembolism in patients with HF and AF: what is the role of NOACs?

Vitamin K antagonists and antiplatelet agents have, until recently, been the only drugs used in the prevention of thrombosis and thromboembolism. However, the slow onset of action and the narrow therapeutic index of warfarin, along with its multiple drug and diet interactions, have negative effects on safety, compliance and efficacy [27]. It is often challenging to maintain the international normalized ratio within the therapeutic range, and this seems particularly true for patients with HF treated with vitamin K antagonists. Thus, from a subanalysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, history of congestive HF and symptoms of HF were associated with less time in the therapeutic range (61% in history of congestive HF and 58% in symptomatic HF versus 65% in the absence of one of these factors [$P < 0.009$ in the first case and $P < 0.004$ in the second case]) [28]. Also, during congestive HF episodes, HF patients are more sensitive to warfarin because of modification of the metabolism of vitamin K antagonists that can lead to increased haemorrhagic risk [29]. Moreover, the risk of bleeding in the AF population is increased by 43% when associated with HF [30].

In contrast to vitamin K antagonists, NOACs target only one coagulation enzyme: either thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban and edoxaban). These new anticoagulant drugs have recently demonstrated effective and safe protection against stroke and systemic embolism in AF [31—34]. The pivotal studies for the four NOACs were included in a meta-analysis by Ruff et al., which included 42,411 patients who received a NOAC and 29,272 who received warfarin [35]. The rate of stroke or systemic embolic events in patients treated with NOACs was significantly reduced by 19% in comparison with warfarin ($P < 0.0001$). This decrease was mainly related to a reduction in the rate of haemorrhagic strokes (relative risk: 0.49). The rates of all-cause mortality and intracranial haemorrhages were also reduced, but the rate of gastrointestinal bleeding was increased (Table 1).

The arrival of new anticoagulant drugs, together with a better understanding of the stroke risk, led the European Society of Cardiology to revise its recommendations for the management of AF [36]. In the 2012 update [36], the guidelines stated that patients with a $CHA_2DS_2$-VASc score of 1 or greater should be considered for stroke prevention with an oral anticoagulant. Owing to ischaemic and haemorrhagic risks, oral anticoagulation therapy is recommended, preferably with NOACs. Most patients with AF and HF have a $CHA_2DS_2$-VASc score $\geq 2$; for example, in a nationwide prospective cohort study using Danish registries, 93.5% of patients with AF and HF had a $CHA_2DS_2$-VASc score $\geq 2$ [11].

Renal insufficiency is frequently associated with HF [37], and has been identified as a risk factor for major bleeding; it is included in the HAS BLED risk score for bleeding [38]. As NOACs are predominantly excreted by the kidney, they are contraindicated in patients with severe renal impairment (estimated glomerular filtration rate < 30 mL/min). This could be a concern in many patients with HF, as stated

in the latest European guidelines for HF, which recommend serial monitoring of renal function when using NOACs [1]. Therefore, analysis of the subgroups of patients with HF in the four clinical trials of NOACs in AF (RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE-AF) was of paramount importance [39—41]. The baseline characteristics of patients with non-valvular AF patients with or without HF are described in Table 2. Of note, patients with HF and AF in the ROCKET-AF and ENGAGE-AF trials were at high ischaemic risk, with a mean $CHADS_2$ score of $\geq 3$.

The percentages of patients with HF varied from 19% to 64% between studies, according to the different definitions of HF used: ejection fraction < 40% documented by echocardiogram, radionuclide or contrast angiogram in the past 6 months, or symptomatic HF, NYHA class II or higher in the past 6 months for RE-LY; HF or left ventricular ejection fraction < 40% for ROCKET-AF; symptomatic HF within the previous 3 months or left ventricular ejection fraction $\leq 40\%$ for ARISTOTLE; American College of Cardiology/American Heart Association classification Class C (structural heart disease with history of or current symptoms of HF, such as shortness of breath, fatigue, decreased exercise tolerance) or Class D (refractory HF requiring specialized interventions) for ENGAGE-AF.

