

Clinical Investigation

Risk of Ischemic Stroke in Patients Newly Diagnosed With Heart Failure: Focus on Patients Without Atrial Fibrillation

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ABSTRACT

Background: Heart failure (HF) is associated with an incremental risk of stroke, but limited real-world data exist in patients with HF without atrial fibrillation (AF).

Objectives: To quantify the incremental risk of ischemic stroke among newly diagnosed patients with HF and without AF.

Methods: Adults with HF and ≥ 18 months of enrollment before their index HF (ie, baseline period) were identified in Truven Health Analytics MarketScan Databases (January 2010–April 2015). Patients without AF during baseline and without an ischemic stroke within 14 days of the index date were propensity score matched 1:1 to individuals with neither HF nor AF and observed for ischemic stroke. A similar analysis was performed for the overall HF population. Incidence rates were compared using incidence rate ratios between HF and non-HF cohorts; Kaplan-Meier analyses with log-rank tests were used to compare incidence rates over time.

Results: A total of 66,414 patients with HF were identified, of which 52,005 did not have AF. Patients with HF without AF had significantly higher rates of ischemic stroke than patients without HF without AF during follow-up (incidence rate ratio 1.91 [95% confidence interval 1.75–2.09], $P < .001$). Ischemic stroke rates remained significantly higher for patients with HF over time among individuals without AF ($P < .001$ for log-rank test at 12, 24, and 36 months). Similar results were found for the overall HF population.

Conclusions: Even in the absence of AF, patients with HF are at heightened risk of ischemic stroke compared with patients without HF. (*J Cardiac Fail* 2019;25:436–447)

Key Words: Heart failure, risk of ischemic stroke, atrial fibrillation.

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Heart failure (HF) is a major public health burden associated with high morbidity and mortality and substantial health care expenditures.^{1,2} In 2016, the American Heart Association reported that there were 5.7 million people age ≥ 20 years living with HF in the United States.² Furthermore, the prevalence of HF is expected to rise steadily in the upcoming years because of an aging population and life prolongation in patients with cardiovascular diseases.^{2–4} Importantly, HF is associated with a higher risk of thromboembolic events, particularly ischemic strokes.^{5–7} Individuals with HF may be predisposed to ischemic strokes because of blood flow abnormalities, vessel wall abnormalities, and abnormal blood constituents.⁸

Although many studies have evaluated the risk of ischemic stroke in patients with HF, results have varied because of the heterogeneity in study designs, follow-up time, and study populations, making it difficult to generalize the

findings to clinical practice.⁵ Moreover, studies dating back to the 1990s and earlier may not reflect recent changes in demographics and medical care.⁹ Hence, there is a need for updated real-world data to provide an in-depth understanding of the risk of ischemic stroke in patients with HF.

Notably, atrial fibrillation (AF) is found in approximately 15%–30% of patients with HF^{10–13} and is known to be associated with a poorer prognosis among patients with HF with respect to stroke risk and survival.¹⁴ However, limited real-world data exist on the risk of stroke in patients with HF with sinus rhythm, who represent 70%–85% of all patients with HF.¹⁵ Furthermore, some interventions aiming to reduce the risk of ischemic stroke, such as anticoagulation, are only indicated for patients with HF with AF.¹⁶ Thus, given the therapeutic implications related to the risk of stroke in patients with HF without AF, assessing the incremental risk of ischemic stroke in this population is of great interest to determine whether stroke prophylaxis may also be warranted in these patients. Therefore, this large real-world study aims to examine the incremental risk of ischemic stroke in patients with HF, with a focus on patients without AF, and to assess the risk of ischemic stroke over time.

Methods

Data Source

This study used health care insurance claims from the Truven Health Analytics MarketScan Databases from January 1, 2010, to April 1, 2015. The databases consist of the Commercial Claims and Encounters and the Medicare Supplemental and Coordination of Benefits databases, combining data from a selection of large employers, health plans, as well as government and public organizations, and representing more than 43.6 million patients from all census regions of the United States in the most recent full year. The databases contain information on patient demographics, health plan enrollment, and claims from inpatient, outpatient, and pharmacy settings. Data are deidentified and comply with the patient requirements of the Health Insurance Portability and Accountability Act.

More specifically for this study, a random sample of 200,000 patients with a diagnosis of HF (International Classification of Diseases, Ninth Edition, Clinical Modifications [ICD-9-CM] code: 428.xx) and 2 million patients without HF were used. The use of a ratio of 1:10 ensured that enough controls (ie, patients without HF) were available to match all cases (ie, patients with HF).

Study Design and Patient Selection

A retrospective matched-cohort study design was used. For the HF cohort, a random sample of 200,000 patients with at least 1 diagnosis (primary or secondary during an hospitalization, emergency room visit, or outpatient visit) of HF (ICD-9-CM code: 428.xx) during the qualifying period were selected from the Truven databases. The date of the claim with the first HF diagnosis was defined as the

index date; patients were required to be at least 18 years old on the index date. For the non-HF cohort, patients without any HF diagnoses were selected from the random sample of the Truven databases and the index date was assigned randomly. Patients in the HF and the non-HF cohorts were required to have at least 18 months of continuous insurance coverage before their index date to serve as the baseline period and to ensure that individuals with new-onset HF were analyzed. In addition, to avoid potential simultaneity of HF and ischemic stroke diagnoses in the claims, patients with an ischemic stroke event in the first 14 days following the HF diagnosis were excluded.

