Ejection fraction and outcomes in patients with atrial fibrillation and heart failure: the Loire Valley Atrial Fibrillation Project

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Received 24 October 2011; revision requested 1 December 2011; accepted 23 December 2011; online publish-ahead-of-print 30 January 2012

Aims
Heart failure (HF) increases the risk of stroke and thrombo-embolism (TE) in non-valvular atrial fibrillation (NVAF), and is incorporated in stroke risk stratification scores. We aimed to establish the role of ejection fraction (EF) in risk prediction in patients with NVAF and HF.

Methods and results
Patients with NVAF, history of HF, and measured EF were included in a retrospective analysis. Patients with HF and preserved ejection fraction (HFPEF) were defined as those with clinical HF and EF $\geq 50\%$ in this study. Among 7156 patients with NVAF, 1276 (17.8\%) patients with HF and measured EF were included. Of these, 747/1276 (58.5\%) patients were on vitamin K antagonists. The stroke/TE event rate per 100 person-years was 1.05 [95\% confidence interval (CI) 0.87–1.25]. Patients with HFPEF were more likely to be female ($P_{0.001}$), older ($P_{0.001}$), and hypertensive ($P_{0.001}$), and less likely to have prior vascular disease ($P_{0.001}$). There were no differences in rates of stroke ($P=0.17$) and stroke/TE ($P=0.11$) between patients with HFPEF and those with HF and reduced EF. There were no significant differences in rates of all-cause mortality when patients were stratified by EF. In multivariate analyses, only previous stroke (hazard ratio 2.36, 95\% CI 1.45–3.86) and vascular disease (1.57, 1.07–2.30) increased the risk of stroke/TE amongst NVAF patients with HF, but EF $<35\%$ did not (0.75, 0.44–1.30).

Conclusion
In NVAF patients with HF, there were no differences in rates of stroke, TE, or death between EF categories. Only previous stroke and vascular disease (and not decreased EF) independently increased risk of stroke/TE in multivariate analyses.

Keywords
Heart failure • Atrial fibrillation • Ejection fraction • Stroke • Thrombo-embolism • Risk

Introduction
With lifetime risks of one in four and one in five, respectively, non-valvular atrial fibrillation (NVAF) and heart failure (HF) present major public health burdens in terms of morbidity, mortality, and costs to health systems, with future increases predicted.1-4 HF is both a cause and an effect of NVAF.5-6 In patients with NVAF, HF is associated with increased risk of stroke and thrombo-embolism (TE),7-9 and has been incorporated in validated risk stratification scores.10-13

Heart failure may be associated with a spectrum of left ventricular (LV) function. There is considerable debate about definitions of HF based on quantitative measures such as LV ejection fraction (EF) and there is variation across guidelines, clinical trials, and epidemiological studies.14,15 For example, the European AF guidelines classify HF (moderate to severe systolic LV dysfunction, defined arbitrarily as LVEF $\leq 40\%$) as a risk factor for stroke and TE, suggesting that HF can be defined not only by symptoms, but also by a decrease in EF in the setting of AF.12 There is lack of consensus with regard to the cut-off for defining "preserved EF,"16 and the
distinction between ‘systolic HF’ and ‘diastolic HF’ is somewhat arbitrary since they often co-exist.\textsuperscript{14,15}

Previous studies have shown differences in risk factor profile and outcomes between patients with HF with preserved EF (HFPEF) and patients with HF with reduced EF (HFREF).\textsuperscript{17–20} HFPEF may represent up to 50\% of patients with HF.\textsuperscript{21} Some studies have indicated similar mortality and morbidity and a more severe risk factor profile in HFPEF compared with HFREF.\textsuperscript{22,23} In patients with systolic dysfunction, EF has been related to mortality and cardiovascular outcomes.\textsuperscript{24}

