Atrial Fibrillation and Heart Failure: Factors influencing the choice of oral anticoagulant.

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Abstract

Atrial fibrillation (AF) and heart failure (HF) frequently coexist. AF is identified in approximately one third of patients with HF and is linked to increased morbidity and mortality than from either condition alone. AF is relatively more common in HF with preserved ejection fraction (HFpEF) than with reduced ejection fraction (HFrEF). Nevertheless, the risk of stroke and systemic embolism (SSE) is significantly increased with both HF types and the absolute risk is heavily influenced by the presence and severity of associated additional stroke risk factors. The European Society of Cardiology has very recently introduced a third HF subtype entitled HF with mid-range ejection fraction (HFmrEF). At present oral anticoagulation is recommended for all patients with AF and HF, independent of HF type. In addition to warfarin there are currently four non-vitamin K oral anticoagulants (NOACs, previously called novel oral anticoagulants) that have been approved for the prevention of SSE. They consist of one direct thrombin inhibitor, dabigatran and three factor Xa inhibitors: rivaroxaban, apixaban and, most recently, edoxaban. In this review article we present an overview of the evidence to support the use of NOACs for the prevention of SSE in patients with AF and HF and review the influence of HF subtype and co-morbidities on the potential choice of oral anticoagulant.

Introduction

Atrial fibrillation (AF) is the most commonly diagnosed sustained cardiac arrhythmia in adults. With better survival among persons with cardiovascular disease and an aging population, it is becoming an increasing health burden, affecting 2% of those under 65 years old, rising to 9% in those over 65, and 1 in 4 persons over their lifetime. [1-3]. In 2010 over 33 million people worldwide had a diagnosis of AF. [4]

AF frequently co-exists with heart failure (HF) [5]. Of patients diagnosed with AF, over 35% will subsequently be diagnosed with HF and vice versa [5,6]. Both conditions are risk factors for stroke and systemic embolism (SSE), and when combined have much worse outcomes [3,5,7,8]. Where AF and HF coexist, oral anticoagulation is recommended to reduce the associated SSE risk [8,9]. With the availability of an increasing number of Non-Vitamin K Oral Anticoagulants (NOACs, previously known as novel oral anticoagulants) in addition to warfarin the potential choice of oral anticoagulant has significantly broadened. In this article we will examine whether HF subtype influences both stroke risk and choice of oral anticoagulant.

Atrial Fibrillation and Heart Failure

HF and AF share many similar risk factors including hypertension, coronary artery disease and increasing age, accounting to some extent for their frequency of occurrence together. However, HF in itself may predispose to the development of AF, with various proposed

mechanisms including impaired left ventricular filling and atrial remodelling [10,11]. In addition, AF can lead to HF by causing a tachymyopathy, and can worsen the severity of HF symptoms. [9,12,13]. In each condition, the development of the second is associated with increased morbidity and mortality, leading to more frequent, and longer, hospitalisation. [14-16]. The proportion of those with HF who also have AF increases with New York Heart Association (NYHA) class, from 5% in NYHA I to 49% in NYHA IV [17].

Heart Failure Subtypes and Atrial Fibrillation

HF syndrome has traditionally been divided into two broad subtypes by assessment of left ventricular function and ejection fraction (EF): HF with reduced ejection fraction (HFrEF), and HF with preserved ejection fraction (HFpEF, of which diastolic heart failure is a subgroup), with each accounting for approximately half of the HF population depending on the population studied. [18-20]. The European Society of Cardiology has very recently defined a third HF subgroup called HF with mid-range ejection fraction (HFmrEF). This new term refers to patients fulfilling the clinical features (symptoms and signs of heart failure) and a left ventricular ejection fraction of 40-49% with HFpEF referring to an ejection fraction of ≥50% [21]. This group has been included to stimulate future research and better define the grey area around ejection fractions of 40-49% on the fringes of both HFrEF and HFpEF.