A subset of patients without AF at baseline was analyzed, and comparisons were performed between patients with and without HF (ie, HF and non-HF cohorts, respectively). For the sake of comparison, all analyses were also performed in the overall population of patients with HF, regardless of their AF status. The observation (follow-up) period spanned from the index date until either the end of the continuous health plan enrollment or the end of data availability, whichever came first.

Study Outcome

The main outcome of the study was ischemic stroke events, defined as a primary diagnosis for ischemic stroke documented during a hospitalization (see [Table 1](#) for the complete list of codes for ischemic stroke).

Matching

Propensity score matching was performed to adjust for potential confounding. To assess the risk of ischemic stroke among individuals recently diagnosed with HF and without AF, propensity scores were calculated using a multivariate logistic regression model in which the probability of having HF was predicted by the following baseline characteristics: age, gender, region, payment type at the index date (commercial or Medicare), insurance type, year of index date, risk factors for ischemic stroke (see detailed list in [Tables 2a-b](#)), Quan-Charlson comorbidity index score,

Table 1. ICD-9-CM Codes for Ischemic Stroke

| |
|---|
| 433.01 Occlusion and stenosis of basilar artery with cerebral infarction |
| 433.11 Occlusion and stenosis of carotid artery with cerebral infarction |
| 433.21 Occlusion and stenosis of vertebral artery with cerebral infarction |
| 433.31 Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction |
| 433.81 Occlusion and stenosis of other specified precerebral artery with cerebral infarction |
| 433.91 Occlusion and stenosis of unspecified precerebral artery with cerebral infarction |
| 434.01 Cerebral thrombosis with cerebral infarction |
| 434.11 Cerebral embolism with cerebral infarction |
| 434.91 Unspecified cerebral artery occlusion with cerebral infarction |
| 436.xx Acute but ill-defined cerebrovascular disease |
| 437.1 Other generalized ischemic cerebrovascular disease |
| 437.3 Cerebral aneurysm, nonruptured |
| 997.02 Iatrogenic cerebrovascular infarction or hemorrhage |

ICD-9-CM, International Classification of Diseases, Ninth Edition, Clinical Modifications.