The outcomes for patients with or without HF are provided on Fig. 1. In these analyses, the efficacy results did not differ from those of the main trials, as described below.

## RE-LY trial [39]

Two fixed doses of dabigatran (110 and 150 mg twice daily) were compared with warfarin in 18,113 patients with AF at increased risk for stroke. For the 4904 patients with HF, annual rates of stroke or systemic embolism were 1.92% for patients on warfarin compared with 1.90% for those on dabigatran 110 mg (HR: 0.99, 95% confidence interval [CI]: 0.69—1.42) and 1.44% for dabigatran 150 mg (HR: 0.75, 95% CI: 0.51—1.10). Annual rates of major bleeding were 3.90% for warfarin versus 3.26% for dabigatran 110 mg (HR: 0.83, 95% CI: 0.64—1.09) and 3.10% for dabigatran 150 mg (HR: 0.79, 95% CI: 0.60—1.03). The rates of intracranial bleeding were significantly lower for both dabigatran dosages compared with warfarin in patients with HF (dabigatran 110 mg: HR: 0.34, 95% CI: 0.14—0.80; dabigatran 150 mg: HR: 0.39, 95% CI: 0.17—0.89). The relative effects of dabigatran versus warfarin on the occurrence of stroke or systemic embolism and major bleeding were consistent among patients with and without HF, and those with low ($\leq 40\%$) or preserved (> 40%) left ventricular ejection fraction. Therefore, the overall benefits of dabigatran for prevention of stroke or systemic embolism and major and intracranial bleeding in comparison with warfarin were similar in patients with and without HF.

## ROCKET-AF trial [42]

A total of 9033 patients were classified as having HF at the time of randomization. The efficacy of rivaroxaban compared with warfarin was similar in patients with HF (1.90 vs. 2.09 per 100 patient-years, respectively) and without HF (2.10 vs. 2.54 per 100 patient-years). The risk of major or non-major clinically relevant bleeding with rivaroxaban was similar to that for warfarin in patients with HF (14.22 vs. 14.02 per 100 patient-years, respectively) and without HF (16.12 vs. 15.35 per 100 patient-years). The rate of haemorrhagic stroke was reduced with rivaroxaban in patients with HF as in the overall trial (HR: 0.38, 95% CI: 0.19—0.76). In patients with HF, the efficacy of rivaroxaban was similar regardless of ejection fraction < 40% or $\geq 40\%$, NYHA class I—II versus III—IV, HF with preserved ejection fraction (HF-PEF) or reduced ejection fraction (HF-REF) or $CHADS_2$ (Cardiac failure, Hypertension, Age, Diabetes, Stroke [Doubled]) score of 2 versus $\geq 3$. It could be concluded that rivaroxaban and warfarin have similar efficacy in patients with both AF and HF.

## ARISTOTLE trial [40]

Patients in this analysis were divided into three groups: patients with left ventricular systolic dysfunction (LVSD) with or without symptoms ($n = 2736$); patients with HF-PEF ($n = 3207$); and patients with no HF symptoms and normal left ventricular function ($n = 8728$). The rates of stroke or systemic embolism were similar in the three groups (1.39, 1.52, and 1.37 per 100 patient-years, respectively). The authors also calculated two composite risks, one including stroke, systemic embolism or death (to take account of competing risks), and the other including stroke, systemic embolism, major bleeding or death (net clinical benefit): the rates of each composite outcome were highest in patients with LVSD (8.06 and 10.46 per 100 patient-years, respectively), intermediate for those with HF-PEF (5.32 and 7.24 per 100 patient-years, respectively), and lowest in patients with no HF/no LVSD (3.46 and 5.27 per 100 patient-years, respectively) ($P < 0.0001$ for each comparison). The rate of each composite outcome was lower in patients treated with apixaban, but statistical significance was not achieved for patients with LVSD and patients with HF-PEF. However, there was no significant interaction between the effect of apixaban and the three subgroups of patients for these two composite endpoints.