Clinical HF has been shown to add predictive value for stroke and TE events in patients with NVAF,\textsuperscript{7} but the role of quantitative EF in risk prediction in NVAF patients remains uncertain. The largest echocardiographic analysis from the AF Investigators found that moderate–severe left ventricular dysfunction on two-dimensional echocardiography was the only independent predictor on multivariate analysis.\textsuperscript{25} A recent systematic review did not find a history of HF to be a consistent or significant risk factor for stroke, but systolic impairment on echocardiography was a risk factor,\textsuperscript{26} driven largely by the AF Investigators’ echocardiographic analysis.\textsuperscript{25}

**Aim**

In this study, we analysed a large hospitalized cohort of patients with NVAF and HF with recorded EF to assess: (i) whether EF was an independent risk factor for stroke/TE and bleeding in this cohort; and (ii) the differences in risk factor profile and outcome between patients with NVAF and HFREF, when compared with patients with NVAF and HFPEF.

**Methods**

**Study population**

At the Centre Hospitalier Régional et Universitaire in Tours (France), all patients diagnosed with NVAF or atrial flutter by the Department of Cardiology between 2000 and 2010 were identified.\textsuperscript{5} Patients were followed from the first record of NVAF after 1 January 2000 (i.e. the index date) up to the latest data collection at the time of study (December 2010). Treatment at discharge was obtained by screening hospitalization reports, and information on co-morbidities was obtained from the computerized coding system. Co-morbidities were characterized using definitions from the International Classification of Diseases (ICD)-10.\textsuperscript{27} For example, hypertension was identified by the physician for each patient using the diagnosis quoted in the appropriate items in ICD-10 (I10–I15), which defines hypertension as ‘a repeatedly elevated blood pressure exceeding 140 over 90 mmHg’. Patients were excluded from the study if there was no history of chronic HF or if echocardiographic assessment of LV function was not available (Figure 1). All patients included in the study underwent two-dimensional and colour Doppler echocardiography at baseline. EF was calculated using Simpson’s rule or the Teichholz method.\textsuperscript{14,15} Patients with any degree of valvular dysfunction were excluded from this study.

For each patient, the CHADS\textsuperscript{10} and CHA\textsubscript{2}-DS\textsubscript{2}-VASc\textsuperscript{11} scores were calculated. The CHADS\textsubscript{2} score was the sum of points obtained after adding one point for congestive heart failure, hypertension, age ≥75, and diabetes, and two points for previous stroke or TE.\textsuperscript{10} The CHA\textsubscript{2}-DS\textsubscript{2}-VASc score was the sum of points after adding one point for congestive heart failure, hypertension, diabetes, vascular disease (including history of coronary, cerebrovascular, or peripheral vascular disease), age 65–74, and female gender, and two points for previous stroke or TE and age ≥75.\textsuperscript{11} According to the two risk scores, patients with a score of 0 on either schema were considered as ‘low risk’, 1 as ‘intermediate risk’, and ≥2 as ‘high risk’ of stroke and TE.

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**Figure 1** Study population in heart failure patients. LV, left ventricular.
Statistical analysis
The study population was stratified into four categories according to EF, i.e., severe LV impairment (EF < 35%), moderate LV impairment (EF 35–40%), mild LV impairment (EF 41–49%), and normal LV function (EF ≥ 50%) (Figure 1). Baseline characteristics were determined separately for the four EF strata, and differences were investigated using χ² test for categorical covariates and Kruskal–Wallis test for continuous covariates. To avoid any confusion, we defined HFPEF as clinical HF with EF ≥ 50% in this study.

In each of the four EF categories, event rates of stroke/TE, bleeding, and death were calculated for AF patients who were not receiving a vitamin K antagonist (VKA). For all the following analyses, a composite endpoint of stroke and TE was used. The χ² test was used to test for differences between event rates, with patients with normal EF (EF ≥ 50%) as the reference group. The risk associated with the individual risk factors of the CHA₂DS₂-VASc score was estimated in Cox proportional hazard models. To increase the power of the analyses, the Cox regression models included patients with and without a VKA; this approach was appropriate since no interaction was found between the effect of the individual risk factors and VKA treatment. Both univariate (including the individual risk factors and VKA treatment only) and multivariate (including all the CHA₂DS₂-VASc risk factors and VKA treatment) Cox regression models were applied. Furthermore, the event rates of stroke/TE were calculated in patients with and without each of the CHA₂DS₂-VASc risk factors. If appropriate, Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) indices were performed to test the additional predictive value of EF.