Whilst the risk of AF is increased with all types of HF, the relative risk is greater with HFpEF than that for HFrEF reflecting the greater burden of AF risk factors, such as advanced age, obesity and hypertension in the former [18,20, 22-24]. Moreover, recent data has shown that HFpEF is more often characterised by increased LA stiffness and HFrEF by greater eccentric

LA remodelling, further explaining the unequal AF burden between the two HF subtypes [11]. Whilst the rates of SSE, hospitalisation and HF symptom progression appear to be broadly similar in HFpEF and HFrEF with AF, mortality is marginally yet significantly higher in HFrEF [18,25,26]. In fact, in a recently published meta-analysis of >30,000 patients with coexisting AF and HF, it was shown that all-cause mortality was significantly higher in AF with HFrEF (risk ratio [RR] 1.24, 95% CI 1.12-1.36, $p<0.001$) [26].

Stroke Risk in Atrial Fibrillation and Heart Failure

AF is a common risk factor for stroke and systemic embolism (SSE), and has been shown to confer a hypercoagulable state which is heavily influenced by the number and type of associated risk factors [27,28]. AF results in increased thrombotic risk via all components of Virchow's triad: Abnormalities of blood flow (due to reduced atrial kick), the vessel wall (with endothelial injury) and hypercoagulability (activation of platelets and clotting factors) have all been demonstrated in AF [28-30]. The loss of systole within the atria results in comparative stasis, which may be worsened by increased ventricular rate and decreasing left atrial filling with HF [28]. This particularly affects the left atrial appendage (LAA) which is the most common site of thrombus formation [31]. AF confers a five-fold increase in stroke risk across all ages, and it is estimated that with increasing age up to 24% of strokes are secondary to AF, with these tending to be larger strokes with more disabling symptoms and worse outcomes. [3,8]

HF has been shown to be an independent risk factor for stroke in AF and the presence of both conditions together leads to an increase in stroke severity and all-cause mortality [5,7,32,33].

Stroke in HF is most commonly associated with AF, however there is evidence that HF 'per se' even in the absence of AF also confers a hypercoagulable state [34,35]. Data from a recent meta-analysis comparing outcomes of patients with atrial fibrillation and HFrEF versus HFpEF have demonstrated that there were no significant differences in the risk of stroke between the two (RR 0.85, 95% CI 0.70-1.03, p=0.094) [26]. However, there was marked variation in the definitions of HFpEF which varied from a left ventricular ejection fraction of >40% to ≥50%. [26]. Nevertheless this data would suggest that a diagnosis of heart failure is the key determinant of stroke risk rather than subtype and is further supported by real world observational data [36].

Whilst there remains little evidence of any benefit from anticoagulation in lone HF without AF [37,38], the case for anticoagulation in AF is well established [9]. In addition to decreasing the risk of SSE, anticoagulation in patients hospitalised with HF and AF has also been show to result in decreased mortality and readmission rates [39].

Stroke risk in HF was thought to increase with worsening left ventricular (LV) dysfunction (LVSD) [40-43]. However, more recent studies of the HF population have demonstrated no difference in risk of stroke or embolic events associated with either LVSD (mild/moderate/severe) or NHYA class [44,45].

Stroke and bleeding risk scoring in AF and HF

Several scoring systems have been developed to estimate thromboembolic risk associated with AF [27,46]. The CHA_2DS_2VASc assessment is the most widely used system and has been incorporated into the majority of contemporaneous guidelines [8,9]. Within its validation HF was typically defined as either symptomatic HF episode or evidence of LV dysfunction [46]. Given that inclusion could be based on clinical HF without assessment of LV function, it likely that patients with both HFrEF and HFpEF were included.

The benefit of anticoagulation to reduce stroke risk needs to be carefully balanced with the increased risk of bleeding related to oral anticoagulation. Whilst many bleeding risk scoring systems are available, HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly and Drugs/alcohol) is perhaps the easiest to use and has gained the greatest widespread current acceptance [8,9,47,48]. No HAS-BLED score represents an absolute contraindication to anticoagulation, however a score ≥ 3 identifies those at highest bleeding risk and should alert clinicians to address any modifiable bleeding risk factors.

Oral Anticoagulation

Warfarin

Until recently, Vitamin K antagonists (VKAs), principally warfarin, were the primary method of oral anticoagulation in atrial fibrillation. Warfarin has been shown to be more effective than either placebo or single and dual antiplatelet therapy in lowering the risk of stroke

[49,50]. Meta-analysis of randomised controlled trials has shown that warfarin leads to a 64% decrease in the risk of SSE compared to placebo, and 39% compared to antiplatelet agents [49].