## ENGAGE-AF trial [41]

Among the 14,071 patients with documented AF randomized to warfarin or the higher dose of edoxaban (60 mg reduced to 30 mg once daily, approved by European Medicines Agency), 6344 (45%) were in NYHA class I—II and 1801 (13%) were in NYHA class III—IV. Compared with no HF, and after adjustment, the rates of stroke or systemic embolism were higher in mild and severe HF: HR: 1.19, 95% CI: 0.99—1.42 ($P = 0.06$) and HR: 1.45, 95% CI: 1.12—1.88 ($P = 0.004$), respectively. Similarly, compared with the no HF group, the risk of major bleeding was increased in patients with mild or severe HF: HR: 1.24, 95% CI: 1.07—1.43 ($P = 0.004$) and HR: 1.31, 95% CI: 1.05—1.65 ($P = 0.02$), respectively. Compared with warfarin, patients randomized to edoxaban had a similar reduction in the primary endpoint (stroke or systemic embolism) whatever the groups (no HF: HR: 0.87, 95% CI: 0.69—1.11; NYHA I—II: HR: 0.88, 95% CI: 0.69—1.12; NYHA III—IV: HR: 0.83, 95% CI: 0.55—1.25). The rate of haemorrhagic stroke was lower in the edoxaban group in both the no HF and HF groups, but the reduction was significant only in no HF patients (no HF: HR: 0.49, 95% CI: 0.29—0.82; NYHA I—II: HR: 0.64, 95% CI:

**Table 2** Baseline characteristics of patient subgroups with heart failure in pivotal studies of non-vitamin K antagonist oral anticoagulants.

| | RE-LY [39] | | ROCKET-AF [42] | | ARISTOTLE [40] | | | ENGAGE-AF [41] | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Drug | Dabigatran | | Rivaroxaban | | Apixaban | | | Edoxaban[a] | | |
| Definition of HF | NYHA class ≥ II, HF symptoms in the 6 months before screening, in patients with a history of admission for CHF | | HF history or LVEF < 40% | | Two groups of patients with a report of both HF status and LV function: (1) LVSD, defined as LVEF ≤ 40% or report of moderate or severe LVSD; with or without symptomatic HF; (2) HF-PEF; LVEF > 40% | | | HF (stage C or D of ACC/AHA classification) | | |
| | HF (*n* = 4904) (27%) | No HF (*n* = 13,209) (73%) | HF (*n* = 9033) (64%) | No HF (*n* = 51,380) (36%) | LVSD (*n* = 2736) (19%) | HF-PEF (*n* = 3207) (22%) | No LVSD, no HF (*n* = 8728) (59%) | NYHA I—II (*n* = 6344) (45%) | NYHA III—IV (*n* = 1801) (13%) | No HF (*n* = 5926) (42%) |
| Mean age (years) | 68 | 73 | — | — | — | — | — | — | — | — |
| Median age (years) | — | — | 72 | 74 | 68 | 69 | 71 | 70 | 69 | 75 |
| Men (%) | 67 | 62 | 61 | 60 | 79 | 58 | 65 | 63 | 62 | 62 |
| History of MI (%) | NR | NR | 22 | 10 | 28 | 18 | 11 | 14 | 16 | 8 |
| Diabetes (%) | 27 | 22 | 42 | 35 | 27 | 25 | 25 | 30 | 31 | 44 |
| Hypertension (%) | 75 | 80 | 93 | 86 | 75 | 89 | 90 | 94 | 94 | 93 |
| History of stroke or TIA (%) | 17[b] | 24[b] | 43 | 70 | 16 | 17 | 20 | 21 | 23 | 38 |
| Mean $CHADS_2$ score | 2.6 | 2.0 | 3.7 | 3.1 | 2.2 | 2.7 | 1.9 | 3.0 | 3.0 | 2.6 |
| LVEF ≤ 40%[c] (%) | 44 | 11 | 34 | 0 | 86 | 0 | 0 | 45 | 62 | 10 |
| CrCl < 50 mL/min (%) | 21 | 19 | — | — | 18 | 17 | 15 | 18 | 19 | 21 |
| Median CrCl (mL/min) | — | — | 68 | 67 | — | — | — | — | — | — |
| Diuretics (%) | 73 | 43 | 71 | 40 | 73 | 70 | 46 | 70 | 80 | 44 |
| Beta-blockers (%) | 69 | 61 | 70 | 56 | 75 | 69 | 62 | 71 | 73 | 59 |
| ACE inhibitors/ARBs (%) | 57 | 40 | 61 | 42 | 81 | 77 | 66 | 70 | 76 | 59 |