A two-sided P-value < 0.05 was considered statistically significant. All analyses were performed with SPSS statistical software version 18.0 (IBM, USA).

Ethics approval
The local ethics committee of our institution was consulted and approved this study. The informed consent of patients was deemed unnecessary for our analyses since this is a retrospective analysis of a single centre cardiology department.

Results
Of 8962 patients with AF, 7156 had NVAF. Of these NVAF patients, 1276 had measured EF data and were included in the analysis (Figure 1). Baseline characteristics are displayed in Table 1, and patients with HFREF are stratified into severe LV impairment (EF < 35%), moderate LV impairment (EF 35–40%), and mild LV impairment (EF 41–49%) in Supplementary material online, Table S1. Patients with normal EF were older (P < 0.001) and, after age adjustment, were more likely to be female (P < 0.001) and hypertensive (P < 0.001), and less likely to have prior vascular disease (P < 0.001). Patients with normal EF had higher CHADS² (P < 0.001) and CHA₂DS₂-VASc scores (P < 0.001). As expected, patients with low EF were more likely to be on treatment for HF (P < 0.001).

There was no difference in type of NVAF (P = 0.64) or bleeding risk by HAS-BLED score (P = 0.10), after adjustment for age or antithrombotic medications (P = 0.51) based on EF. As all patients had a history of HF, no patient had a CHADS² or CHA₂DS₂-VASc score of 0. Supplementary material online, Table S2, shows that patients with HF are older, and more likely to have other risk factors (except dyslipidaemia and prior stroke) and to receive antithrombotic and HF therapies when compared with patients without HF, even after age adjustment.

Of our cohort, 747/1276 (58.5%) patients were on VKAs. The overall stroke/TE event rate per 100 person-years was 1.05 (95% confidence interval (CI) 0.87–1.25). Corresponding rates in patients with and without VKA therapy were 1.06 (0.84–1.32) and 1.03 (0.76–1.38), respectively. Table 2 displays event rates per 100 person-years in patients with AF and HF, and Supplementary material online, Table S3, shows the same data by EF ranges: < 35%, 35–40%, 41–49%, and ≥ 50%. Comparing HFPEF and HFREF patients, there were no statistical differences in stroke, stroke/TE, all-cause death, or bleeding. The rates of stroke (P = 0.02) and stroke/TE (P = 0.02) were significantly different between patients with EF < 35% and patients with EF ≥ 50%, but bleeding (P = 0.63), all-cause death (P = 0.10), and the composite outcome of stroke/TE and death (P = 0.82) were not (Supplementary material online, Table S3). The observed rates of the composite endpoint of ‘stroke/TE/death’ were highest in patients with severe LV impairment (EF < 35%); these patients also had lower rates of stroke/TE and bleeding compared with patients with HFPEF. Overall, patients with mild LV impairment (EF 41–49%) had the highest rates of stroke/TE.

Cox regression analyses for all AF patients with HF are presented in Table 3. On univariate analyses, age ≥ 75 years [hazard ratio (HR) 1.72, 95% CI 1.10–2.70], previous stroke (2.56, 1.59–4.14), vascular disease (1.43, 1.01–2.03), and female gender (1.49, 1.05–2.13) significantly increased the risk of stroke and TE, although on multivariate analysis the associations with age ≥ 75 and female gender were not significant. The risks associated with age 65–74, hypertension, diabetes, EF (whether defined as EF < 35%, EF = 35–49%, or EF ≥ 50%, or as a continuous variable) were not statistically significant. Given this non-significant result on multivariate analysis, further calculations using the NRI and IDI indices were not performed.
Table 4 displays event rates for patients with and without each of the individual risk factors in patients with AF and HF who were not receiving a VKA.

