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A Propensity-Matched Study of Hypertension and Increased Stroke-Related Hospitalization in Chronic Heart Failure

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Abstract

Hypertension is a risk factor for heart failure and stroke. However, the effect of hypertension in patients with heart failure has not been well studied. In the Digitalis Investigation Group trial, 3674 (47%) of the 7788 patients had a history of hypertension. Probability or propensity scores for a history of hypertension were calculated for each patient using a multivariable logistic regression model, and were then used to match 2386 pairs of patients without and with a history of hypertension. Kaplan-Meier and matched Cox regression analyses were used to estimate associations of a history of hypertension hospitalization due to stroke during 37 months of median follow up. After matching, patients without and with a history of hypertension had a mean systolic blood pressure of 127 mm Hg. Hospitalization due to stroke occurred in 90 patients (rate, 129/10,000 person-years of follow-up) without a history of hypertension and 121 patients (rate, 178/10,000 person-years of follow-up) with a history of hypertension (hazard ratio {HR} = 1.52; 95% confidence interval {CI} = 1.11–2.08; P=0.010). This association was also observed among patients with baseline systolic blood pressure <140 mm Hg (HR = 1.35; 95% CI = 1.01–1.81; P=0.044). A history of hypertension was associated with increased risk of hospitalization due to stroke among heart failure patients balanced in all measured baseline covariates including blood pressure.

Keywords

heart failure; NYHA class; natural history; outcomes; stroke; mortality

High blood pressure is a risk factor for stroke and normalization of blood pressure has been shown to reduce incident stroke.^{1–3} Hypertension is also a risk factor for heart failure (HF) and the prevalence of hypertension is high in patients with HF. The prevalence of stroke is also

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high in patients with HF.⁴ However, to what extent a history of hypertension, regardless of the level of blood pressure control, may be associated with incident stroke in HF is unknown. We studied the effect of a history of hypertension on hospitalizations due to stroke in a propensity-matched population of ambulatory chronic systolic and diastolic HF patients in normal sinus rhythm who were well balanced in all measured baseline covariates including blood pressure.

Methods

We used a public-use copy of the Digitalis Investigation Group (DIG) trial dataset obtained from the National Heart, Lung and Blood Institute. The design of the DIG trial has been previously described.⁵ Of the 7788 ambulatory patients with chronic HF enrolled in the DIG trial, 3674 (47%) had a history of hypertension and no baseline history of stroke was reported. Most patients were receiving angiotensin-converting enzyme inhibitor and diuretics. The presence of baseline hypertension was ascertained by investigators based on chart documentation of past medical history. For the purpose of the current analysis, hospitalization due to stroke was the primary outcome. Data on type of stroke were not available. Hospitalization due to stroke was a pre-specified secondary outcome in the DIG trial. The diagnosis leading to hospitalization was classified by DIG investigators, who were blinded to the patient's study-drug assignment. However, these diagnoses were not centrally adjudicated. Patients were followed up for a median duration of 38 months and follow up was 99% complete.⁶

Due to the significant imbalance in baseline covariates between patients with and without hypertension (Table 1), we used propensity score matching to assemble a balanced cohort of patients. The propensity score is the conditional probability of receiving an exposure (e.g. hypertension) given a set of measured covariates.^{7–9} We estimated propensity scores for hypertension for each of the 7788 patients, using a non-parsimonious multivariable logistic regression model (c statistic=0.76) and used that to match 2386 pairs of patients with and without hypertension.^{10–14} We assessed the effectiveness of matching and bias reduction by estimating standardized differences, expressed as a percentage of the pooled standard deviations. We also provide paired-sample t- and McNemar tests to describe the baseline characteristics of patients with and without hypertension.

We used Kaplan-Meier and matched Cox regression analyses to determine the effect of baseline hypertension on outcome. Even though our matched cohort was well-balanced in all measured baseline covariates, we cannot rule out hidden bias due to imbalances in unmeasured covariates. Therefore, we conducted a formal sensitivity analysis to quantify the degree of a hidden bias that would need to be present to invalidate our main conclusions.¹⁵

To determine if the effect of a history of hypertension on incident stroke was modified by baseline blood pressure control, we conducted a subgroup analysis among patients with normal (<140 mm Hg) and above-normal ($\geq$ 140 mm Hg) baseline systolic blood pressure using the pre-match cohort and adjusting for propensity scores. All data analyses were performed using SPSS-15 for Windows.¹⁶ All P values were 2-sided and P < 0.05 was regarded as statistically significant.