ACC: American College of Cardiology; ACE: angiotensin-converting enzyme; AHA: American Heart Association; ARB; angiotensin receptor blocker; $CHADS_2$: Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled); CHF: congestive heart failure; CrCl: creatinine clearance; HF: heart failure; HF-PEF: heart failure with preserved ejection fraction; LV: left ventricular; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic dysfunction; MI: myocardial infarction; NR: not reported; NYHA: New York Heart Association; TIA: transient ischaemic attack.

[a] For ENGAGE-AF study, only results for the highest dose (European Medicines Agency-approved dose) are reported in this table.

[b] Stroke, TIA, systemic embolism.

[c] < 50% for ENGAGE-AF study.

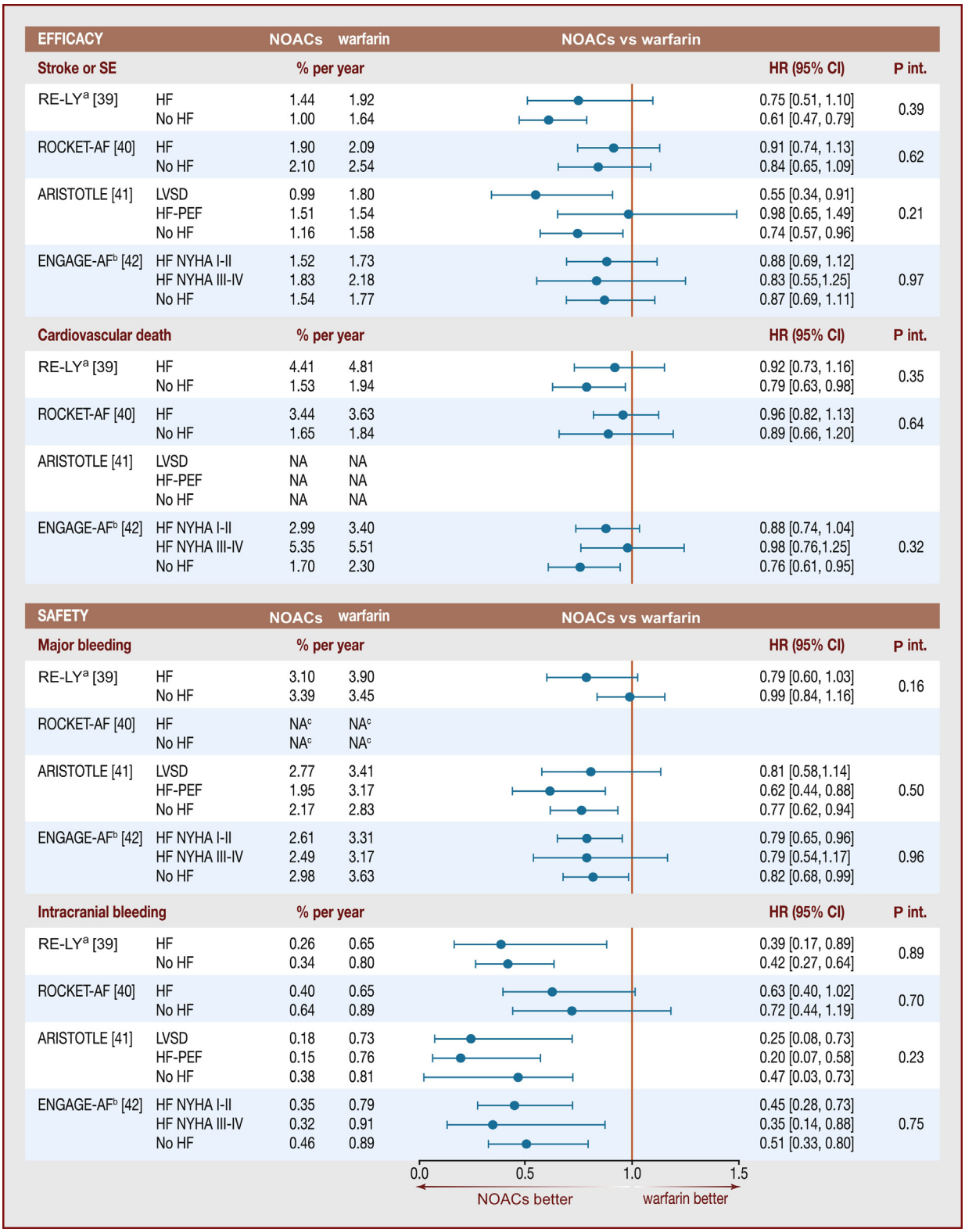


**Figure 1.** Effects of non-vitamin K antagonist oral anticoagulants (NOACs) versus warfarin in patients with or without heart failure (HF) in phase 3 studies. CI: confidence interval; HF-PEF: heart failure with preserved ejection fraction; HR: hazard ratio; LVSD: left ventricular systolic dysfunction; NA: not available; NYHA: New York Heart Association; *P* int: *P*-value for interaction; SE: systemic embolism. [a]For RE-LY study, only results for the highest dose are reported in this table. [b]For ENGAGE-AF study, only results for the highest dose (European Medicines Agency-approved dose) are reported in this table. [c]For ROCKET study, the primary safety endpoint was major or non-major clinically relevant bleeding.

0.38—1.09; NYHA III—IV: HR: 0.40, 95% CI: 0.13—1.29). However, no significant interaction was observed between the effect of edoxaban on the different endpoints and the three groups of patients.