Whilst warfarin has been shown to be effective in reducing SSE risk, there are problems in its use. A narrow therapeutic window, slow onset and offset, and multiple food and drug interactions mean that the time spent in therapeutic range is low, undermining its efficacy. [51,52]. This is more of a problem in HF, where patients have been shown to persistently spend less time in therapeutic range than those with AF alone [53]. Other factors often associated with HF such as a high burden of additional medication, and frequent hospital admissions, have also been shown to predict poor INR control [53,54].

Four NOACs have been licensed for use in stroke prevention in patients with non-valvular AF (NVAF). All have fixed doses and do not require regular blood tests for efficacy monitoring and therefore present an attractive alternative to warfarin in terms of ease of use. In addition, they provide a consistent and rapid onset/offset of anticoagulation and lack the number of food and drug interactions that undermine warfarin [9,55]. Their extended licences to include other conditions that not infrequently co-exist with AF such as thromboembolic disease have also further enhanced their use.

Dabigatran

The first of the NOACs to market, dabigatran is the only currently available oral direct thrombin inhibitor. The initial RE-LY trial, published in 2009, compared open label warfarin with two blinded doses of dabigatran, 110mg and 150mg BD [56]. Both doses were shown to be non-inferior to warfarin in prevention of SSE. Subsequently, data for participants with HF have been published in a subgroup analysis. [57].

From a total of 18113 patients in the RE-LY trial, 4904 patients were classified as having HF for subgroup analysis. HF was defined as the presence of NYHA class II or higher symptoms in the six months before screening, in patients with history of previous admission for congestive HF. Within this subgroup, similar findings to the overall trial were found with respect to primary outcomes of SSE and safety with both doses of dabigatran being non-inferior to warfarin with respect to the primary end point of SSE. Annual rates of SSE were 1.92% for warfarin, 1.9% for 110mg dabigatran (hazard ratio (HR) 0.99, 95% confidence interval (CI) 0.69-1.42) and 1.44% for 150mg dabigatran (HR 0.75, 95% CI 0.51-1.10). The rates of major bleeding were also consistent with the main trial and were not influenced by HF symptom class (NYHA II versus III, IV) or type (ejection fraction >40% versus $\leq$40%) (P for interaction not significant). However, intracranial bleeding was significantly lower for both dabigatran dosages compared with warfarin (dabigatran 110 mg vs. warfarin (HR 0.34, 95% CI 0.14–0.80; dabigatran 150 mg vs. warfarin, HR 0.39, 95% CI 0.17–0.89) [57].

As expected the SSE rates were numerically higher in patients with HF irrespective of their allocated treatment (1.75% per year vs. 1.35%) and HF remained as an independent and powerful independent predictor of both vascular death (adjusted HR 2.26, 95% CI 1.96–2.61) and all-cause hospitalization (adjusted HR 1.13, 95% CI 1.07–1.20 per year)

Rivaroxaban

Rivaroxaban is a direct factor Xa inhibitor and the second NOAC to obtain a licence for the prevention of SSE. Its key efficacy data is derived from the ROCKET AF trial [58]. This was an international, multicentre, double blind, double dummy, randomised non-inferiority trial of 20mg OD dosing of rivaroxaban (15mg in defined groups) vs. warfarin in 14,264 patients with NVAF. In ROCKET 9033 (63.7%) patients had HF, which was defined as either a history of HF or a left ventricular EF <40% [59]. Rivaroxaban was noted to be non-inferior to warfarin and its efficacy for SSE prevention was consistent with the main trial in those with HF (1.90 versus 2.09%) and without HF (2.10 versus 2.54%; P-interaction=0.62) [59]. The risk of major or non-major clinically relevant bleeding with rivaroxaban was also similar to warfarin irrespective of HF history (P-interaction=0.99). The significant reduction in haemorrhagic stroke that was observed in the main trial was maintained in those with HF (adjusted HR, 0.38; 95% CI, 0.19-0.76; P-interaction=0.067). Consistent with previously published data the efficacy of rivaroxaban was not influenced by ejection fraction (<40 or ≥ 40%; P-interaction=0.38) or NYHA class (I-II versus III-IV; P-interaction=0.68).