**Discussion**

In this large ‘real world’ cohort of patients with NVAF and HF, our analyses revealed the following findings. Firstly, AF patients with HFPEF had a risk factor profile different from that of patients with HFREF in that they were more likely to be female and hypertensive, but less likely to have prior vascular disease, or be on HF therapy. Secondly, there were no statistically significant differences in rates of stroke and stroke/TE between HFPEF and HFREF. Thirdly, EF does not provide additional value in risk prediction for stroke/TE or bleeding in NVAF patients with HF. Finally, among NVAF patients with HF, previous stroke and vascular...
persistent NVAF. That EF had no additional predictive value for the development of HFPEF among HF patients, and several studies show that HFPEF is a particular patient group. A recent study of patients with HF found that EF was associated with stroke and TE in our NVAF cohort, although other studies have been unconvincing. However, previous studies support moderate–severe LV impairment as an independent risk predictor of outcomes in NVAF patients, – EF was not a risk predictor of stroke/TE or bleeding in the present study. EF will not improve stroke/TE risk prediction and, therefore, further calculations using the NRI and IDI indices were unwarranted. We have previously reported that HF is independently associated with stroke and TE in our NVAF cohort, although other studies have been unconvincing. EF carries similar mortality and morbidity to HFREF. An increasingly important patient group appears to be those patients with HF with recovered EF, who are reported to have milder symptoms and fewer HF hospitalizations than both HFREF and HFPEF. No study to date has considered this patient population with respect to NVAF. Indeed, EF does not remain constant over time, and future research is needed to assess the effect of change in EF over time on adverse outcomes in patients with NVAF and HF.

Although there were differences between stroke/TE outcomes by EF category in our study (Supplementary material online, Table S3), Cox regression models suggested that the addition of EF will not improve stroke/TE risk prediction and, therefore, further calculations using the NRI and IDI indices were unwarranted. We have previously reported that HF is independently associated with stroke and TE in our NVAF cohort, although other studies have been unconvincing. However, previous studies support moderate–severe LV impairment as an independent risk predictor of outcomes in NVAF patients. EF was not a risk predictor of stroke/TE or bleeding in the present study population. Nonetheless, a previous analysis has shown that reduced EF as a continuous variable was an independent predictor of outcomes in NVAF patients.25,26,28–35 EF was not a risk predictor of stroke/TE or bleeding in the present study population. Nonetheless, a previous analysis has shown that reduced EF as a continuous variable was an independent predictor of outcomes in NVAF patients.25,26,28–35 EF was not a risk predictor of stroke/TE or bleeding in the present study population.

### Table 2 Event rates (95% confidence interval) per 100 person-years in patients with heart failure and measured ejection fraction

<table>
<thead>
<tr>
<th>Without risk factor</th>
<th>With risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction 35–49%</td>
<td>1.14 (0.77–1.71)</td>
</tr>
<tr>
<td>Ejection fraction ≥50%</td>
<td>1.04 (0.96–1.12)</td>
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</tbody>
</table>

### Table 3 Hazard ratio (95% confidence interval) of stroke and thrombo-embolism in patients with heart failure and measured ejection fraction

<table>
<thead>
<tr>
<th>Without risk factor</th>
<th>With risk factor</th>
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</thead>
<tbody>
<tr>
<td>Hypertension 1.14 (0.80–1.63)</td>
<td>0.91 (0.62–1.43)</td>
</tr>
<tr>
<td>Age ≥75 1.72 (1.10–2.70)</td>
<td>1.37 (0.85–2.20)</td>
</tr>
<tr>
<td>Diabetes 1.05 (0.70–1.57)</td>
<td>0.94 (0.62–1.34)</td>
</tr>
<tr>
<td>Previous stroke 2.56 (1.59–4.14)</td>
<td>2.36 (1.45–3.86)</td>
</tr>
<tr>
<td>Vascular disease 1.43 (1.01–2.03)</td>
<td>1.57 (1.07–2.30)</td>
</tr>
<tr>
<td>Age 65–74 1.15 (0.71–1.89)</td>
<td>1.06 (0.64–1.74)</td>
</tr>
<tr>
<td>Female sex 1.49 (1.05–2.13)</td>
<td>1.43 (0.96–2.13)</td>
</tr>
<tr>
<td>Ejection fraction &lt;35% 0.72 (0.45–1.15)</td>
<td>0.75 (0.44–1.30)</td>
</tr>
<tr>
<td>Ejection fraction 35–49% 1.14 (0.77–1.71)</td>
<td>1.27 (0.83–1.93)</td>
</tr>
<tr>
<td>Ejection fraction ≥50% 1.04 (0.96–1.12)</td>
<td>1.05 (0.97–1.13)</td>
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</tbody>
</table>