### Comparison of studies: meta-analysis

Recently, Xiong et al. [43] published a meta-analysis with HF subgroups from four randomized trials (RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE-AF). Among 19,122 AF patients with HF treated with NOACs at the European Medicines Agency-approved doses for rivaroxaban, apixaban and edoxaban and dabigatran, only dabigatran 150 mg significantly reduced the risk of stroke/systemic embolism events by 14% (odds ratio 0.86, 95% CI: 0.76—0.98), and the risk of major bleeding by 24% (odds ratio 0.76, 95% CI: 0.67—0.86). In addition, after pooling available data across three trials, there was a 41% significant reduction in intracranial haemorrhages among patients with AF and HF (odds ratio 0.59, 95% CI: 0.40—0.87).

These findings support the use of NOACs as an alternative to warfarin in patients with both AF and HF.

## HF and sinus rhythm: is oral anticoagulation mandatory?

Current knowledge regarding the use of NOACs to prevent thromboembolism risk in patients with HF without known AF remains limited. As a prothrombotic state is associated with HF, it has been suggested that patients with HF with sinus rhythm could also benefit from anticoagulant therapy [44,45]. In a recent Danish cohort [11], it was shown for the first time that the $CHA_2DS_2$-VASc score can predict the risk of ischaemic stroke, thromboembolism and death in patients with HF, whether or not AF is present. In their HF population without AF, patients with a $CHA_2DS_2$-VASc score $\geq 2$ had a stroke rate of 1.5% per year. In patients with HF and a $CHA_2DS_2$-VASc score $\geq 4$, the absolute risk of thromboembolic events was even higher in patients without AF compared with in those with AF.