Apixaban

Apixaban is an oral direct factor Xa inhibitor and the third NOAC to be approved for the prevention of SSE in AF. The key evidence in support of apixaban vs. warfarin for the prevention of SSE in AF was from the ARISTOTLE trial, which was a double-blind, double-dummy randomized trial comparing twice daily dosage of 5mg oral apixaban (2.5mg with

key lower dosing criteria) with warfarin, in 18201 patients with AF and $CHADS_2$ Score $\geq$1 [60]. This showed apixaban to be superior to warfarin in preventing SSE, in addition resulting in fewer bleeds and lower mortality [60].

From ARISTOTLE, for patients where EF and HF status were known, three groups were defined. Those with EF >40% and no HF symptoms (n=8728), a group with EF >40% and HF symptoms (n=2971), referred to as HFpEF, and a third group with EF $\leq$40% with or without HF symptoms (n=2736), referred to as left ventricular systolic dysfunction (LVSD) [61]. In patients with LVSD, apixaban was shown to be favourable to warfarin in the primary outcome of SSE (annual rate 0.99% vs. 1.80%, HR 0.55,) and in all other efficacy end points including major, or clinical relevant bleeding (rate 5.05 vs. 6.01%, HR 0.84), ISTH major bleeding (2.77 versus 3.41; HR 0.81), total and intracranial bleeding. Within the HFpEF group, apixaban was comparable or preferable to warfarin in primary outcome, efficacy endpoints and safety outcomes other than gastrointestinal bleeding (rate 1.08% vs. 0.53%, HR 2.03) which was the only endpoint where there was a notable interaction by group (LVSD, HFpEF and no HF) with a higher event rate in the apixaban versus warfarin group (P- interaction 0.043).

Edoxaban

Edoxaban is the most recent oral anticoagulant to the market, and is a direct factor Xa inhibitor. The randomised, double blind, double dummy ENGAGE AF trial published in 2013 compared warfarin with once daily high (60mg down to 30mg) and low (30mg down to 15mg) dose edoxaban in patients with AF and a $CHADS_2$ score of $\geq$2 [62]. Of the 21,205

patients in the ENGAGE-AF Study, 12,124 (57.4%) were recorded to have HF, which was defined as the current presence or prior history of HF class C (structural heart disease with prior or current symptoms or HF such as shortness of breath, fatigue or decreased exercise tolerance) or class D (refractory HF requiring specialised interventions) [63]. Both high dose (annual rate 1.18%, HR 0.79 p<0.001) and low dose (annual rate 1.61%, HR 1.07, p=0.005) edoxaban were shown to be non-inferior to warfarin (annual rate 1.50%) in reducing the primary endpoint of SSE.

The rate of major bleeding was 3.43% in warfarin, 2.75% in high dose edoxaban (HR 0.80, p<0.001) and 1.61% in low dose edoxaban (HR 0.47, p<0.001). The rate of gastrointestinal bleeding was highest in the high dose edoxaban group (1.51%) compared to warfarin (1.23%) but lowest in the low dose edoxaban group (0.82%).

Meta-analysis of NOACs in HF

A recent meta-analysis of the HF subgroups from the four key randomised trials of NOACs for the prevention of SSE endorses their efficacy in HF and consists of 19 122 patients treated with NOAC of which 13 384 receiving single-/high-dose NOAC regimens, and 13 390 who received warfarin. [64]. Although no significant benefit was identified in individual trials, this analysis demonstrated that single/high-dose NOACs significantly reduced the risk of SSE by 14% (Odds ratio, OR 0.86; 95% CI .76-0.98: p=0.02). In addition, these regimens had a 24% lower risk of major bleeding compared to warfarin (OR, 0.76, p<0.00001). Low dose NOACs showed similar reductions in SSE to warfarin and a non-significant decrease in major bleeding risk.

Choice of anticoagulant in heart failure

Current guidelines [8,9] advocate the use of anticoagulation for the prevention of SSE in AF with a CHA_2DS_2-VASc score $\geq$1 (unless 1 is due to female sex alone). Therefore, all patients with HF and AF should be strongly considered for anticoagulation.

The choice of agent in these patients is reliant on multiple factors and it is difficult to make direct comparisons across the four studies given their differences in trial design and study populations. In addition, the published data for all four NOACS in HF is derived from observational data of subgroup analyses with definition of heart failure and available information about ejection fraction and symptoms varying widely, requiring consideration when applying this to patients on an individual basis.

