Relationship Between Degree of Left Ventricular Dysfunction, Symptom Status, and Risk of Embolic Events in Patients With Atrial Fibrillation and Heart Failure

Roopinder K. Sandhu, MD, MPH; Stefan H. Hohnloser, MD; Marc A. Pfeffer, MD, PhD; Fei Yuan, MMa; Robert G. Hart, MD; Salim Yusuf, MBBS, DPhil; Stuart J. Connolly, MD; Finlay A. McAlister, MD, MSc; Jeff S. Healey, MD, MSc

Background and Purpose—Limited data exists regarding the relationship between left ventricular systolic dysfunction (LVSD) and heart failure (HF) symptoms and embolic risk among patients with atrial fibrillation.

Methods—Participants in the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) trials with HF, but not randomized to oral anticoagulation, were categorized as having preserved versus reduced ejection fraction. If reduced, LVSD was classified as mild, moderate, or severe. Symptoms were quantified using New York Heart Association class.

Results—There were 3487 antiplatelet-treated patients with HF at baseline. Of these patients, 969 (46.8%) had HF with preserved ejection fraction and 1103 (53.2%) had HF with reduced ejection fraction. During 3.6 years of mean follow-up, first occurrence of stroke, transient ischemic attack, or systemic embolism occurred in 386 patients. The strongest independent predictors of embolic events were age ≥75 years (hazard ratio 2.55; confidence interval, 1.85–3.53), prior stroke or transient ischemic attack (hazard ratio 2.07; 95% confidence interval, 1.65–2.60), and female sex (hazard ratio 1.37; confidence interval, 1.11–1.69). However, ejection fraction <0.50, degree of LVSD, and New York Heart Association class did not predict embolic events. Patients with HF with preserved ejection fraction exhibited similar risk of embolic events as those with HF with reduced ejection fraction: 4.3% versus 4.4% per 100 person-years (hazard ratio 1.01; 95% confidence interval, 0.78–1.31). Risk of embolic events was similar across categories of LVSD (P for trend =0.96) and New York Heart Association class (P for trend =0.57).

Conclusion—Among HF patients in ACTIVE, neither the presence of LVSD or degree of symptom severity influenced risk of embolic events. (Stroke. 2015;46:667-672. DOI: 10.1161/STROKEAHA.114.007140.)

Key Words: atrial fibrillation • heart failure • stroke

See related article, p 608.

Heart failure (HF) is a major component of the widely applied CHADS2 (congestive HF, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack (TIA)) stroke risk stratification scheme.1–4 Although risk stratification scores are used to decide which nonvalvular atrial fibrillation (NVAF) patients should be offered anticoagulation, the definition of HF and physician application of HF criteria varies widely, which may explain conflicting results with respect to HF-related stroke risk.5–11 In prior studies, HF has been defined using administrative codes or based on symptoms within the past 100 days, whereas other reports have included patients with any episode of HF.2,12 The definition of left ventricular systolic dysfunction (LVSD) also varies with a mix of both qualitative (moderate to severely reduced)5,10,11 and quantitative (ejection fraction [EF] ≤40% or 35%) descriptions.1,4

Several studies found an increased stroke risk associated with HF when defined as a history or the presence of a HF episode5–7; however, a clinical diagnosis of HF was not an independent stroke risk factor in 2 recent systematic reviews13,14 or in a prior multivariate analysis of Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-W) study.15 This finding from ACTIVE-W could be the result of HF simply being the weakest of the stroke risk factors tested or that modern HF therapies may have diminished the risk of stroke. Other work...
found no significant association between HF symptoms (New York Heart Association [NYHA] class >II) and stroke risk. Among studies focusing on multiple definitions of HF, including recent HF episode, left ventricular shortening <25%, or an EF <0.50, only left ventricular dysfunction was a significant independent risk factor for stroke, although several of these studies contained overlapping clinical trial populations. The Apxiban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) investigators found no significant increase in risk of stroke or systemic embolism among groups of patients with LVSD (EF ≤0.40 or report of moderate or severe LVSD) with and without HF and preserved EF (>0.40, normal or mild LVSD) with HF compared with patients without both LVSD and HF. However, all patients were treated with oral anticoagulation, which may have mitigated any excess embolic risks. There is a paucity of data exploring the relationship between magnitude of LV dysfunction or HF symptoms and risk of embolic events among patients with NVAF not being treated with oral anticoagulation.

Therefore, we evaluated the associations between LV dysfunction, the severity of HF symptoms and risk of stroke, TIA, systemic embolism among 3487 participants of the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) trial who had NVAF, a history of HF, and were randomized to receive antiplatelet therapy alone.

