Blood Pressure and Stroke in Heart Failure in the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study

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Background and Purpose—The prevalence of stroke is increased in individuals with heart failure (HF). The stroke mechanism in HF may be cardiogenic embolism or cerebral hypoperfusion. Stroke risk increases with decreasing ejection fraction and low cardiac output is associated with hypotension and poor survival. We examine the relationship among blood pressure level, history of stroke/transient ischemic attack (TIA), and HF.

Methods—We compared the prevalence of self-reported history of stroke or TIA in the REasons for Geographic And Racial Differences in Stroke (REGARDS) participants with HF (as defined by current digoxin use) and without HF. We excluded participants with atrial fibrillation or missing data. We examined the relationship between HF and history of stroke/TIA within tertiles of systolic blood pressure (SBP) adjusting for patient demographic and health characteristics.

Results—Prevalent stroke/TIA were reported by 66 (26.3%) of 251 participants with and 1805 (8.5%) of 21 202 participants without HF (P < 0.0001). Within each tertile of SBP, the unadjusted OR (95% CI) for prior stroke/TIA among those with HF compared with those without HF (the reference group) was, 4.0 (2.8 to 5.8) for SBP <119.5 mm Hg, 2.7 (1.8 to 3.9) for SBP ≥119.5 but <131.5 mm Hg, and 2.3 (1.6 to 3.2) for SBP ≥131.5 mm Hg. After adjustment, the relationship between prior stroke/TIA and HF remained significant only within the lowest tertile of SBP (<119.5 mm Hg; 3.0; 1.5 to 6.1).

Conclusions—The odds of prevalent self-reported stroke/TIA are increased in participants with HF and most markedly increased in participants with low SBP. Longitudinal data are needed to determine whether this reflects stroke/TIA secondary to thromboembolism from poor cardiac function or secondary to cerebral hypoperfusion. (Stroke. 2009;40:3706-3710.)

Key Words: brain infarction ■ cardiac disease ■ hypertension

Cardiac disease is a major independent risk factor for stroke, ranking third after age and hypertension. Atrial fibrillation (AF) is the cardiac disorder most frequently associated with stroke with approximately 105 000 strokes per year in the United States.1 Heart failure (HF) ranks second as a cause of cardiogenic stroke with approximately 60 000 strokes per year,2 although HF affects approximately twice the number of individuals in the population in the United States (5 million) than are affected by AF (2.3 million).3 Two community studies have shown the risk of stroke in HF to be 2 to 3 times that of the general population. In the Framingham study, the adjusted risk of stroke associated with HF was 2.1 in women and 2.7 in men.4 In a recent study in Olmsted County, Minn, the stroke risk among those with HF was 2.9 times the control population risk over 5 years.5

Hypertension, particularly systolic hypertension, is a major risk factor for stroke.6,7 Hypertension doubles the lifetime risk of developing HF,8 but there are inconsistent data on whether hypertension is a risk factor for stroke in patients with HF. A population study did not find hypertension to be a risk factor for stroke in HF in a multivariable analysis.5 Hypertension was not a risk factor for stroke in a study of patients with left ventricular systolic dysfunction,9 and in Studies of Left Ventricular Dysfunction, hypertension imparted a small relative risk of stroke only in men (relative risk, 1.32; 95% CI, 1.04 to 1.69; P = 0.02) but no significant risk in women.10 Two recent substudies of the Digitalis Investigation Group trial,11,12 however, showed a history of hypertension to be an independent predictor of stroke (adjusted OR, 1.46; 95% CI, 1.11 to 1.94)12 and a risk

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factor for hospitalization for stroke (hazard ratio, 1.52; 95% CI, 1.11 to 2.08) among patients with HF.

Reduced ejection fraction has been found to be a risk factor for stroke in several studies,6,9,10,13,14 but there are some inconsistencies and an interaction with cerebrovascular disease may be important for the development of stroke in patients with low ejection fraction.2 Both hypotension6,15 and low ejection fraction16 have been found to be risk factors for cognitive impairment in patients with HF, and cognitive impairment may signal undiagnosed or “whispering” stroke.17 Decreasing blood pressure is associated with worse survival in HF, because hypotension probably reflects poor cardiac pump function in advanced HF.18 This study was initiated to investigate the association among blood pressure level, prevalent stroke, and HF.