### Table 4 Event rates (95% confidence interval) per 100 person-years in patients with heart failure and measured ejection fraction and not receiving a vitamin K antagonist

<table>
<thead>
<tr>
<th>Without risk factor</th>
<th>With risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension 1.46 (1.10–1.91)</td>
<td>1.99 (1.58–2.48)</td>
</tr>
<tr>
<td>Age ≥75 1.66 (1.28–2.11)</td>
<td>1.82 (1.41–2.31)</td>
</tr>
<tr>
<td>Diabetes 1.70 (1.38–2.07)</td>
<td>1.86 (1.29–2.58)</td>
</tr>
<tr>
<td>Previous stroke 1.58 (1.30–1.90)</td>
<td>3.92 (2.40–6.06)</td>
</tr>
<tr>
<td>Vascular disease 1.51 (1.16–1.93)</td>
<td>2.02 (1.57–2.55)</td>
</tr>
<tr>
<td>Age 65–74 1.66 (1.28–2.11)</td>
<td>1.77 (1.21–2.49)</td>
</tr>
<tr>
<td>Female sex 1.55 (1.22–1.94)</td>
<td>2.08 (1.57–2.70)</td>
</tr>
<tr>
<td>Ejection fraction &lt;35% 1.95 (1.61–2.36)</td>
<td>1.13 (0.72–1.70)</td>
</tr>
<tr>
<td>Ejection fraction ≥50% 1.57 (1.21–2.00)</td>
<td>1.94 (1.50–2.46)</td>
</tr>
</tbody>
</table>

Disease were the strongest independent predictors of stroke and TE.

Our observations suggest that HFPEF and HFREF in the setting of NVAF have broadly similar risk factor profiles to HF in patients without NVAF. Patients with HFPEF had higher scores in existing risk stratification systems for stroke/TE and bleeding than patients with HFREF, but there were no differences in the rates of oral anticoagulation across all categories of EF.

Few studies have considered the impact of EF on progression or pattern of NVAF in a ‘real world’ population setting, although small studies have suggested the predictive value of EF for NVAF in particular patient groups. A recent study of patients with HF found that EF had no additional predictive value for the development of persistent NVAF.

Previous studies have highlighted the considerable burden of HFPEF among HF patients, and several studies show that HFPEF carries similar mortality and morbidity to HFREF. An increasingly important patient group appears to be those patients with HF with recovered EF, who are reported to have milder symptoms and fewer HF hospitalizations than both HFREF and HFPEF. No study to date has considered this patient population with respect to NVAF. Indeed, EF does not remain constant over time, and future research is needed to assess the effect of change in EF over time on adverse outcomes in patients with NVAF and HF.

Although there were differences between stroke/TE outcomes by EF category in our study (Supplementary material online, Table S3), Cox regression models suggested that the addition of EF will not improve stroke/TE risk prediction and, therefore, further calculations using the NRI and IDI indices were unwarranted. We have previously reported that HF is independently associated with stroke and TE in our NVAF cohort, although other studies have been unconvincing. However, previous studies support moderate–severe LV impairment as an independent risk predictor of outcomes in NVAF patients. EF was not a risk predictor of stroke/TE or bleeding in the present study population. Nonetheless, a previous analysis has shown that reduced EF as a continuous variable was an independent predictor...
of all-cause mortality in NVAF patients. A recent study showed that AF and EF predicted mortality in HF patients receiving cardiac resynchronization therapy. Since HFPEF and HREF are a focus of both pathophysiological and echocardiographic studies of HF, future studies must include patients with NVAF in order to better understand these interlinked disease processes.