Methods

Study Population

The ACTIVE A (NCT 00243178) and W (NCT 00249873) trial design and results have been previously published. Briefly, participants with NVAF documented on ECG and ≥1 other risk factor for stroke were randomized to clopidogrel or aspirin (ACTIVE A) or clopidogrel plus aspirin versus oral anticoagulation therapy (ACTIVE W). Stroke risk factors were defined as ≥7 years, hypertension on treatment, previous stroke, TIA, or non–central nervous system embolism, left ventricular ejection fraction (LVEF) <0.45, peripheral arterial disease; patients 55 to 74 without one of the above inclusion criteria were required to have either diabetes mellitus or coronary artery disease. For this analysis, we included patients with a baseline history of HF from the ACTIVE A trial (n=2496) or the clopidogrel plus aspirin arm of ACTIVE W trial (n=991). Of these 3487 patients with HF, we had data on HF symptom severity in 3483 and an estimated degree of systolic dysfunction was available in 2061 patients (with measured EF reported in 2072 patients).

Definition of HF, LVSD, and HF Symptoms

Patients with any history of HF at baseline were included. Left ventricular function was assessed by any of the following methods: nuclear, MRI, echocardiogram, or angiography in the preceding 6 months before enrollment. Left ventricular ejection fraction was reported as a percentage or by an estimated degree of LVSD (none, mild, moderate, or severe). For this analysis, HF patients were categorized as having preserved versus reduced ejection fraction (HF-PEF ≥0.50 and HF-REF <0.50). HF symptom severity was assessed using the NYHA classification scheme.

Outcomes

The primary outcome for this analysis was first occurrence of stroke, TIA, or systemic embolism. Stroke was defined as sudden onset of a focal neurological deficit lasting >24 hours and further categorized as ischemic and hemorrhagic.

Statistical Analysis

Baseline characteristics for HF-PEF and HF-REF were compared using a χ² test or Wilcoxon rank-sum test for continuous variables and χ² tests for categorical variables. Cox-proportional hazards models were used to compute a hazard ratio (HR) and 95% confidence interval (CI) to determine independent predictors of stroke, TIA, or systemic embolism, including prior stroke or TIA, diabetes mellitus, age (65–74 years and ≥75 years), systolic BP (per 1 mmHg, time varying), diastolic BP (per 1 mmHg, time varying), coronary artery disease, peripheral artery disease, female sex, history of hypertension, LVEF ≤0.50, LVSD (mild, moderate, and severe), and NYHA II–IV. In addition, hazard ratios (95% CI) were calculated for embolic events for LVEF <0.50 and across categories of LVSD (no LVSD as referent) and HF symptom severity (NYHA class I as referent) in all analyses. The proportional hazard assumption was verified by including a survival time into the Cox proportional hazard models and testing interactions between time and various variable; no interaction term was found to be statistically significant.

To evaluate whether the association between LVSD or HF symptom severity and our primary outcome differs by AF type or randomized treatment assignment, prespecified analyses examining effect modification by AF type and randomized treatment assignment were separately performed. AF type was categorized as nonpermanent (paroxysmal and persistent) and permanent. Statistical analysis was performed with SAS statistical software (SAS Institute Inc., Cary NC) version 9.1. A 2-tailed value of P<0.05 was considered to indicate statistical significance.

Results

Baseline Characteristics

Patients with HF-PEF were older, female, had higher blood pressure, body mass index, and CHADS, score and were more likely to have paroxysmal AF than those patients with HF-REF, but had a lower NYHA class and smaller LA size. HF-REF patients were more likely to be treated with angiotensin-converting enzyme inhibitors, β-blockers, diuretic, or digoxin (Table 1). During a median follow-up of 3.6 years, first occurrence of stroke, TIA, or systemic embolism occurred in 386 patients. Overall, there were 286 strokes, 89 TIA, and 43 systemic embolism with 32 patients having >1 event.

Independent Predictors of Stroke, TIA, or Systemic Embolism

In multivariate analyses, age ≥75 years (HR 2.55; 95% CI, 1.85–3.53), prior stroke or TIA (HR 2.07; 95% CI, 1.65 to 2.60), and female sex (HR 1.37; 95% CI, 1.11–1.69) were the strongest independent predictors of stroke (Table 2). Neither LVEF <0.50 or HF symptom severity was independently associated with subsequent rates of stroke, TIA, or systemic embolism after adjustment of variable included in Table 2. In a separate model, we found neither severity of LV dysfunction (P=0.45) or HF symptom severity (0.09) was significantly associated with stroke, TIA, or systemic embolism after adjusting for the same covariates except for LVEF <0.50.

