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Epidemiology of Stroke in Chronic Heart Failure Patients with Normal Sinus Rhythm: Findings from the DIG Stroke Sub-Study

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Abstract

Background—Little is known about the epidemiology of stroke in chronic systolic and diastolic heart failure (HF) patients in normal sinus rhythm (NSR) receiving angiotensin-converting enzyme (ACE) inhibitors. Because all HF patients in the Digitalis Investigation Group (DIG) trial (N=7788) were in NSR and nearly all were receiving ACE inhibitors, a survey-based stroke sub-study was conducted but its findings have never been published.

Methods—DIG investigators confirmed a total 222 cases of stroke of which 144 had neurological deficit ≥24 hours. We used logistic regression models to determine predictors of incident stroke among all 7788 patients and predictors of neurological deficit ≥24 hours and all-cause mortality among 222 stroke patients.

Results—Age ≥65 years (adjusted odds ratio {AOR}, 1.36; 95% confidence interval {CI}, 1.02–1.80; P=0.035), nonwhite race (AOR, 0.65; 95% CI, 0.42–0.99; P=0.047), hypertension (AOR, 1.46; 95% CI, 1.11–1.94; P=0.008), diabetes mellitus (AOR, 1.37; 95% CI, 1.03–1.82; P=0.030), and cardiomegaly (AOR, 1.39; 95% CI, 1.03–1.86; P=0.030) were independent predictors of stroke. However, among those with stroke, nonwhites had higher odds of neurological deficits ≥24 hours (AOR, 2.86; 95% CI, 1.01–8.07; P=0.047) and death (AOR, 3.28; 95% CI, 1.30–8.30; P=0.012).

Conclusion—Older age, hypertension, diabetes and cardiomegaly were associated with increased incidence of stroke among HF patients with NSR receiving ACE inhibitors. The association of race and stroke, however, was complex. While nonwhite race was associated with decreased risk of stroke, among those with stroke, nonwhite race was associated with increased stroke severity and mortality.

Keywords

heart failure; stroke; epidemiology; outcomes; race

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1. Introduction

Atrial fibrillation (AF) is a risk factor for stroke, both in general population and in those with heart failure (HF) [1–4]. However, little is known about the epidemiology of stroke in chronic systolic and diastolic HF patients with normal sinus rhythm (NSR) receiving angiotensin-converting enzyme (ACE) inhibitors. Because all chronic HF patients enrolled in the Digitalis Investigation Group (DIG) trial had NSR and over 90% were receiving ACE inhibitors, a survey-based stroke sub-study was conducted to understand the stroke epidemiology in these patients. However, to the best of our knowledge, those data have never been published. We used public-use copies of the DIG datasets, obtained from the National Heart, Lung, and Blood Institute, to report the findings of the DIG stroke sub-study.

2. Methods

2.1. Patient population

The DIG trial was conducted between 1991 and 1993 in the United States and Canada. The rationale, design and results of the DIG trial have been published previously [5,6]. Briefly, 7788 chronic systolic and diastolic HF patients were enrolled from 306 centers in the United States and Canada and were randomized to receive digoxin or placebo. These patients were followed for a mean of 2.9 years. All patients were in NSR and over 90% patients were receiving ACE inhibitors. Race was self-identified by patients and 1128 (15.5%) were nonwhites, of whom 80% were African Americans [7].

2.2. Ascertainment of stroke

The DIG Steering Committee sent a letter to DIG investigators, who reported stroke (including mini-stroke and transient ischemic attack), asking for additional data on computerized tomographic scans and duration of neurological deficit. The DIG investigators reported 222 cases of stroke of which 144 had neurological deficit lasting ≥ 24 hours. In the DIG trial, 366 patients had hospitalizations due to stroke [6,8]. Hospitalization due to stroke was a secondary outcome in the trial. The causes of hospitalization were classified by DIG investigators and were not centrally adjudicated [6].

2.3. Statistical analysis

Because of a significant association between race and stroke, baseline patient characteristics are presented by race. Bivariate and multivariable logistic regression models were used to determine predictors of stroke in all 7788 patients, and to determine predictors of neurological deficit ≥ 24 hours and all-cause mortality among those with stroke. Variables in all three multivariable models included age, gender, race, myocardial infarction, hypertension, diabetes mellitus, cardiomegaly, serum creatinine and left ventricular ejection fraction. Variables were selected based on their significant ($P < 0.10$) bivariate associations with stroke or their clinically significant associations with stroke. All statistical tests were two-sided, and tests with P -value < 0.05 were considered significant. Confidence intervals were computed based on a 95% confidence levels. SPSS for Windows (Version 15) was used for all data analyses [9].