International guidelines, however, recommend against treatment with anticoagulants in patients with HF in sinus rhythm [1]. These recommendations are based on the results from four randomized controlled trials that assessed the efficacy of warfarin in patients with HF who were in sinus rhythm (WARCEF, WATCH, HELAS and WASH) [46—49]. None of these trials evidenced a decrease in the rate of the combined endpoint of cardiovascular morbidity and mortality in comparison with placebo or aspirin. In the largest trial (WARCEF), a significant decrease in the risk of ischaemic stroke was reported with warfarin (0.72 vs. 1.36 events per 100 patient-years; HR: 0.52, 95% CI: 0.33—0.82; $P < 0.005$) [46]. A similar decrease in stroke (but which did not achieve statistical significance) was reported for warfarin versus aspirin in the WATCH study (HR: 0.58, 95% CI: 0.25—1.3) [47]. The benefit of the reduced rate of strokes in the WARCEF trial was, however, counterbalanced by an increase in the risk of major haemorrhage (1.78 vs. 0.87 events per 100 patient-years; adjusted rate ratio 2.05, 95% CI: 1.36—3.12). The rates of death were the same in both randomized groups (6.5 per 100 patient-years). This absence of a benefit of warfarin in patients with HF suggests that mortality in this setting is perhaps not caused by thromboembolic events but by progression of the disease.

The availability of NOACs has renewed interest in a possible benefit of anticoagulant treatment in patients with HF in sinus rhythm. Only randomized controlled trials with statistical power sufficient for the number of expected events could assess the efficacy of NOACs in preventing stroke in HF patients in sinus rhythm. The on-going COMMANDER-HF study (NCT01877915) will assess the benefit of rivaroxaban in 5000 participants with HF and significant coronary artery disease (i.e. only HF of ischaemic origin), but without AF, for the reduction in rates of death, myocardial infarction and stroke [50]. In addition, as mentioned already, some HF patients could be considered to be in sinus rhythm, but have some silent episodes of paroxysmal AF that could increase their stroke risk.

## HF and prevention of venous thromboembolism complications during hospitalization

Several European and national guidelines, including the French Agency for the Safety of Health Products (ANSM) recommend thromboprophylaxis with heparin, low-molecular-weight heparin, or fondaparinux in hospitalized medical patients, including those with HF [1,51]. Until now, NOACs have been studied in these settings in two studies (MAGELLAN and ADOPT), both of which included some patients with HF. Two other trials are in process: MARINER (NCT02111564) and APEX (NCT01583218). A meta-analysis of MAGELLAN and ADOPT results has shown a benefit of NOACs on efficacy outcome during the prolonged treatment period (HR: 0.79; $P = 0.008$), with an increased risk of major bleeding (HR: 2.69; $P < 0.0001$) [52].

In a subgroup analysis from the MAGELLAN study, concerning hospitalized patients diagnosed with HF ($n = 2593$ patients with NYHA class III—IV), Mebazaa et al. [53] confirmed that more severe HF was associated with an increased risk of venous thromboembolism. Of interest, the association between venous thromboembolism risk and HF severity observed in the enoxaparin/placebo group was not seen in the extended-duration rivaroxaban group, thus suggesting that patients with severe HF could benefit from NOAC treatment. Moreover, these results suggest that N-terminal pro-B natriuretic peptide and D-dimers could allow the identification of patients with a particularly high thrombotic risk [54], who would be suitable for enrolment in future studies aimed at assessing the utility of NOACs in HF.

## Conclusions

Chronic HF is a common and serious disease with an increased risk of ischaemic stroke, sudden death and venous thromboembolism, which contribute to its morbidity and mortality. Oral anticoagulation is well established and successful, and is recommended in evidenced-based guidelines for patients with HF and AF. Similar outcomes for NOACs and warfarin were obtained in patient subgroups with both non-valvular AF and HF in the pivotal studies of NOACs.

The results of the recent meta-analysis of these four pivotal trials confirmed that NOACs in patients with HF and non-valvular AF were more effective (less stroke/systemic embolism) and even safer (fewer cases of intracranial haemorrhage) than vitamin K antagonists [43]. In the absence of evidence so far from specifically designed trials, there is no clinical argument for administering NOACs in patients with HF who are in sinus rhythm. Therefore, these recent analyses support the use of NOACs as an alternative to warfarin in patients with both non-valvular AF and HF.

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