Results

The mean ($\pm$ SD) age of the 4772 matched patients was 64 ($\pm$ 11) years (range 21–94), 24% were women, and 12% were non-whites. There were no significant imbalances in any measured baseline covariates between patients with and without hypertension after matching (Table 1). Before matching, mean systolic and diastolic blood pressures were higher in those with a history of hypertension but was similar after matching. After matching, absolute standardized

differences for all baseline covariates were less than 10% and most were <5%, suggesting substantial bias reduction (Figure 1).

Hospitalizations due to stroke occurred in 90 (rate, 129/10,000 person-years) patients without a history of hypertension and 121 (rate, 178/10,000 person-years) patients with a history of hypertension (hazard ratio {HR}=1.52; 95% confidence interval {CI}=1.11–2.08; P=0.001; Figure 2 and Table 2). Extrapolated to an estimated 5 million HF patients in the United States, a history of hypertension would be responsible for an additional 40422 hospitalizations due to stroke. The rates of hospitalizations due to stroke before matching are also displayed in Table 2. Our sensitivity analysis reveals that an unmeasured binary covariate would need to increase the odds of “not having hypertension” by more than 10.6% to explain away this association (z-statistic=2.61; two-tailed p = 0.0093), suggesting that these results are insensitive to modest hidden biases.

Of the 7788 pre-match patients, 2363 (30.3%) had baseline systolic blood pressure ≥ 140 mmHg. Among patients with normal baseline systolic blood pressure (<140 mm Hg), stroke hospitalization occurred in 3.4% (115/3360) and 4.8% (99/2065) of patients without and with a history of hypertension (HR=1.35; 95% CI =1.01–1.81; P=0.044). Among patients with above-normal baseline systolic blood pressure (≥ 140 mm Hg), stroke hospitalization occurred in 4.8% (36/754) and 7.2% (116/1609) of patients without and with a history of hypertension (HR =1.35; 95% CI =0.91–2.02; P=0.139). There was no interaction between a history of hypertension and baseline systolic blood pressure. The effect of a history of hypertension on stroke hospitalization was similar in both genders and regardless of ejection fraction (data not shown). A history of hypertension was also associated with all-cause hospitalization (HR=1.13; 95% CI=1.03–1.23; P=0.009) and cardiovascular hospitalization (HR =1.13; 95% CI =1.03–1.23; P=0.009) but had no association with all-cause mortality (HR =1.02; 95% CI =0.92–1.15; P=0.689).

Discussion

These findings of the current analysis suggest that in ambulatory patients with chronic mild to moderate HF, a history of hypertension was common and was associated with increased risk of incident hospitalization due to stroke despite similar baseline blood pressure. Further, a history of hypertension was associated with increased risk of stroke among those with normal baseline blood pressure.

The findings of our study are consistent with those in the literature suggesting a positive association between hypertension and stroke. Though the effect of blood pressure and hypertension on stroke has been well studied in the general population, less is known about the effect of a history of hypertension regardless of the level of blood pressure control on stroke in those with HF.^{17,18} To the best of our knowledge this is the first report of the effect of a history of hypertension on stroke in a propensity-matched cohort of HF patients who were well balanced in all measured covariates including baseline blood pressure.

Despite the increased risk for stroke in HF, currently there is no evidence that antiplatelet or anticoagulation therapy is effective in preventing stroke in these patients and current guidelines do not recommend the routine use of anticoagulants in HF patients with normal sinus rhythm.^{19–21} This highlights the importance of identifying HF patients at high risk for stroke such as those with a history of hypertension. The effect of hypertension on stroke may be attenuated with the reduction of blood pressure.^{1,2,22–24} However, it is unlikely to fully explain the reduction in the risk of stroke in patients receiving anti-hypertensive therapy.^{25,26} Activation of the renin-angiotensin-aldosterone system in stroke is believed to play a major role in causing ischemic vascular injury to vital organs including the brain and their inhibitors may provide

benefit beyond blood pressure control.^{27–29} However, differences in the use of ACE inhibitors may not explain the results of our analysis as over 90% of patients in the DIG trial were receiving ACE inhibitors and patients were balanced in all measured baseline covariates including use of ACE inhibitors.