LV Systolic Function, HF Symptom Severity, and Outcomes

The risk per 100 person years and HR and 95% CI for stroke, TIA, or systemic embolism according to LV function and HF symptom severity are shown in Table 3. The risk of embolic events were similar for HF-PEF and HF-REF (4.3% versus 4.4%). There was no significant difference between both
groups and embolic events ($P$ for trend $=0.95$). Similarly, magnitude of LVSD ($P$ for trend $=0.96$) and HF symptom severity ($P$ for trend $=0.57$) were not significantly associated with subsequent stroke, TIA, or systemic embolism.

We then explored whether the association between LVSD and HF symptom severity and embolic events differed by randomized treatment assignment (Table I in the online-only Data Supplement) and AF type (Table 4). Overall, aspirin plus clopidogrel was associated with a 24% lower embolic risk compared with aspirin alone. The benefit of aspirin plus clopidogrel was similar among HF-PEF and HF-REF across categories of LV dysfunction and classes of HF symptom severity.
several independent risk factors for stroke.3,6,7,11,16,24 In our analysis, limited to HF patients, the presence of LVSD or worsening HF symptoms were not independent predictors for subsequent embolic events. This does not mean that HF is not a risk factor for stroke, but rather that once a patient has a diagnosis of HF, then further information about the HF, such as symptom status or LVEF, do not influence stroke risk estimation. The updated European guidelines consider HF used in stroke risk scores as moderate to severe LV dysfunction or recent decompensated HF irrespective of ejection fraction.4 Similarly, CHADS2 as or LVEF, do not influence stroke risk estimation. The updated European guidelines consider HF used in stroke risk scores as moderate to severe LV dysfunction or recent decompensated HF irrespective of ejection fraction.4 Similarly, CHADS2 as

Among populations with varying degrees of HF, LVSD or symptom severity were not consistently found to be independent risk factors for stroke.5,6,8,11,16,24 In our analysis, limited to HF patients, the presence of LVSD or worsening HF symptoms were not independent predictors for subsequent embolic events. This does not mean that HF is not a risk factor for stroke, but rather that once a patient has a diagnosis of HF, then further information about the HF, such as symptom status or LVEF, do not influence stroke risk estimation. The updated European guidelines consider HF used in stroke risk scores as moderate to severe LV dysfunction or recent decompensated HF irrespective of ejection fraction.4 Similarly, CHADS2, as first described in the National Registry of Atrial Fibrillation focused on a recent decompensated HF history alone.2

Our study has also clarified that the prognostic importance of HF is the same for NVAF patients with HF-PF versus HF-REF. In a previously published retrospective study of hospitalized AF patients (58.5% of whom were taking Vitamin K antagonists), no statistically significant differences were observed in the rates of stroke or stroke/thromboembolism between those with HF-PF versus HF-REF or across categories of LV impairment (mild, moderate, and severe).25 These data and our results confirm a recent systematic review that found no statistically significant difference in stroke risk between patients with AF and preserved or reduced ejection fraction.26 In a post hoc analysis, ARISTOTLE investigators found no significant association between LVSD or HF-PF (defined as LVEF >0.40) and risk of stroke and systemic embolism compared with patients without both HF and LVSD after multivariable adjustment (P=0.71). However, all patients in ARISTOTLE were on anticoagulation therapy and the group defined by LVSD comprised those with and without a history of clinical HF. It is possible that the large proportion of patients treated with oral anticoagulation mitigated the risk

Discussion

Among a cohort of HF patients with NVAF who were not treated with oral anticoagulants in the ACTIVE trials, we found a similar risk of embolic events for patients with HF-PF versus HF-REF. Our data further suggests that the degree of LVSD and HF symptom severity does not influence embolic risk. In stratified analyses, embolic risk associated with HF-PF and HF-REF had a borderline significance among those with permanent AF compared with nonpermanent AF (P for interaction =0.047), whereas embolic risk associated with degree of LVSD or HF symptom severity did not vary significantly among those with and without permanent AF. After considering the issue of multiple testing, these relationships were no longer statistically significant.