3. Results

3.1. Baseline patient characteristics

Overall, patients had a mean ($\pm$ SD) age of 64 (± 11) years, 25% were women, 15% were nonwhite, 29% had history of diabetes, and 47% had hypertension. The baseline patient characteristics by race are presented in Table 1. Compared to whites, nonwhite patients were

more likely to be younger, women, and have a history of hypertension (and higher mean baseline blood pressure) and diabetes but less likely to have prior myocardial infarction and chronic kidney disease (Table 1). Of the 222 patients with stroke, 26 (12%) were nonwhites, 151 (68%) had computerized tomographic scans, of whom 118 (78%) had an abnormal scan and 94 (80%) of the 118 had findings compatible with a non-hemorrhagic stroke. There was no racial variation in the receipt of computerized tomographic scans (68% of whites versus 69% of nonwhites; $P=0.888$).

3.2. Predictors of stroke

Age ≥ 65 years (adjusted odds ratio {AOR}, 1.36; 95% confidence interval {CI}, 1.02–1.80; $P=0.035$), hypertension (AOR, 1.46; 95% CI, 1.11–1.94; $P=0.008$), diabetes (AOR, 1.37; 95% CI, 1.03–1.82; $P=0.030$), and cardiomegaly (AOR, 1.39; 95% CI, 1.03–1.86; $P=0.030$) were independent predictors of increased stroke. Nonwhite race had a non-significant bivariate association with reduced odds of incident stroke (unadjusted OR, 0.78; 95% CI, 0.51–1.18; $P=0.235$), which became stronger and significant after multivariable risk adjustment (AOR, 0.65; 95% CI, 0.42–0.99; $P=0.047$; Table 2). Other bivariate predictors of stroke are displayed in Table 2.

3.3. Predictors of neurological deficits ≥ 24 hours

The 222 patients with stroke had a mean ($\pm$ SD) age of 66 (± 10) years, 27% were women, 12% were nonwhite, 36% had history of diabetes, and 57% of hypertension (data not presented). Among these patients with a stroke, age ≥ 65 years had both a bivariate (AOR, 1.88; 95% CI, 1.07–3.29; $P=0.027$) and a multivariable-adjusted (AOR, 2.15; 95% CI, 1.18–3.92; $P=0.012$) association with neurological deficits ≥ 24 hours. Nonwhite race had a non-significant bivariate association with increased odds of neurological deficits ≥ 24 hours (unadjusted OR, 1.94; 95% CI, 0.74–5.04; $P=0.176$), which became stronger and significant after multivariable risk adjustment (AOR, 2.86; 95% CI, 1.01–8.07; $P=0.047$; Table 3). Similarly, the non-significant bivariate association of female gender with neurological deficits ≥ 24 hours (unadjusted OR, 0.66; 95% CI, 0.36–1.21; $P=0.176$) became stronger and significant after multivariable risk adjustment (AOR, 0.45; 95% CI, 0.21–0.98; $P=0.044$; Table 3).

3.4. Predictors of death among those with stroke

Among the 222 chronic HF patients in NSR who developed stroke, only age ≥ 65 years (unadjusted OR, 2.04; 95% CI, 1.15–3.63; $P=0.015$) and race (unadjusted OR, 3.01; 95% CI, 1.30–7.00; $P=0.010$) had bivariate associations with increased mortality. Both these associations remained significant after multivariable adjustment: age (AOR, 2.05; 95% CI, 1.11–3.81; $P=0.022$) and race (AOR, 3.28; 95% CI, 1.30–8.30; $P=0.012$).

4. Discussion

In ambulatory chronic systolic and diastolic HF patients in NSR, older age, hypertension, diabetes, and cardiomegaly were strong predictors of increased risk of incident stroke but nonwhite race was associated with a lower risk of stroke. However, among those who suffered a stroke, older age and nonwhite race were associated with increased risk while female gender was associated with reduced risk of neurological deficit ≥ 24 hours. Older age and nonwhite race were also associated with increased risk of all-cause mortality. The paradoxical association of race and lower incident stroke in HF and NSR is intriguing but may be explained by a survival cohort effect as data from population studies suggests that nonwhites are more likely to suffer from stroke at a younger age and that they are also more likely to suffer from more severe stroke and stroke-related deaths.