Table 2. Demographics and Clinical Characteristics of Patients

| Characteristics | Unmatched Cohorts | | | Matched Cohorts* | | |
|---|----------------------------|----------------------------|--------------|----------------------------|----------------------------|--------------|
| | HF Cohort | Non-HF Cohort | Std Diff (%) | HF Cohort | Non-HF Cohort | Std Diff (%) |
| | (N = 52,005) | (N = 893,572) | | (N = 52,005) | (N = 52,005) | |
| a. Recent HF Diagnosis Without AF at Baseline | | | | | | |
| <i>Matching factors</i> | | | | | | |
| Demographics[†] | | | | | | |
| Age, y, mean [median] (SD) | 68.3 [68] (15.4) | 58.5 [64] (20.1) | 54.7 | 68.3 [68] (15.4) | 68.9 [71] (15.4) | 3.7 |
| Gender, female, n (%) | 25,993 (50.0) | 488,856 (54.7) | 9.5 | 25,993 (50.0) | 26,073 (50.1) | 0.3 |
| Region, n (%)[†] | | | | | | |
| South | 17,205 (33.1) | 299,372 (33.5) | 0.9 | 17,205 (33.1) | 17,353 (33.4) | 0.6 |
| North central | 14,664 (28.2) | 212,070 (23.7) | 10.2 | 14,664 (28.2) | 14,360 (27.6) | 1.3 |
| Northeast | 11,068 (21.3) | 180,539 (20.2) | 2.7 | 11,068 (21.3) | 11,276 (21.7) | 1.0 |
| West | 7997 (15.4) | 180,369 (20.2) | 12.6 | 7997 (15.4) | 7953 (15.3) | 0.2 |
| Unknown | 1071 (2.1) | 21,222 (2.4) | 2.1 | 1071 (2.1) | 1063 (2.0) | 0.1 |
| Payment type, n (%)[†] | | | | | | |
| Commercial | 22,387 (43.0) | 457,653 (51.2) | 16.4 | 22,387 (43.0) | 21,757 (41.8) | 2.5 |
| Medicare | 29,618 (57.0) | 435,919 (48.8) | 16.4 | 29,618 (57.0) | 30,248 (58.2) | 2.5 |
| Insurance type, n (%)[†] | | | | | | |
| PPO | 24,426 (47.0) | 488,648 (54.7) | 15.4 | 24,426 (47.0) | 24,391 (46.9) | 0.1 |
| HMO | 5266 (10.1) | 103,028 (11.5) | 4.5 | 5266 (10.1) | 5332 (10.3) | 0.4 |
| Comprehensive | 15,080 (29.0) | 153,453 (17.2) | 28.1 | 15,080 (29.0) | 15,220 (29.3) | 0.6 |
| POS | 2686 (5.2) | 39,933 (4.5) | 3.3 | 2686 (5.2) | 2585 (5.0) | 0.9 |
| CDHP | 1347 (2.6) | 24,165 (2.7) | 0.7 | 1347 (2.6) | 1334 (2.6) | 0.2 |
| EPO | 575 (1.1) | 13,194 (1.5) | 3.3 | 575 (1.1) | 584 (1.1) | 0.2 |
| POS capitated | 113 (0.2) | 3081 (0.3) | 2.4 | 113 (0.2) | 124 (0.2) | 0.4 |
| HDHP | 724 (1.4) | 21,771 (2.4) | 7.6 | 724 (1.4) | 710 (1.4) | 0.2 |
| Not specified | 1788 (3.4) | 46,299 (5.2) | 8.6 | 1788 (3.4) | 1725 (3.3) | 0.7 |
| Year of index date, n (%)[†] | | | | | | |
| 2011 | 8557 (16.5) | 270,363 (30.3) | 32.6 | 8557 (16.5) | 8566 (16.5) | 0.0 |
| 2012 | 15,939 (30.6) | 292,588 (32.7) | 4.5 | 15,939 (30.6) | 16,233 (31.2) | 1.2 |
| 2013 | 13,111 (25.2) | 162,831 (18.2) | 16.9 | 13,111 (25.2) | 13,153 (25.3) | 0.2 |
| 2014 | 11,930 (22.9) | 137,978 (15.4) | 19.0 | 11,930 (22.9) | 11,723 (22.5) | 0.9 |
| 2015 | 2468 (4.7) | 29,812 (3.3) | 7.2 | 2468 (4.7) | 2330 (4.5) | 1.3 |
| Comorbidity index scores, mean [median] (SD)[†] | | | | | | |