Finally, among our NVAF patients with HF, previous stroke and vascular disease were the strongest independent predictors of outcomes. Age, which was a strong predictor of stroke/TE in our previous analysis of this cohort, was not significantly associated with outcomes in NVAF patients with HF. Nonetheless, AF patients with HFREF were more likely to be on aspirin than patients with HFPEF, and this may at least partially explain the fact that reduced EF did not predict stroke/TE or bleeding in NVAF patients with HF. Although atrial structural remodelling is increasingly recognized in the development and progression of NVAF, the role of EF in pathogenesis of NVAF is still unclear. For example, maintenance of sinus rhythm in patients with NVAF can improve EF. Future clinical trials and prospective epidemiological studies involving NVAF patients should be statistically powered to consider subgroups by risk factor, including HF.

Study limitations

The limitations of this ‘real world’ registry have been previously reported. Briefly, there are inherent limitations of diagnostic coding and case ascertainment, particularly if an enrolled patient moved away from the area or had an outcome event in another area. Despite adjustment for several risk factors, the non-randomized design does not exclude the possibility of residual confounding factors. Oral anticoagulation therapy was determined at baseline, and not adjusted for changes in treatment status during follow-up; however, this limitation did not have an effect on the results in a similar Danish cohort study. Despite inclusion of >1200 patients with NVAF, analyses in specific subgroups had reduced statistical power. Of 3630 patients with HF, only 1276 had echocardiographic assessment of EF; either because echocardiography was not performed or because EF could not be accurately measured from available data, which is a major limitation of this analysis. Supplementary material online, Table S4, shows the characteristics of patients with and without measured EF, and patients without measured EF were older and, even after age adjustment, they were more likely to have hypertension and less likely to have previous vascular disease (including stroke), previous bleeding, and smoking history. EF assessment was only undertaken at baseline and therefore the effect of changes in EF cannot be analysed in this data set. In addition, no data regarding duration of AF or burden of AF were available. New data suggest that duration of HF and/or AF may add important information to risk stratification, and future cohorts must include these data to assess these potential associations. Data regarding cause of death were not available for analysis and, therefore, some deaths could be attributable to stroke, which would influence the study conclusions regarding stroke outcomes. Finally, we have refrained from speculations on the possible pathophysiological explanations for our observations, given the multifactorial and complex pathogenesis of AF influencing stroke, HFPEF, and HREF.

Conclusions

In this large ‘real world’ cohort of NVAF patients with HF, rates of stroke, stroke/TE, death, and bleeding are similar in HFPEF and HREF. Only previous stroke and vascular disease independently increased the risk of stroke/TE in these patients. Thus, EF may not provide additional value to stroke risk prediction in patients with NVAF and HF, and the increased risk of adverse outcomes associated with clinical HF in patients with NVAF was not significantly influenced by EF measurement.

Supplementary material

Supplementary material is available at European Journal of Heart Failure online.

Conflicts of interest: J.B.O has received travel grants from AstraZeneca and Boehringer Ingelheim. S.T. has received funding for research from Sanofi Aventis. D.A.L has received funding for research, conference travel, and educational symposia from Bayer Healthcare and Boehringer Ingelheim, and is a member of the ACCP9 Writing Committee. G.Y.H.L. has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi Aventis, Biotronik, BMS/Pfizer, and Boehringer Ingelheim, and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis. L.F. has served as a consultant for Bayer, Medtronic, and Sanofi Aventis, and has received funding for conference travel and educational symposia from Boehringer Ingelheim, Bayer, Medtronic, and Sanofi Aventis. A.B. and B.L. report no conflicts of interest.

Authors’ contributions: L.F., B.L., and S.T. made the primary contribution to data collection. A.B., J.B.O., G.Y.H.L., D.A.L., and L.F. contributed to the study conception and design. A.B. performed the analyses. All authors contributed to interpretation of results, revising the manuscript critically for important intellectual content, and all approved the final manuscript.

References