Based on the incidence of 222 stroke events in 7788 patients during a mean follow up of 2.9 years, the incidence rate for stroke may be estimated to be about 1% annually. This suggests that the incidence of stroke among HF patients in NSR is higher than that in the general population but lower than that in HF patients in general. It has been conservatively estimated that the annual incidence of stroke in the United States is about 0.3% [10]. On the other hand, the annual incidence of stroke in HF patients has been reported to be between 0.8–4% in HF patients enrolled in clinical trials and 1.7–10.4% among HF patients in the community [11–14]. These findings are important as the vast majority of HF patients do not have AF. The prevalence of AF in HF has been reported to be about 30% in clinical trial and about 40% in community-dwelling HF patients [2,11].

The findings of significant independent associations of older age, hypertension, diabetes and cardiomegaly in this cohort of ambulatory patients with HF and NSR may not be surprising as all these are known risk factors for stroke[15–24]. Interestingly, nonwhite race was associated with a non-significant 22% reduction in the risk of stroke (unadjusted OR, 0.78; 95% CI, 0.51–1.18; P=0.235). This was counterintuitive as despite their younger age, nonwhites had a higher prevalence of hypertension, diabetes and cardiomegaly, and these risk factors would have been expected to increase their risk of stroke. When we adjusted for these and other covariates in a multivariable regression model, this association became stronger and significant (adjusted OR, 0.65; 95% CI, 0.42–0.99; P=0.047). This was not surprising as the multivariable risk adjustment attenuated/eliminated the effect of these confounders, thus further reducing the risk for stroke for nonwhites. To determine the magnitude of confounding by hypertension, diabetes and cardiomegaly, we ran a post hoc multivariable regression model adjusting for these three covariates only and observed that the association between nonwhite race and stroke became strong and significant (adjusted OR, 0.64; 95% CI, 0.42–0.98; P=0.041). This suggests that had it not been for the higher prevalence of these three conditions among nonwhites, the bivariate association between race and reduced risk of stroke would also have been significant. So, how do we explain this apparent intrinsic association between nonwhite race and reduced risk of stroke in HF patients with NSR?

One potential explanation for an inverse association between nonwhite race and incident stroke is that stroke may have more severe and fatal effect among nonwhites, which may have precluded hospitalization for stroke in those patients. Data from our analysis suggest that nonwhite race was associated with increased stroke severity and mortality. Severe stroke may be associated with sudden death and between 10 to 20% of all sudden deaths are due to stroke [25,26]. The decreased incidence of stroke among nonwhites may also be a survival cohort effect. Data from population studies indicated that African Americans are more likely to suffer from stroke at a younger age and have more severe stroke [23,27–29]. Compared to whites, nonwhites are known to have excess stroke mortality [30,31]. In the National Longitudinal Mortality Study (N=275,729), compared to whites, African Americans had about a fourfold increased risk of stroke-related death at age 45 years [30]. In that study, the rate of fatal stroke before age 60 years was 6% for whites and >15% for both Hispanics and African Americans. The authors of that study concluded that the excess stroke mortality in African Americans mainly occurs at younger ages between 45 and 55 years. An analysis based on National Center for Health Statistics Compressed Mortality File also reported disproportionately (nearly threefold) higher rates of stroke mortality among African Americans in the 45–64 years age group than in those ≥65 years [31]. African Americans are also at a higher risk of stroke at younger age than whites [23]. Thus, higher rates of incident stroke in general and severe and fatal stroke in particular among nonwhites at a younger age may have resulted in the selection of an older cohort with lower risk of stroke. Nonwhite patients in our analysis had a mean age of 60 years and thus may have survived early stroke-related deaths.

The race-related survivor cohort phenomenon is not unique to stroke and can also be observed in other disease conditions. Data from the Acute Decompensated Heart Failure National Registry (ADHERE) registry (N=105388) indicate that among HF patients with chronic kidney disease, defined by an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m², stages 3 (moderate, eGFR 30–59), 4 (severe, eGFR 15–29) and 5 (end-stage, eGFR <15), 15%, 15% and 33% respectively were African Americans [32]. On the other hand, among those with normal kidney function (eGFR ≥90), 39% were African Americans [32]. These findings suggest that African Americans with HF were less likely to develop chronic kidney disease, but were more likely to progress into a more advanced stage 5 disease, often requiring chronic dialysis. A similar association between race and chronic kidney disease was also observed in the general population. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS), while the overall prevalence of chronic kidney disease (eGFR <60 ml/min/1.73 m²) was higher among whites, the prevalence of stage 4 and 5 disease was higher among African Americans [33].