| Quan-Charlson comorbidity index | 2.5 [2] (2.5) | 0.9 [0] (1.6) | 77.2 | 2.5 [2] (2.5) | 2.3 [2] (2.6) | 6.9 |
| CHA ₂ DS ₂ -VASc score | 3.0 [3] (1.8) | 2.0 [2] (1.6) | 63.8 | 3.0 [3] (1.8) | 3.0 [3] (1.9) | 0.6 |
| HAS-BLED score | 1.8 [2] (1.1) | 1.1 [1] (1.0) | 59.9 | 1.8 [2] (1.1) | 1.7 [2] (1.2) | 1.2 |
| Stroke risk factors, n (%) | | | | | | |
| Hypertension | 38,151 (73.4) | 359,643 (40.2) | 66.8 | 38,151 (73.4) | 38,565 (74.2) | 1.8 |
| Hyperlipidemia | 28,861 (55.5) | 324,741 (36.3) | 38.4 | 28,861 (55.5) | 28,913 (55.6) | 0.2 |
| Diabetes | 18,812 (36.2) | 130,506 (14.6) | 49.6 | 18,812 (36.2) | 18,660 (35.9) | 0.6 |
| COPD | 9,924 (19.1) | 46,388 (5.2) | 42.5 | 9924 (19.1) | 9094 (17.5) | 4.1 |
| Cerebrovascular accident (stroke/TIA) | 8269 (15.9) | 49,940 (5.6) | 33.3 | 8269 (15.9) | 7849 (15.1) | 2.2 |
| Depression | 6942 (13.3) | 68,538 (7.7) | 18.5 | 6942 (13.3) | 6468 (12.4) | 2.7 |
| Obesity | 6665 (12.8) | 46,591 (5.2) | 26.5 | 6665 (12.8) | 6356 (12.2) | 1.8 |
| Previous VTE | 2936 (5.6) | 12,409 (1.4) | 23.1 | 2936 (5.6) | 2419 (4.7) | 4.5 |
| Myocardial infarction | 2577 (5.0) | 4729 (0.5) | 27.1 | 2577 (5.0) | 1622 (3.1) | 9.3 |
| Acute coronary syndrome | 2397 (4.6) | 6376 (0.7) | 24.2 | 2397 (4.6) | 1752 (3.4) | 6.3 |
| Family history of CVD | 451 (0.9) | 5559 (0.6) | 2.9 | 451 (0.9) | 465 (0.9) | 0.3 |
| Health care resource utilization, mean [median] (SD)[†] | | | | | | |
| Hospitalizations | 0.48 [0] (0.9) | 0.13 [0] (0.4) | 48.5 | 0.48 [0] (0.9) | 0.38 [0] (0.8) | 11.5 |
| ER visits | 0.94 [0] (1.9) | 0.36 [0] (1.0) | 36.9 | 0.94 [0] (1.9) | 0.78 [0] (1.9) | 8.4 |
| Outpatient visits | 26.5 [19] (29.1) | 14.3 [9] (17.1) | 51.2 | 26.5 [19] (29.1) | 24.8 [18] (25.3) | 6.5 |
| Health care cost, \$US 2015, mean (SD)[†] | | | | | | |
| Total health care cost | \$36,971 (166,885) | \$11,121 (28,845) | 21.6 | \$36,971 (166,885) | \$29,197 (63,142) | 6.2 |
| Hospitalizations | \$12,729 (44,622) | \$2675 (15,198) | 30.2 | \$12,729 (44,622) | \$9168 (31,507) | 9.2 |
| ER visits | \$1663 (5623) | \$598 (2755) | 24.1 | \$1663 (5623) | \$1404 (5233) | 4.8 |
| Outpatient visits | \$15,117 (53,337) | \$5354 (18,238) | 24.5 | \$15,117 (53,337) | \$12,591 (42,102) | 5.3 |
| Pharmacy | \$5028 (12,053) | \$1974 (5872) | 32.2 | \$5028 (12,053) | \$4346 (11,475) | 5.8 |
| <i>Nonmatching factors</i> | | | | | | |
| Observation period, days, mean [median] (SD)[§] | 471.5 [380] (370.9) | 472.1 [374] (377.5) | 0.1 | 471.5 [380] (370.9) | 450.2 [364] (343.2) | 6.0 |
| Type of index visit, n (%)[†] | | | | | | |
| Hospitalization | 19,601 (37.7) | - | - | 19,601 (37.7) | - | - |
| ER visit | 5,387 (10.4) | - | - | 5,387 (10.4) | - | - |
| Outpatient visit | 25,008 (48.1) | - | - | 25,008 (48.1) | - | - |
| Other visit | 2,009 (3.9) | - | - | 2,009 (3.9) | - | - |