Table 2. Prevalence and Multivariate HR (95% CI) for Independent Predictors of Stroke, TIA, or Systemic Embolism

<table>
<thead>
<tr>
<th>Risk Factor and Prevalence</th>
<th>Multivariate–Adjusted HR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke or TIA (n=525)</td>
<td>2.07 (1.65–2.60)</td>
</tr>
<tr>
<td>Diabetes mellitus (n=812)</td>
<td>1.30 (1.04–1.64)</td>
</tr>
<tr>
<td>Age category, y</td>
<td></td>
</tr>
<tr>
<td>&lt;65 (n=833)</td>
<td>Referent</td>
</tr>
<tr>
<td>65–74 (n=1166)</td>
<td>1.78 (1.27–2.50)</td>
</tr>
<tr>
<td>≥75 (n=1486)</td>
<td>2.55 (1.85–3.53)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg, (n=3486)</td>
<td>1.003 (0.998–1.009)</td>
</tr>
<tr>
<td>Coronary artery disease (n=1280)</td>
<td>0.93 (0.75–1.15)</td>
</tr>
<tr>
<td>Peripheral artery disease (n=139)</td>
<td>1.38 (0.86–2.21)</td>
</tr>
<tr>
<td>Female sex (n=1417)</td>
<td>1.37 (1.11–1.69)</td>
</tr>
<tr>
<td>History of hypertension (n=2860)</td>
<td>0.76 (0.58–1.00)</td>
</tr>
<tr>
<td>LVEF&lt;0.50 (n=982)</td>
<td>1.10 (0.87–1.39)</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
</tr>
<tr>
<td>I (n=702)</td>
<td>Referent</td>
</tr>
<tr>
<td>II (n=2058)</td>
<td>0.88 (0.68–1.13)</td>
</tr>
<tr>
<td>III or IV (n=723)</td>
<td>0.73 (0.53–1.01)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and TIA, transient ischemic attack.

Among populations with varying degrees of HF, LVSD or symptom severity were not consistently found to be independent risk factors for stroke.3,6,7,11,16,24 In our analysis, limited to HF patients, the presence of LVSD or worsening HF symptoms were not independent predictors for subsequent embolic events. This does not mean that HF is not a risk factor for stroke, but rather that once a patient has a diagnosis of HF, then further information about the HF, such as symptom status or LVEF, do not influence stroke risk estimation. The updated European guidelines consider HF used in stroke risk scores as moderate to severe LV dysfunction or recent decompensated HF irrespective of ejection fraction.4 Similarly, CHADS2, as first described in the National Registry of Atrial Fibrillation focused on a recent decompensated HF history alone.2
of stroke and systemic embolism. The findings from our study among HF patients randomized to antplatelet agents alone is consistent with ARISTOTLE data, suggesting the presence or absence of LVSD does not influence risk of embolic events.

We also found no significant association between HF symptom severity and risk of embolic events consistent with previous reports.\(^6,16\) The apparent lower risk of embolic events among HF symptom class III or IV compared with HF symptoms class II may be a result of competing risks. Annual mortality increases with severity of NYHA functional class; it is possible that patients with NYHA class III or IV died before suffering an embolic event and thus it seems as if the embolic risk is lower than those with less severe symptoms.\(^27\) Furthermore, our data suggests a higher embolic risk for HF-REF patients with permanent AF, whereas risk for embolic events was higher among patients with HF-REF and paroxysmal/persistent AF. These findings need further confirmation in future studies.

There are several limitations of our study. First, this is a retrospective post hoc analysis of 2 randomized clinical trials conducted to answer a different question. Thus, the distribution of demographics and comorbidities in our population reflects randomized clinical trial participants rather than real world clinical practice. However, the prevalence of diabetes mellitus, hypertension, and prior stroke/TIA in our population is similar to that reported for patients with concomitant HF and NVAF in population-based cohorts.\(^28\) Second, the definition of HF has varied widely in the stroke prediction literature, and we used any history of HF for our analyses. Left ventricular function was assessed in the preceding 6 months before enrollment. Future studies should explore whether the inimacy of HF episode affects stroke risk (certainly it is known that the highest risk for mortality or hospitalization is seen in patients with recent HF exacerbations compared with those with more remote episodes).\(^29\) Third, we did not have the ability to perform a time-varying analysis to evaluate whether the relationship between LVEF or HF symptom severity and risk of embolic events changes over time.

### Conclusions

Among patients with HF in the antplatelet arms of ACTIVE, the risk of embolic events did not differ between those with HF-REF versus HF-PEF, degree of LVSD, nor HF symptom severity. Thus, decisions about the risks versus benefits of anticoagulation for HF patients with AF should not be influenced by an ejection fraction or symptom status.

### Sources of Funding

Finlay McAlister is supported by a salary award from Alberta Innovates-Health Solutions and the Capital Health/University of Alberta Chair in Cardiovascular Outcomes Research. This work was supported by a personnel award from the Heart and Stroke Foundation, Ontario Provincial Office (Jeff S. Healey, MC 7450).