Methods

Design

The REasons for Geographic And Racial Differences in Stroke (REGARDS) study is a population-based study of adults aged ≥45 years in the United States19 seeking to determine causes of racial and geographic differences in stroke. Enrollment began in January 2003 and was completed in October 2007. The cohort consists of 30,228 participants, 45% men and 55% women (50:50 planned); 58% white and 42% black (50:50 planned); 56% residing in the Stroke Belt region of southeastern United States and 44% in the remaining 40 contiguous United States (50:50 planned), each of whom is being followed biannually by telephone to ascertain cognitive assessment, stroke, and cardiovascular outcomes.19

Procedures

REGARDS is approved by the Institutional Review Boards of all participating institutions. Participants were recruited from commercially available lists of US residents using mail and telephone contact methods. Those who agreed to participate answered demographic, quality-of-life, health behavior, and medical history information; reported HF symptoms (2 questions); and reported stroke history and symptoms using the Questionnaire for Verifying Stroke-free Status,20 all through a computer-assisted telephone interview. During a subsequent home visit, written informed consent was obtained as well as blood and urine samples, electrocardiogram, and blood pressure and body mass index measures. Medication audits also were performed during the home visit. Further methodological details are available elsewhere.19

Measures

Heart Failure

We used current use of digoxin at baseline as the proxy for HF diagnosis. The only current clinical indications for digoxin are AF and HF; digoxin use has a specificity of approximately 99% and a sensitivity of approximately 28% for the diagnosis of HF.21

History of Stroke/Transient Ischemic Attack

The Questionnaire for Verifying Stroke-free Status20 contains 8 items. The first 2 items elicit history of physician-verified stroke, ministroke, or transient ischemic attack (TIA); a positive response on either of these items indicates a positive stroke/TIA history.

Demographics

Age, sex, race, and region were ascertained by self-report.

Socioeconomic Status

Socioeconomic status was represented by income and education levels. Annual income was categorized into 3 levels: <$25 000, ≥$25 000, and unreported. Education was categorized into 2 levels: high school or below and greater than high school.

| Table 1. Description of Population Overall and by HF Status |
|-------------|-------------|-------------|
|             | Total       | No HF,      | HF,          |
|             | Participants| No. (%)     | No. (%)      |
| Prior stroke/TIA* | 1871       | 1805 (8.5)  | 66 (26.3)    |
| Race (white)     | 12 604     | 12 459 (58.7)| 145 (57.7)  |
| Male sex*        | 10 065     | 9903 (46.7) | 162 (65.5)   |
| Income ≥$25 000* | 15 056     | 14 911 (70.3) | 154 (57.8)  |
| Current alcohol use* | 11 478 | 11 385 (53.7) | 93 (37.1)   |
| Current smoker† | 3180       | 3154 (14.9) | 26 (10.4)    |
| Diabetes*        | 4506       | 4393 (20.7) | 113 (45.1)   |
| Hypertension*    | 12 433     | 12 250 (57.8) | 183 (72.9)  |
| Ischemic heart disease* | 4465 | 4318 (20.4) | 147 (58.6)   |
| Mean age (SD)*  | 64.5 (±9.2) years | 70.0 (±8.7) years |
| Mean hemoglobin (SD)† | 13.7 (±1.4) g/dL | 13.3 (±1.6) g/dL |

*P<0.0001. †P<0.05.

Health Behaviors

Alcohol and smoking histories were defined as follows: alcohol consumption—dichotomized as current versus previous or no (life-long abstinence) use; and smoking—current versus never or past smoker.

Vascular Comorbidities

The following definitions were used: diabetes—fasting glucose ≥126 mL/dL, nonfasting glucose ≥200 mL/dL, or self-reported use of diabetes medications; hypertension—systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg (average of 2 blood pressure measurements), or self-reported use of hypertension medications; AF—based on electrocardiographic diagnosis or a positive response to the question “Has a doctor or other health professional ever told you that you had atrial fibrillation?”; ischemic heart disease, based on self-reported history of myocardial infarction, coronary bypass, angioplasty, or stenting or based on electrocardiographic evidence of myocardial infarction; hemoglobin level was determined from blood assays.

Statistical Methods

Descriptive statistics were computed overall and for those with and without HF. Logistic regression models were fitted to examine the relationship between HF and history of stroke/TIA. Incremental multivariable models were assessed with covariates entered into the models in groups. Groups of variables are defined as follows: demographics—age, sex, race, and region; socioeconomic status factors—education and income; health behaviors—alcohol use and smoking; and comorbidities—diabetes, hypertension, heart disease, and hemoglobin. Frequency of stroke/TIA history among those with and without HF was compared within each tertile of SBP.