b. Recent HF Diagnosis

| Characteristics | Unmatched Cohorts | | | Matched Cohorts* | | |
|--|---------------------------|--------------------------------|-----------------|---------------------------|-------------------------------|-----------------|
| | HF Cohort (N = 66,414) | Non-HF Cohort (N = 932,616) | Std Diff (%) | HF Cohort (N = 66,414) | Non-HF Cohort (N = 66,414) | Std Diff (%) |
| <i>Matching factors</i> | | | | | | |
| Demographics† | | | | | | |
| Age, y, mean [median] (SD) | 70.1 [71] (15.2) | 59.3 [66] (20.1) | 61.1 | 70.1 [71] (15.2) | 70.8 [73] (15.0) | 4.5 |
| Gender, female, n (%) | 32,568 (49.0) | 506,976 (54.4) | 10.7 | 32,568 (49.0) | 32,643 (49.2) | 0.2 |
| Region, n (%)† | | | | | | |
| South | 21,504 (32.4) | 311,699 (33.4) | 2.2 | 21,504 (32.4) | 21,481 (32.3) | 0.1 |
| North central | 18,952 (28.5) | 221,584 (23.8) | 10.9 | 18,952 (28.5) | 18,819 (28.3) | 0.4 |
| Northeast | 14,291 (21.5) | 189,429 (20.3) | 3.0 | 14,291 (21.5) | 14,472 (21.8) | 0.7 |
| West | 10,330 (15.6) | 187,890 (20.1) | 12.0 | 10,330 (15.6) | 10,261 (15.5) | 0.3 |
| Unknown | 1337 (2.0) | 22,014 (2.4) | 2.4 | 1337 (2.0) | 1381 (2.1) | 0.5 |
| Payment type, n (%)† | | | | | | |
| Commercial | 25,071 (37.7) | 460,558 (49.4) | 23.5 | 25,071 (37.7) | 23,799 (35.8) | 4.0 |
| Medicare | 41,343 (62.3) | 472,058 (50.6) | 23.5 | 41,343 (62.3) | 42,615 (64.2) | 4.0 |
| Insurance type, n (%)† | | | | | | |
| PPO | 30,385 (45.8) | 506,452 (54.3) | 17.1 | 30,385 (45.8) | 30,404 (45.8) | 0.1 |
| HMO | 6598 (9.9) | 107,240 (11.5) | 5.1 | 6598 (9.9) | 6611 (10.0) | 0.1 |
| Comprehensive | 20,844 (31.4) | 166,782 (17.9) | 31.3 | 20,844 (31.4) | 21,118 (31.8) | 0.9 |
| POS | 3209 (4.8) | 41,025 (4.4) | 2.1 | 3209 (4.8) | 3127 (4.7) | 0.6 |
| CDHP | 1509 (2.3) | 24,376 (2.6) | 2.2 | 1509 (2.3) | 1469 (2.2) | 0.4 |
| EPO | 713 (1.1) | 13,509 (1.4) | 3.4 | 713 (1.1) | 710 (1.1) | 0.0 |
| POS capitated | 130 (0.2) | 3125 (0.3) | 2.7 | 130 (0.2) | 120 (0.2) | 0.3 |
| HDHP | 799 (1.2) | 21,938 (2.4) | 8.7 | 799 (1.2) | 697 (1.0) | 1.5 |
| Not specified | 2227 (3.4) | 48,169 (5.2) | 9.0 | 2227 (3.4) | 2158 (3.2) | 0.6 |
| Year of index date, n (%)† | | | | | | |
| 2011 | 10,966 (16.5) | 283,402 (30.4) | 32.8 | 10,966 (16.5) | 11,426 (17.2) | 1.9 |
| 2012 | 20,309 (30.6) | 305,275 (32.7) | 4.6 | 20,309 (30.6) | 20,375 (30.7) | 0.2 |
| 2013 | 16,873 (25.4) | 170,264 (18.3) | 17.3 | 16,873 (25.4) | 16,944 (25.5) | 0.2 |
| 2014 | 15,147 (22.8) | 143,069 (15.3) | 19.0 | 15,147 (22.8) | 14,790 (22.3) | 1.3 |
| 2015 | 3119 (4.7) | 30,606 (3.3) | 7.2 | 3119 (4.7) | 2879 (4.3) | 1.7 |
| Comorbidity index scores, mean [median] (SD)‡ | | | | | | |
| Quan-Charlson comorbidity index | 2.6 [2] (2.6) | 0.9 [0] (1.6) | 78.5 | 2.6 [2] (2.6) | 2.5 [2] (2.7) | 5.4 |
| CHA ₂ DS ₂ -VASc score | 3.2 [3] (1.8) | 2.0 [2] (1.6) | 69.2 | 3.2 [3] (1.8) | 3.2 [3] (1.9) | 0.9 |
| HAS-BLED score | 1.8 [2] (1.2) | 1.1 [1] (1.1) | 63.9 | 1.8 [2] (1.2) | 1.8 [2] (1.1) | 0.0 |
| Atrial fibrillation, n (%)‡ | | | | | | |
| Atrial fibrillation | 14,409 (21.7) | 39,044 (4.2) | 52.2 | 14,409 (21.7) | 13,239 (19.9) | 4.3 |
| Stroke risk factors, n (%)‡ | | | | | | |
| Hypertension | 50,327 (75.8) | 390,578 (41.9) | 68.9 | 50,327 (75.8) | 51,328 (77.3) | 3.6 |
| Hyperlipidemia | 37,626 (56.7) | 348,688 (37.4) | 38.6 | 37,626 (56.7) | 37,866 (57.0) | 0.7 |
| Diabetes | 23,910 (36.0) | 140,900 (15.1) | 47.9 | 23,910 (36.0) | 23,891 (36.0) | 0.1 |
| COPD | 13,384 (20.2) | 52,098 (5.6) | 43.5 | 13,384 (20.2) | 12,384 (18.6) | 3.8 |
| Cerebrovascular accident (stroke/TIA) | 11,902 (17.9) | 57,888 (6.2) | 36.0 | 11,902 (17.9) | 11,680 (17.6) | 0.9 |
| Depression | 8777 (13.2) | 72,273 (7.7) | 17.8 | 8777 (13.2) | 8409 (12.7) | 1.7 |
| Obesity | 8321 (12.5) | 49,325 (5.3) | 25.4 | 8321 (12.5) | 7990 (12.0) | 1.5 |
| Previous VTE | 4248 (6.4) | 15,001 (1.6) | 24.4 | 4248 (6.4) | 3673 (5.5) | 3.7 |
| Myocardial infarction | 3510 (5.3) | 5828 (0.6) | 27.5 | 3510 (5.3) | 2514 (3.8) | 7.2 |
| Acute coronary syndrome | 3159 (4.8) | 7642 (0.8) | 23.9 | 3159 (4.8) | 2538 (3.8) | 4.6 |
| Family history of CVD | 559 (0.8) | 5819 (0.6) | 2.6 | 559 (0.8) | 550 (0.8) | 0.1 |
| Health care resource utilization, mean [median] (SD)‡ | | | | | | |
| Hospitalizations | 0.53 [0] (0.9) | 0.14 [0] (0.4) | 53.3 | 0.53 [0] (0.9) | 0.45 [0] (0.8) | 9.1 |
| ER visits | 0.99 [0] (2.0) | 0.38 [0] (1.0) | 38.4 | 0.99 [0] (2.0) | 0.87 [0] (2.0) | 5.8 |
| Outpatient visits | 28.6 [21] (29.2) | 15.0 [10] (17.7) | 56.1 | 28.6 [21] (29.2) | 27.1 [20] (26.7) | 5.1 |
| Health care cost, \$US 2015, mean (SD)‡ | | | | | | |
| Total health care cost | \$38,837 (151,858) | \$11,943 (30,836) | 24.5 | \$38,837 (151,858) | \$32,777 (68,817) | 5.1 |
| Hospitalizations | \$14,152 (45,781) | \$3039 (16,878) | 32.2 | \$14,152 (45,781) | \$11,270 (38,910) | 6.8 |
| ER visits | \$1739 (5,780) | \$633 (2,862) | 24.3 | \$1739 (5,780) | \$1553 (5,363) | 3.3 |
| Outpatient visits | \$15,374 (51,046) | \$5653 (19,046) | 25.2 | \$15,374 (51,046) | \$13,524 (43,154) | 3.9 |
| Pharmacy | \$5102 (12,024) | \$2049 (5,961) | 32.2 | \$5102 (12,024) | \$4575 (12,397) | 4.3 |
| <i>Nonmatching factors</i> | | | | | | |
| Observation period, days, mean [median] (SD)§ | 470.0 [380] (370.3) | 472.0 [375] (377.2) | 0.5 | 470.0 [380] (370.3) | 445.5 [360] (340.2) | 6.9 |

(continued)