In a study of systolic HF patients in the Studies of left ventricular dysfunction (SOLVD) prevention and treatment trials that were in NSR, diabetes was found to be an independent predictor of stroke in both men and women, and age and hypertension were risk factors for men only [24]. However, in that study, stroke was part of combined endpoints of thromboembolic events that also included pulmonary and peripheral embolism. However, unlike our study, that study was restricted to patients with left ventricular ejection fraction <35%, only half of the patients were receiving ACE inhibitors, and there was no data on race. A propensity-matched study of the effect of race on outcomes in DIG trial did not find any significant association between race and stroke hospitalization [34]. However, that analysis was not based on the DIG stroke sub-study data and misclassification of stroke is possible as hospitalization was not centrally adjudicated. Conversely, patients included in the stroke sub-study had their diagnosis of stroke specifically verified by study investigators.

The apparent intrinsic inverse association between nonwhite race and stroke among HF patients in NSR should not be misinterpreted and should not lead to complacency. Diabetes mellitus and hypertension are two major risk factors for stroke [35], and both conditions were more common among nonwhites in our study. Therefore, the importance of prevention and treatment of diabetes mellitus and hypertension among nonwhites with HF, especially those with younger age, cannot be overemphasized, which may have important implications for reducing stroke severity and mortality in these patients. Racial disparity in access to care is well documented and African American stroke patients have been documented to receive suboptimal care [18,36,37]. Proper care of nonwhite HF patients with stroke may help reduce the burden of stroke in these patients.

Our study has several limitations. Our analysis was based on hospitalized stroke patients and we had no data on fatal stroke. The diagnosis of stroke was not centrally adjudicated. We had no data on the number of DIG investigators who had received the letter from the DIG Steering Committee requesting additional data for the stroke sub-study and also had no data on the number of investigators who responded to it. We also did not have data on computerized tomographic scan and type of stroke on all patients with stroke. Patients in this analysis were predominantly young, men and in NSR from pre beta blocker era of heart failure therapy, and one must be very careful to extrapolate these data to contemporary HF populations. Patients may have developed atrial fibrillation after baseline. However, the prevalence of stroke in HF patients with and without atrial fibrillation has been described to be similar [38]. Over 90% of our patients were receiving ACE inhibitors, which have been shown to prevent the development of atrial fibrillation in HF [39–42].

In conclusion, in HF patients in NSR receiving ACE inhibitors, the incidence of stroke was relatively low. Older age, hypertension, diabetes, and cardiomegaly were independent predictors of stroke. The association of race and stroke, however, was complex. While nonwhite race was associated with decreased risk of stroke, among those with stroke, nonwhite race was associated with increased stroke severity and mortality. This paradoxical association of nonwhite race with lower odds of stroke in HF and NSR is intriguing but may be explained by a survival cohort effect as data from population studies suggests that nonwhites are more likely to suffer from stroke at a younger age, more severe stroke and stroke-related deaths. Further studies are needed to elucidate the complex relationship between race and stroke in HF.

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Table 1

Baseline characteristics of chronic heart failure patients in normal sinus rhythm by race

N (%) or mean ($\pm$ SD)	Whites (N=6660)	Nonwhites (N=1128)	P value
Age (years)	65 ($\pm$ 11)	60 ($\pm$ 12)	<0.0001
Female	1572 (24%)	354 (31%)	<0.0001
Body mass index (kg/m ²)	27 ($\pm$ 5)	28 ($\pm$ 6)	<0.0001
Duration of heart failure (months)	30 ($\pm$ 36)	30 ($\pm$ 36)	0.580
Primary cause of heart failure			
Ischemic	4891 (73%)	469 (42%)	<0.0001
Hypertensive	468 (7%)	337 (30%)	
Idiopathic	916 (14%)	195 (17%)	
Others	385 (6%)	127 (11%)	
Prior myocardial infarction	4486 (67%)	422 (37%)	<0.0001
Current angina pectoris	1894 (28%)	221 (20%)	<0.0001
Hypertension	2862 (43%)	812 (72%)	<0.0001
Diabetes mellitus	1829 (28%)	389 (35%)	<0.0001
Chronic kidney disease	3215 (48%)	312 (28%)	<0.0001
Medications			
Pre-trial digoxin use	2856 (43%)	509 (45%)	0.160
Trial use of digoxin	3331 (50%)	558 (50%)	0.734
Angiotensin-converting enzyme inhibitors	6214 (93%)	1060 (94%)	0.403
Diuretics	5129 (77%)	947 (84%)	<0.0001
Potassium sparing diuretics	551 (8%)	45 (4%)	<0.0001
Potassium supplement	1830 (28%)	369 (33%)	<0.0001
Symptoms and signs of heart failure			
Dyspnea at rest	1348 (20%)	357 (32%)	<0.0001
Dyspnea on exertion	5076 (76%)	786 (70%)	<0.0001
Activity limitation	5099 (77%)	804 (71%)	<0.0001
Jugular venous distension	807 (12%)	213 (19%)	<0.0001
Third heart sound	1575 (24%)	271 (24%)	0.784
Pulmonary râles	1084 (16%)	217 (19%)	0.014
Lower extremity edema	1319 (20%)	314 (28%)	<0.0001
New York Heart Association functional class			
I	929 (14%)	174 (15%)	0.567
II	3631 (55%)	613 (54%)	
III	1968 (30%)	319 (28%)	
IV	132 (2%)	22 (2%)	
Heart rate (beats per minute)	78 ($\pm$ 12)	82 ($\pm$ 13)	<0.0001
Blood pressure, systolic (mm Hg)	127 ($\pm$ 20)	130 ($\pm$ 22)	<0.0001
Blood pressure, diastolic (mm Hg)	74 ($\pm$ 11)	79 ($\pm$ 13)	<0.0001