The relationship between HF and prior stroke/TIA was examined as a function of SBP tertile. The tertiles were defined as: t1, SBP <119.5 (n=7222); t2, 119.5≤SBP<131.5 (n=7890); and t3, 131.5≤SBP (n=8192). After assessing the interaction between SBP tertile and HF, analyses were stratified by SBP tertile, and the relationship was examined before and after adjustment for all factors in the final model. The SBP tertile analysis was repeated using only subjects with a history of hypertension.

Results

Table 1 presents the description of the population both overall and by HF status. Of the 30,228 participants recruited to REGARDS, 223 were excluded due to no information regard-
ing prior stroke, 3691 were excluded due to no reported income information, an additional 2920 participants were excluded due to missing one or more covariates, and 1942 participants with AF were excluded. The final sample size for analysis was 21 453.

Among this community-dwelling cohort, prevalent stroke/TIA was present in 26.3% and 8.5% of participants with and without HF, respectively (P<0.0001). Table 2 presents the results of the incremental logistic regression modeling. The results indicate that the likelihood of prior stroke is higher among those with HF. This association was attenuated after multivariable adjustment, but remained significant with an OR of 2.2 (95% CI, 1.5 to 3.4).

The tertile analysis (Table 3) shows that the odds of stroke/TIA are higher for participants with HF than without HF within all SBP tertiles, and the association was strongest among those in the lowest SBP tertile. Participants with HF were equally distributed among the 3 tertiles. In the unadjusted model, the probability value for the interaction between HF and tertile of SBP was marginally significant (0.067). Relative to those without HF, the unadjusted ORs (95% CI) for prior stroke/TIA among those with HF within ascending tertiles of SBP were, respectively, 4.0 (2.8 to 5.8), 2.7 (1.8 to 3.9), and 2.3 (1.6 to 3.2), which remained significant after multivariable adjustment in the lowest tertile (<119.5 mm Hg; 3.3; 1.6 to 6.5). On repeating the analysis using only subjects with a history of hypertension, the unadjusted OR (95% CI) for prior stroke/TIA among those with HF within ascending tertiles of SBP were, respectively, 3.9 (2.0 to 7.4), 2.0 (1.0 to 3.9), and 3.2 (2.0 to 5.1). After multivariable adjustment, the observed associations were attenuated, although the relationship remained significant among participants in the lowest tertile: (OR, 1.27; 95% CI, 1.1 to 6.6).

**Discussion**

Our findings confirm that after multivariable adjustment, HF (defined as patients without AF using digoxin), is associated with an increase in prevalent stroke/TIA. In HF participants, prior stroke/TIA was present 2.2 times the prevalence in participants without HF. The frequency of HF in patients with stroke (14%) is higher than in the general population, and patients with HF constitute an important subgroup of patients with stroke, because they have a poor outcome and high rates of mortality and stroke recurrence. The high prevalence of stroke/TIA history in participants with HF in our study (26.3%) may partly be due to the high enrollment rate of

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<th>Table 2. Association Between HF and Stroke/TIA</th>
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<th>Table 3. Odds of Prior Stroke/TIA for Participants With HF Compared With Participants Without HF by SBP Tertiles</th>
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<tr>
<td>SBP                                      Unadjusted OR (95% CI) for Prior Stroke/TIA</td>
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<tr>
<td>&lt;119.5 mm Hg                              4.0 (2.8–5.8)</td>
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<tr>
<td>≥119.5, &lt;131.5 mm Hg                       2.7 (1.8–3.9)</td>
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<tr>
<td>≥131.5 mm Hg                              2.3 (1.6–3.2)</td>
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*Adjusted for demographics, socioeconomic status, health behaviors, functional status, and comorbidities.

blacks (who constitute 42% of the REGARDS population). Blacks have a much higher rate of HF than whites. Another factor is that TIAs were included in our study in addition to stroke.