Does HF severity or presentation with HFPEF versus HFREF influence the choice of anticoagulant?

The NOAC trials have included both HFpEF and HFrEF and all categories of NYHA symptomatology. As discussed above, the type of HF does not appear to influence the efficacy of anticoagulants, and therefore the choice of agent. However, there are differences in the usage and risk profile between agents that may come into play in selecting the agent used. Patients with HF will frequently have other indications for anticoagulation that may need to be considered. Patients with the newly defined heart failure category of HFmrEF

[21] have not been studied in clinical practice and represent an avenue for future comparative studies in terms of stroke risk and anticoagulation efficacy in atrial fibrillation.

Valvular heart disease

Valvular heart disease is commonly found in patients with heart failure. Definitions of valvular atrial fibrillation vary among consensus guidelines. The European Heart Rhythm Association EHRA) guidelines refer to AF occurring in the presence of mechanical heart valves, or moderate to severe mitral stenosis (usually of rheumatic origin) [65] whereas the American Heart Association (AHA) and the American College of Cardiology (ACC) guidance includes these categories, but also bioprosthetic valve replacements and mitral valve repair [8]. Patients with significant native valvular disease and prosthetic valves were excluded from the NOAC trials.

Sub-analysis of the ARISTOTLE trial, however, has shown no significant difference in the effect of apixaban compared to warfarin in reducing SSE in those with or without non valvular (mechanical valves and significant mitral stenosis excluded) heart disease (HR 0.7 and 0.84 respectively, P-interaction 0.38) with less bleeding (HR 0.79 and 0.65 respectively, P-interaction 0.23) [66]. This finding in terms of efficacy versus warfarin for the prevention of SSE has also been endorsed by recently published sub-analyses of both the ROCKET and RE-LY studies in which important coexisting valvular disease was identified in 14.1% and 21.8% of the study cohorts respectively [67,68].

At present the EHRA recommends that NOACs should be avoided in patients with mechanical prosthetic valves and moderate-to-severe mitral stenosis where warfarin and oral vitamin K antagonists should be used. In the light of more recent data the EHRA suggests that NOACs can be used in patients with mild-to-moderate other native valvular disease and in severe aortic stenosis. The EHRA also state that NOACs can be used following both mitral valve repair and tissue valve replacements (excluding the first three months post operatively). They also support their use in hypertrophic cardiomyopathy, which is well recognised cause of HF, despite the recognised paucity of data [65].

Patients with concomitant CAD

Coronary artery disease is the leading risk factor for HFrEF and is observed in >50% of patients with HF, independent of subtype. Hence, it is not uncommon for there to be an indication for either single or dual antiplatelet therapy. Whilst it is well established that the concomitant use of any oral anticoagulant with either single or dual antiplatelet therapy dramatically increases bleeding risk the competing needs for both therapies is a not infrequent issue [69]. Phase III Trials looking at the use of NOACs in Acute Coronary Syndromes have demonstrated significantly higher risks of bleeding with both apixaban and rivaroxaban when combined with dual antiplatelet therapy. [70,71]. In the case of rivaroxaban, this effect was seen even with much lower doses (2.5mg BD) than used for the prevention of SSE.

Where there is an indication for anticoagulation for SSE in AF, and separately an indication for single or dual antiplatelet treatment, decisions must be made on an individual patient basis

carefully balancing the thrombotic versus bleeding risks. There is much greater experience with the use of warfarin in combination with dual anti-platelet therapy (triple therapy) than for the NOACs. There are also limited data from clinical trials on the use of NOACs in combination with clopidogrel and even less for newer antiplatelet agents such as prasugrel and ticagrelor. The increased major gastrointestinal bleeding rates observed with both dabigatran and rivaroxaban versus warfarin from RE-LY and ROCKET-AF respectively add to the concern. Despite its more favourable side effect profile, even in the double blinded randomised APPRAISE-2 study, apixaban at the lowest dose of 2.5 mg bd led an important increase in major and clinically relevant non-major bleeding (including gastrointestinal bleeding) versus placebo (hazard ratio, 1.78; 95% confidence interval, 0.91 to 3.48; P=0.09) in patients with acute coronary syndrome. Hence, where triple therapy is necessary use of a proton pump inhibitor is recommended and the period of triple therapy minimised to the shortest period possible without substantially compromising efficacy [65].