The risk of stroke in HF patients with controlled hypertension was similar to those with new-onset hypertension (baseline high systolic blood pressure in those without a history of hypertension). This suggests that factors other than the level of blood pressure control may be associated with the pathogenesis of stroke in these patients.³⁰ However, this also suggests that lower baseline blood pressure was associated with fewer strokes, highlighting the importance of monitoring and controlling blood pressure in HF.

Our study has several limitations. In the DIG trial, the incidence of hospitalization due to stroke was not a major endpoint and was not centrally adjudicated. Therefore, misclassification is possible. However, because this was likely a random misclassification, it may have underestimated the association observed in the current analysis. Imbalances in unmeasured covariates, may explain our findings, if such covariates are strongly correlated with a history of hypertension and incident stroke, and not strongly correlated with covariates used to estimate propensity scores (Table 1). We had no data on duration and control of hypertension and other anti-hypertensive drugs used. It is possible that some patients without baseline history of hypertension may have developed hypertension during follow up. However, this regression dilution may have underestimated the association observed in our analysis. Finally, patients in our analysis are relatively young male HF patients in normal sinus rhythm from the early 1990s and their relevance to contemporary HF patients is unknown.

In conclusion, a history of hypertension was associated with increased risk of hospitalizations due to stroke in HF patients with normal sinus rhythm who were well-balanced in all measured baseline covariates including blood pressure and that this association persisted in the subgroup with normal blood pressure. Future studies are needed to better understand factors associated with increased risk of stroke in HF patients with a history of hypertension and normal blood pressure.

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Figure 1.

Absolute standardized differences before and after propensity score matching comparing covariate values for patients with and without a history of hypertension

Number of patients at risk

No history of hypertension	2386	2128	1863	1314	531
History of hypertension	2386	2067	1827	1260	468

Figure 2.

Kaplan-Meier plots for hospitalization due to stroke for patients with and without a history of hypertension

Baseline patient characteristics in patients with and without a history of hypertension, before and after propensity score matching