The association of stroke/TIA history with lower SBP raises the possibility that cerebral hypoperfusion could be an important pathogenetic mechanism for stroke in patients with HF. Vulnerability of the brain to hypoperfusion in HF is also supported by a report of increased risk of cognitive impairment with lower blood pressures in patients with HF. Increasing severity of HF and decreasing ejection fraction are associated with decreased cerebrovascular reactivity and decreased global cerebral blood flow. Cerebral infarcts are larger in patients with left ventricular systolic dysfunction than in control subjects with normal ejection fraction, particularly distal to a high-grade stenosis, and focal cerebral hypoperfusion distal to a stenosis could be a mechanism for an increased prevalence of stroke in patients with HF. The second SBP tertile analysis we performed using only participants with a history of hypertension is against cerebral hypoperfusion being an important pathogenetic mechanism in stroke in HF, however. This analysis showed a lower odds ratio for stroke in the lowest SBP tertile compared with the first SBP tertile analysis of participants with both normotensives and hypertensives. Hypertensives have altered cerebrovascular reactivity and require higher SBP to maintain cerebral blood flow than normotensives, and this makes them more vulnerable to hypotension. We would have expected there would be a higher OR of stroke/TIA in the lowest SBP tertile in hypertensives than in the population with both normotensives and hypertensives if the pathogenesis of stroke in HF was due to cerebral hypoperfusion.

An alternative explanation is that low blood pressure selects out patients with HF with poor cardiac function and low cardiac output. These patients may be at increased risk of intraventricular thrombus formation and cerebral embolism due to poor function of the left ventricle. This is supported by the finding that decreasing blood pressure is associated with increasing mortality in an analysis of pooled HF studies. Low blood pressure in these patients is most likely due to poor cardiac output because its association with decreased survival is independent of pharmacological treatment. This association of low blood pressure and poor survival in patients with HF is the opposite to what is seen in the general population. If patients with HF and low SBP are at increased risk of cardiogenic embolism, anticoagulation treatment has the potential of reducing the risk of stroke in these
patients. This is currently being investigated in the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction study.\textsuperscript{30} This is the first cohort study to show a connection between lower SBP levels and risk of stroke/TIA in HF. These cross-sectional results may have potential implications for management of blood pressure in patients with HF. Pharmacological treatments for HF, including angiotensin-converting enzyme inhibitors and \( \beta \)-blockers, lower the blood pressure. Reducing SBP to the “lowest level tolerated” has been recommended in patients with HF.\textsuperscript{31} If patients with HF are at risk for hypoperfusion-related cerebral injury, excessive lowering of SBP could increase the risk of stroke, particularly in patients with prior stroke in whom the risk of stroke recurrence is higher. Further research is needed to determine whether SBP-lowering in patients with HF may carry a risk of stroke and, if so, to attempt to determine safe lower limits for SBP in these patients.

The limitations of this study include its cross-sectional nature. Because our study was a cross-sectional analysis of a cohort study, we are unable to establish a time directionality between onset of HF and of stroke/TIA. It is possible that the association of lower SBP and prevalent stroke could reflect more aggressive blood pressure control in participants with HF after a stroke compared with patients with HF without stroke. This is unlikely, however, because hypertension is a risk factor for recurrent stroke and remains elevated after stroke. This is unlikely, however, because hypertension is a risk factor for recurrent stroke and remains elevated after stroke despite antihypertensive treatment.\textsuperscript{32} Definitive determination of the directionality of the relationship between HF or hypertension and stroke will require a longitudinal study and the ongoing REGARDS and REGARDS-MI studies, which are tracking incident stroke and cardiac events and hospitalizations, will provide an appropriate context for such a study. The basing of diagnosis of HF on digoxin use is also a limitation of the study. Use of digoxin to diagnose HF may have resulted in patients with diastolic HF being excluded from our HF group. Diastolic HF is not an established risk factor for stroke/TIA and studies reporting HF as a risk factor have almost identical in patients with HF using digoxin or not have a very high specificity but modest sensitivity.\textsuperscript{21} The low sensitivity may have biased our results toward the null but is unlikely to have qualitatively affected our results, because the prevalence of HF in the general population is only approximately 5\% at the mean age of our study participants,\textsuperscript{33} and misclassified participants with HF would only constitute a small minority of our “no HF” group. Exclusion of patients who were not using digoxin from our HF group is unlikely to have altered our study results because the rate of stroke is almost identical in patients with HF using digoxin or not using digoxin.\textsuperscript{34} A major strength of this study is the large cohort size, which has allowed for a statistically robust analysis in subgroups of SBP tertiles. The large proportion of black participants in this study is also a strength.

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Disclosures

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References


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