Table 2 (Continued)

| Characteristics | Unmatched Cohorts | | | Matched Cohorts* | | |
|---|-------------------|---------------|--------------|------------------|---------------|--------------|
| | HF Cohort | Non-HF Cohort | Std Diff (%) | HF Cohort | Non-HF Cohort | Std Diff (%) |
| | (N = 66,414) | (N = 932,616) | | (N = 66,414) | (N = 66,414) | |
| Type of index visit, n (%)[†] | | | | | | |
| Hospitalization | 23,989 (36.1) | - | - | 23,989 (36.1) | - | - |
| ER visit | 6966 (10.5) | - | - | 6966 (10.5) | - | - |
| Outpatient visit | 32,632 (49.1) | - | - | 32,632 (49.1) | - | - |
| Other visit | 2827 (4.3) | - | - | 2827 (4.3) | - | - |

CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke, vascular disease, age 65–74 years, and sex category; CDHP, consumer directed health plan; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; EPO, exclusive provider organization; ER, emergency room; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, and drugs or alcohol; HDHP, high-deductible health plan; HF, heart failure; HMO, health maintenance organization; POS, point-of-service; PPO, preferred provider organization; SD, standard deviation; Std diff, standardized difference; TIA, transient ischemic attack; VTE, venous thromboembolism.

*Patients with HF were matched 1:1 with patients without HF using propensity score calipers of 5%. Variables assessed at the index date (unless otherwise indicated) used in the propensity score calculation included: age, gender, region, payment type, insurance type, year, atrial fibrillation during baseline, baseline risk factors for stroke, Quan-Charlson comorbidity index during baseline, CHA₂DS₂-VASc score during baseline, HAS-BLED score during baseline, and baseline health care resource utilization and costs.

[†]Evaluated at the index date.

[‡]Evaluated during the 18-month baseline period.

[§]Period ends at the earliest of end of data availability or end of continuous health plan enrollment.

CHA₂DS₂-VASc (ie, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke, vascular disease, age 65–74 years, and sex category) and HAS-BLED (ie, hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, and drugs or alcohol) scores, and health care resource utilization and costs. Patients with HF were matched 1:1 to patients without HF, both without AF, by random selection within propensity score intervals of 5% based on percentiles. Standardized differences were calculated to compare the balance of patients' baseline characteristics before and after matching. Matching between cohorts was considered adequate if standardized differences were $< 10\%$.^{17–20}

The risk of ischemic stroke in the overall population of patients with HF was also examined using the previously mentioned 1:1 propensity score-matching strategy. Of note, the presence of AF at baseline was added to the propensity score calculation to ensure that both cohorts have a similar proportion of patients with this condition at baseline in the overall population.

Statistical Analysis

For each set of matched cohorts, patient baseline characteristics evaluated during the 18 months before the index date were summarized using means, medians, and standard deviations for continuous variables, and frequencies and proportions for categorical variables.

The risk of ischemic stroke was assessed during the observation period for matched cohorts (HF vs non-HF) using the number of events (censored at the first event for each patient), person-years of observation period, and incidence rate (IR; calculated as the number of events divided by person-years of observation). IRs per 100 person-years were reported and compared between the matched HF and

the non-HF cohorts using Poisson regression models; incidence rate ratios (IRRs) with 95% confidence intervals (CIs) and *P* values were reported.

Kaplan-Meier survival analysis was used to describe the time to ischemic stroke in each cohort, and rates of ischemic stroke were compared at 12, 24, and 36 months with log-rank tests. In addition, the incremental risk of ischemic stroke resulting from HF was evaluated at 6-month intervals. Finally, as supplemental material, we produced for results including patients with an ischemic stroke in the first 14 days following the index HF diagnosis.

Results

Patient Characteristics

From the random sample of 200,000 patients with at least 1 claim for HF, 66,414 individuals had new-onset HF, including 52,005 (78.3%) without AF at baseline. Before matching among patients without AF, those with 1 claim for HF were older, more frequently male, on Medicare, had a higher risk of ischemic stroke, and had more comorbidities including hypertension, diabetes, myocardial infarction, and acute coronary syndrome vs patients without HF (N = 893,572; Table 2a). All 52,005 patients with HF were matched to patients without HF. Patient characteristics, including demographics, comorbidities, and risk factors for ischemic stroke and bleeding were well balanced after matching between HF and non-HF cohorts (the percentage of non-overlap of the distribution of each baseline covariate for the cohorts of patients with and without HF was $< 10\%$; Table 2a). Similar observations were made pre- and post-matching with regard to the comparison of baseline characteristics between the overall HF (N = 66,414) and non-HF cohorts (N = 932,616; Table 2b).

Table 3. Risk of Ischemic Stroke Among Patients With Recent HF Diagnosis^{*,†}

| | | Frequency of Event | | Incidence Rate* (per 100 Person-Years) | | IRR (95% CI) | P Value |
|------------------------------------|--|---------------------|---------------------|---|---------------|------------------|---------|
| | | HF Cohort | Non-HF Cohort | HF Cohort | Non-HF Cohort | | |
| Overall Analysis | Number of patients | 66,414 | 66,414 | | | | |
| | Observation period, days, mean [median] (SD) [†] | 460.2 [368] (367.2) | 440.2 [354] (338.3) | | | | |
| | Total person-years | 83,730 | 80,100 | | | | |
| | Ischemic stroke | 2023 | 1137 | 2.42 | 1.42 | 1.70 (1.58–1.83) | < .001 |
| Patients Without AF at Baseline | Number of patients | 52,005 | 52,005 | | | | |
| | Observation period, days, mean [median] (SD) [†] | 462.2 [369] (368.0) | 445.7 [359] (341.6) | | | | |
| | Total person-years | 65,861 | 63,507 | | | | |
| | Ischemic stroke | 1466 | 740 | 2.23 | 1.17 | 1.91 (1.75–2.09) | < .001 |

AF, atrial fibrillation; IRR, incidence rate ratio; SD, standard deviation; other abbreviations as in Table 2.