N (%) or mean ($\pm$ SD)	Whites (N=6660)	Nonwhites (N=1128)	P value
Pulmonary congestion by chest x-ray	883 (13%)	226 (20%)	<0.0001
Cardiothoracic ratio >0.5	3829 (58%)	861 (76%)	<0.0001
Serum potassium (mEq/L)	4.35 ($\pm$ 0.43)	4.27 ($\pm$ 0.47)	<0.0001
Serum creatinine (mg/dL)	1.28 ($\pm$ 0.37)	1.29 ($\pm$ 0.39)	0.286
Estimated glomerular filtration rate (ml/min per 1.73 m ²)	62 ($\pm$ 21)	74 ($\pm$ 26)	<0.0001
Ejection fraction (%)	32 ($\pm$ 12)	31 ($\pm$ 13)	0.020
Ejection fraction >45%	851 (13%)	137 (12%)	0.555

Table 2

Predictors of stroke in chronic heart failure patients in normal sinus rhythm (N=7788)

	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Age ≥65 years	1.40 (1.07–1.84), P=0.015	1.36 (1.02–1.80), P=0.035
Female	1.11 (0.82–1.50), P=0.518	0.92 (0.67–1.27), P=0.610
Non-white	0.78 (0.51–1.18), P=0.235	0.65 (0.42–0.99), P=0.047
Prior myocardial infarction	0.84 (0.64–1.10), P=0.210	0.82 (0.62–1.09), P=0.175
Diabetes mellitus	1.43 (1.08–1.89), P=0.012	1.37 (1.03–1.82), P=0.030
Hypertension	1.52 (1.16–1.98), P=0.003	1.46 (1.11–1.94), P=0.008
Cardiothoracic ratio >0.5	1.42 (1.07–1.89), P=0.017	1.39 (1.03–1.86), P=0.030
Serum creatinine (mg/dL)	1.04 (0.73–1.48), P=0.832	0.89 (0.61–1.29), P=0.530
Ejection fraction <35%	0.94 (0.71–1.24), P=0.651	0.97 (0.73–1.30), P=0.847

Table 3

Predictors of neurological deficit ≥ 24 hours in chronic heart failure patients in normal sinus rhythm and stroke (N=222)

	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Age ≥ 65 years	1.88 (1.07–3.29), P=0.027	2.15 (1.18–3.92), P=0.012
Female	0.66 (0.36–1.21), P=0.176	0.45 (0.21–0.98), P=0.044
Nonwhite	1.94 (0.74–5.04), P=0.176	2.86 (1.01–8.07), P=0.047
Prior myocardial infarction	1.50 (0.86–2.63), P=0.152	1.52 (0.83–2.78), P=0.171
Diabetes mellitus	1.43 (0.80–2.57), P=0.230	1.63 (0.87–3.06), P=0.130
Hypertension	0.89 (0.51–1.56), P=0.695	0.91 (0.49–1.71), P=0.771
Cardiothoracic ratio >0.5	1.01 (0.56–1.81), P=0.987	1.07 (0.56–2.03), P=0.839
Serum creatinine (mg/dL)	0.94 (0.44–2.02), P=0.875	0.67 (0.30–1.51), P=0.334
Ejection fraction $<35\%$	0.97 (0.54–1.72), P=0.905	0.74 (0.37–1.48), P=0.393