Renal dysfunction

Renal dysfunction is commonly found in HF with some epidemiological studies estimating that fewer than 10% of the HFrEF population have normal renal function [72]. The prevalence of renal dysfunction in those with HFpEF is estimated between 30-60% [73,74]. Worsening HF (rising NYHA class) appears to be associated with worsening renal function. There is very limited data on the use of NOACs in patients with creatinine clearance <30 ml/minute, and in most cases warfarin is thought to be preferable [65]. Where the use of a NOAC is felt to be necessary, NOACs with the lowest rate of renal clearance are preferable

and dabigatran should be avoided. Where the estimated creatinine clearance is 15-29 it is the authors preference to use apixaban at 2.5mg BD. [75].

Left ventricular thrombus

Warfarin and the Vitamin K antagonists have been the accepted standard oral anticoagulation in the treatment of left ventricular thrombus with or without atrial fibrillation, despite a paucity of evidence. Where atrial fibrillation and left ventricular thrombus exist it is the authors opinion that NOACs could be considered within their licensed indications (based on the CHA_2DS_2-VASC Sores) however, NOACs should be avoided in the absence of atrial fibrillation.

Reversal agent

An initial concern regarding the use of NOACs was the lack of reversal agent. However, in October 2015 the FDA approved the first reversal agent for dabigatran, idarucizumab. This followed trials demonstrating rapid reversal of anticoagulant effect within minutes both in patients requiring reversal for uncontrollable bleeding, and those where reversal was required for urgent surgery or invasive procedures [76]. The novel factor Xa inhibitor Andexanet has been shown to be highly effective at reversing the effects of both apixaban and rivaroxaban in a recent phase III trial of 67 patients presenting with acute major bleeding within 18 hours after the administration of a factor Xa inhibition. [77].

Concomitant device therapy

A potential additional benefit to NOACs in the context of HFrEF is their use in patients requiring pacemaker or ICD insertion. Their rapid on- and offset of action allows for a short window where the procedure can be carried out without the need for bridging therapy. However, data gathered from centres adopting this approach has shown variability in both timings of discontinuation and rates of bleeding complications [78].

Conclusion

HF and AF frequently coexist and the presence of HF increases the risk of SSE across all HF subtypes. The choice of OAC for the prevention of SSE has greatly increased in recent years and there are currently five agents to choose from with warfarin and four approved NOACs. Overall, the generally more favourable bleeding profile, and ease of use, without the requirement for frequent monitoring, in patients who are likely to already be on a significant number of other medications, favours NOACs for the majority of patients. The choice NOAC is influenced by individual patient circumstances such as concomitant medication, renal function and the familiarity of the prescriber. While heart failure subtype may influence these factors, in itself it is not a determinant for the type of oral anticoagulant recommended.

Table 1 – Distribution of heart failure patients amongst NOAC trials

	Dabigatran	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Trial	Re-LY	ROCKET	ARISTOTLE	ENGAGE AF-TIMI 48
Trial Design	Randomised open label warfarin versus two blinded dabigatran doses	Randomised double-blinded	Randomised double-blinded	Double-blind, double-dummy
Main trial, n	18113	14,264	18201	21105
Oral treatment doses	110mg or 150mg bid	20 mg/15mg od	5mg/2.5 bid	60mg vs. 30mg od
Inclusion criteria	$CHADS_2 \geq 1$*	$CHADS_2 > 2$	$CHADS_2 \geq 1$	$CHADS_2 \geq 2$
HF population, n (%) (% of main study)	4904 (27.1%)	9033 (63.7%)	5943 (32.7%)	12124
-LVEF ≤40%, n (%)	856 (17.5%)	2145 (23.7%)	2736 (46.1%)	NA
NYHA Class				
I	74.3% (I/II)	13.2%	21.2%	78.3% (I/II)
II		55.5%	56.3%	
IIII	25.7% (III/IV)	27.8%	21.5%	21.7% (III/IV)
IV		1.5%	0.9%	

HF, Heart failure; SSE stroke and systemic embolism; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; *aged 65-74 years included if diabetes, hypertension or coronary artery disease; NA, not yet available (unpublished)

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