*The incidence rate is calculated as the frequency of event divided by the total person-years.

†The observation period was truncated at the time of the first event. Period ends at the earliest of time of the first event, end of data availability, or end of continuous health plan enrollment.

Risk of Ischemic Stroke

In patients with HF without AF at baseline, the IR of ischemic stroke per 100 person-years was 2.23 in the HF cohort vs 1.17 in the non-HF cohort (IRR 1.91 [95% CI 1.75–2.09]; $P < .001$; Table 3). Compared with patients with neither HF nor AF, those with HF and without AF had significantly higher Kaplan-Meier rates of ischemic stroke at 12 months after the index date (2.4% vs 1.2%), 24 months (4.3% vs 2.3%), and 36 months (5.9% vs 3.3%, $P < .001$; Fig. 1a). In addition, there was an incremental risk of ischemic stroke associated with HF among patients without AF over all 6-month intervals analyzed up to 3 years of follow-up, with the incremental risk most pronounced for 0–6 and 6–12 months post-index date. The incremental risk of ischemic stroke associated with HF remained significant until 30 months post-index (all P values $< .001$ for each 6-month interval), after which statistical significance was lost, although the risk remained numerically higher (Fig. 2a).

In the overall population, the incremental risk of ischemic stroke was consistent with previous findings in the subgroup without AF at baseline. In fact, compared with patients without HF, patients diagnosed with HF, regardless of their AF status, had a significantly higher rate of ischemic stroke events. The IR of ischemic stroke per 100 person-years was 2.42 in the HF cohort vs 1.42 in the non-HF cohort (IRR 1.70 [95% CI 1.58–1.83]; $P < .001$; Table 3). Compared with patients without HF, the Kaplan-Meier rate of ischemic stroke was also significantly higher among patients with HF at 12, 24, and 36 months after the index date ($P < .001$; Fig. 1b). The incremental risk of ischemic stroke associated with HF remained significant over all 6-month intervals up to 3 years post-index date (all P values $< .05$; Fig. 2b). Of note, the IR of ischemic stroke per 100 person-years was also evaluated among patients with HF with AF at baseline and found to be higher at 3.12.

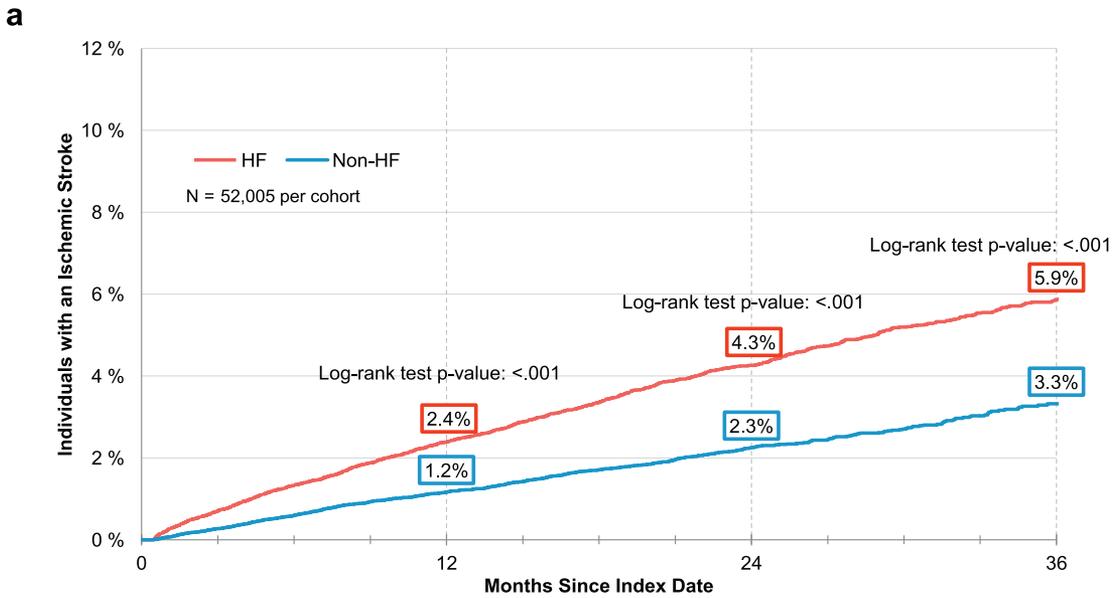
With the inclusion of patients with an ischemic stroke event in the first 14 days following the index date, the rate of ischemic stroke at 12, 24, and 36 months after the index

date was significantly higher among patients with HF and without AF (Table A1 and Fig. A1).