### Disclosures

Drs Sandhu, McAlister, Hart and F. Yuan report no conflicts of interest. Dr Hohnloser receives consulting fees from Bayer, Boehringer Ingelheim, Sanofi Aventis and Bristol-Myers Squibb, St Jude Medical, Johnson & Johnson, and Pfizer. Dr Pfeffer has received grant support from Amgen, Celladon, Novaratis, and Sanofi Aventis; consultant for Aastrom, Amgen, Bristol-Myers Squibb, Cerenis, Concert, Genzyme, Hamilton Health Sciences, Keryx, Medtronic, Merck, Novartis, Roche, Servier, Teva, University of Oxford, and Xoma. Dr Yusuf has received grant support from Boehringer Ingelheim. Dr Connolly receives consulting fees, honoraria, and research support from Bristol-Myers Squibb, Boehringer Ingelheim, Boston Scientific, Sanofi Aventis, and Bayer. Dr Healey has received honoraria and research support from St Jude Medical, Medtronic, Bristol-Myers Squibb, Pfizer, and Boehringer Ingelheim.

### References

1. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 Guidelines for the Management


Relationship Between Degree of Left Ventricular Dysfunction, Symptom Status, and Risk of Embolic Events in Patients With Atrial Fibrillation and Heart Failure

Roopinder K. Sandhu, Stefan H. Hohnloser, Marc A. Pfeffer, Fei Yuan, Robert G. Hart, Salim Yusuf, Stuart J. Connolly, Finlay A. McAlister and Jeff S. Healey

Stroke. 2015;46:667-672; originally published online January 27, 2015; doi: 10.1161/STROKEAHA.114.007140

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/3/667

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2015/01/27/STROKEAHA.114.007140.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL
Relationship Between Degree of Left Ventricular Dysfunction, Symptom Status and Risk of Embolic Events in Patients with Atrial Fibrillation and Heart Failure
Supplementary Table I. Hazard Ratios and 95% CI of Stroke, TIA or Systemic Embolism According to Left Ventricular function and Heart Failure Symptom Severity Stratified by Randomized Treatment Assignment

<table>
<thead>
<tr>
<th>Composite stroke/TIA/systemic embolism (per year)</th>
<th>Overall (n=3487)</th>
<th>ASA (n=1256)</th>
<th>ASA + Clopidogrel (n=2231)</th>
<th>ASA + Clopidogrel vs ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk N(% per 100 person years)</td>
<td>Risk N(% per 100 person years)</td>
<td>Risk N(% per 100 person years)</td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Overall</td>
<td>386 (4.5)</td>
<td>189 (5.1)</td>
<td>197 (9.0)</td>
<td>0.76 (0.62-0.93)</td>
</tr>
<tr>
<td>HF-PEF</td>
<td>110 (4.3)</td>
<td>33 (4.6)</td>
<td>57 (4.0)</td>
<td>0.85 (0.58-1.24)</td>
</tr>
<tr>
<td>HF-REF</td>
<td>115 (4.4)</td>
<td>52 (4.5)</td>
<td>63 (4.3)</td>
<td>0.90 (0.62-1.31)</td>
</tr>
<tr>
<td>LV dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>82 (4.2)</td>
<td>40 (4.6)</td>
<td>42 (3.9)</td>
<td>0.81 (0.53-1.26)</td>
</tr>
<tr>
<td>Mild</td>
<td>58 (4.2)</td>
<td>29 (4.4)</td>
<td>29 (4.0)</td>
<td>0.88 (0.52-1.48)</td>
</tr>
<tr>
<td>Moderate</td>
<td>57 (4.6)</td>
<td>26 (5.3)</td>
<td>31 (4.2)</td>
<td>0.77 (0.45-1.30)</td>
</tr>
<tr>
<td>Severe</td>
<td>27 (4.4)</td>
<td>9 (3.2)</td>
<td>18 (5.4)</td>
<td>1.67 (0.74-3.77)</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>84 (4.8)</td>
<td>42 (5.6)</td>
<td>42 (4.2)</td>
<td>0.70 (0.45-1.08)</td>
</tr>
<tr>
<td>II</td>
<td>235 (4.5)</td>
<td>118 (5.2)</td>
<td>117 (4.0)</td>
<td>0.76 (0.59-0.98)</td>
</tr>
<tr>
<td>III or IV</td>
<td>67 (4.1)</td>
<td>29 (4.2)</td>
<td>38 (3.9)</td>
<td>0.82 (0.50-1.34)</td>
</tr>
</tbody>
</table>