Table 1

Variables	Before matching		After matching		P value
	No (N =4114)	History of hypertension Yes (N =3674)	No (N =2386)	History of hypertension Yes (N =2386)	
Age (years)	63.4 (±11.2)	64.5 (±10.5)	64.3 (±11.2)	64.4 (±10.2)	0.776
Women	836 (20%)	1090 (30%)	589 (25%)	560 (24%)	0.334
Non-whites	316 (8%)	812 (22%)	283 (12%)	294 (12%)	0.628
Body mass index (kg/m ²)	26.5 (±4.8)	28.2 (±5.8)	27.3 (±5.1)	27.1 (±4.9)	0.394
Heart failure duration (months)	30.5 (±36.5)	29.0 (±36.2)	29.8 (±35.6)	29.1 (±36.2)	0.510
Ischemic cause of heart failure	3054 (74%)	2306 (63%)	1677 (70%)	1671 (70%)	0.873
Prior myocardial infarction	2790 (68%)	2118 (58%)	1516 (64%)	1517 (64%)	1.000
Current angina pectoris	1104 (27%)	1011 (28%)	647 (27%)	661 (28%)	0.667
Diabetes mellitus	903 (22%)	1315 (36%)	679 (29%)	692 (29%)	0.688
Chronic kidney disease	1740 (42%)	1787 (49%)	1130 (47%)	1120 (47%)	0.794
Medications					
Digoxin (pre-trial use)	1875 (46%)	1490 (41%)	1070 (45%)	1035 (43%)	0.324
Digoxin (by randomization)	2057 (50%)	1832 (50%)	1181 (50%)	1190 (50%)	0.814
Angiotensin-converting enzyme inhibitors	3829 (93%)	3445 (94%)	2234 (94%)	2238 (94%)	0.859
Hydralazine and Nitrates	29 (1%)	82 (2%)	25 (1%)	26 (1%)	1.000
Non-potassium-sparing diuretics	3067 (75%)	3009 (82%)	1891 (79%)	1890 (79%)	1.000
Potassium-sparing diuretics	329 (8%)	267 (7%)	200 (8%)	191 (8%)	0.673
Potassium supplement	1048 (26%)	1151 (31%)	699 (29%)	698 (29%)	1.000
Symptoms and signs of heart failure					
Dyspnea at rest	755 (18%)	950 (26%)	505 (21%)	506 (21%)	1.000
Dyspnea on exertion	3092 (75%)	2770 (75%)	1785 (75%)	1809 (76%)	0.436
Jugular venous distension	488 (12%)	532 (15%)	316 (13%)	318 (13%)	0.966
Third heart sound	1006 (25%)	840 (23%)	574 (24%)	560 (24%)	0.661
Pulmonary rales	624 (15%)	677 (18%)	377 (16%)	396 (17%)	0.478
Lower extremity edema	670 (16%)	963 (26%)	486 (20%)	470 (20%)	0.586
New York Heart Association functional class					
I	580 (14%)	523 (14%)	348 (15%)	334 (14%)	
II	2245 (55%)	1999 (54%)	1317 (55%)	1302 (55%)	0.496
III	1212 (30%)	1075 (29%)	674 (28%)	701 (29%)	
IV	77 (2%)	77 (2%)	47 (2%)	49 (2%)	
Heart rate (beats per minute)	78 (±12)	79 (±13)	78 (±13)	78 (±13)	0.986
Systolic blood pressure (mm Hg)	121 (±17)	135 (±21)	127 (±17)	127 (±18)	0.735
Diastolic blood pressure (mm Hg)	72 (±10)	78 (±12)	75 (±10)	75 (±11)	0.677
Chest radiograph findings					
Pulmonary congestion	538 (13%)	571 (16%)	319 (13%)	336 (14%)	0.502
Cardiothoracic ratio > 0.5	2306 (56%)	2384 (65%)	1446 (61%)	1447 (61%)	1.000
Serum concentrations					
Creatinine (mg/dL)	1.3 (±0.3)	1.3 (±0.4)	1.3 (±0.4)	1.3 (±0.4)	0.826
Potassium (mEq/L)	4.4 (±0.4)	4.3 (±0.5)	4.3 (±0.5)	4.3 (±0.4)	0.761
Estimated glomerular filtration rate (ml/min per 1.73 m ²)	65 (±21)	62 (±24)	63 (±20)	63 (±25)	0.322
Ejection fraction >45 %	398 (10%)	590 (16%)	289 (12%)	288 (12%)	1.000
Ejection fraction (%)	31 (±12)	34 (±13)	32 (±12)	32 (±12)	0.792

Table 2
History of hypertension and hospitalization due to stroke, before and after propensity score matching

Outcomes	Rate/10,000 person-years (events/total follow up years)		Absolute increase in rate/10000 person-years	Increase in the number of stroke hospitalizations in the US**	Hazard ratio (95% confidence interval)	P value
	No history of hypertension	History of hypertension				
Before matching Hospitalization due to stroke	(n =4,114) 126 (151/11,978)	(n =3,674) 207 (215/10,391)	+ 80	+ 40,422 (103,454 – 63,032)	1.63 (1.33–2.01)	<0.0001
After matching Hospitalization due to stroke	(n =2,386) 129 (90/6,996)	(n =2,386) 178 (121/6,789)	+ 49	+ 24,792 (89,115 – 64,322)	1.52 (1.11–2.08)	0.010

* Absolute rate differences were calculated by subtracting the rates of hospitalizations due to stroke in the no hypertension group from the rate in the hypertension group (before values were rounded).

** Number of hospitalizations for stroke for an estimated 5 million heart failure patients in the US was calculated by subtracting the number of hospitalizations due to stroke in the no hypertension group from that in the hypertension group (before values were rounded).