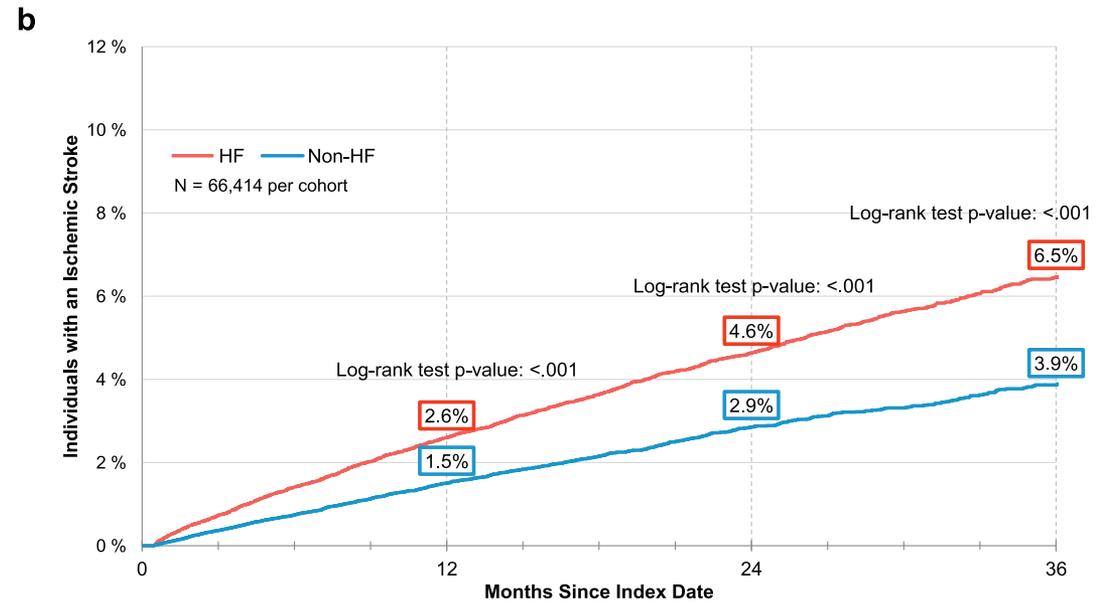
Discussion

In this retrospective matched-cohort study of a large commercially and Medicare insured population in the United States, the rate of ischemic stroke in patients newly diagnosed with HF and without AF was almost 2 times higher (2.23 vs 1.17 events per 100 person-years) than that of patients with neither HF nor AF, suggesting that the presence of HF alone significantly contributes to the risk of stroke events. Applied to the entire HF population without AF in the United States (ie, an estimated 5 million patients with HF alone, or 70%–85% of the 6.2 million patients with HF),^{10–13} a difference of around 1 percentage point translates into approximately 50,000 stroke events, which is considerable, especially considering severe nature of stroke events. Moreover, the difference in the risk of stroke observed between patients with HF and patients without HF increased over time from 1 percentage point at 12 months to 3 percentage point at 36 months (Kaplan-Meier rates of 5.9% vs 3.3%, $P < .001$).

Although numerous studies support that the overall population of patients with HF,^{9,21} and particularly those with AF,^{22,23} are at higher risk of stroke, such evidence in patients with HF without AF is not as clear. For example, in the population-based Reasons for Geographic and Racial Differences in Stroke study, the rates of ischemic stroke reached 0.69 (95% CI 0.49–0.93) among patients with HF without AF, and 0.40 (95% CI 0.37–0.44) among patients with neither HF nor AF.²² Two other studies reached similar conclusions using national registry data in Denmark.^{24,25} In 1 of these studies conducted by Lip et al., individuals without AF or prior stroke were included and a hazard ratio of 2.3 (95% CI 1.8–3.0) was reported for ischemic stroke in patients with vs without incident HF.²⁴ In another Danish study, Melgaard et al. found that patients without AF and a CHA₂DS₂-VASc score ≥ 2 had an ischemic stroke risk



| No. at risk | |
|-------------|--|
| HF | 52,005 36,641 26,178 18,596 12,562 7,704 4,331 |
| Non-HF | 52,005 36,962 25,654 17,813 11,190 6,323 3,069 |



| No. at risk | |
|-------------|--|
| HF | 66,414 46,567 33,359 23,689 15,936 9,710 5,412 |
| Non-HF | 66,414 47,051 32,450 22,350 13,798 7,702 3,745 |

Fig. 1. a, Kaplan-Meier rates of ischemic stroke in the HF- and non-HF-matched cohorts—excluding individuals with AF at baseline. b, Kaplan-Meier rates of ischemic stroke in the HF- and non-HF-matched cohorts. AF, atrial fibrillation; HF, heart failure

>1% after 1 year of follow-up.²⁵ Furthermore, in the same study, the increase in the absolute risk of ischemic stroke was reported to be similar between patients with vs without AF for patients with a CHA₂DS₂-VASc score ≥4.²⁵ Although Abdul-Rahim et al. reported that a clinical trial population of patients with HF with AF had a higher average annual incidence rate of stroke compared with patients

with HF and without AF (1.6% vs 1.2%), the rate of stroke appeared nonetheless substantial in the latter population.⁸ The results of the current study therefore add to the growing body of evidence suggesting that the higher risk of ischemic strokes may not only be restricted to patients with HF with AF, but can also be observed in patients with HF with sinus rhythm.

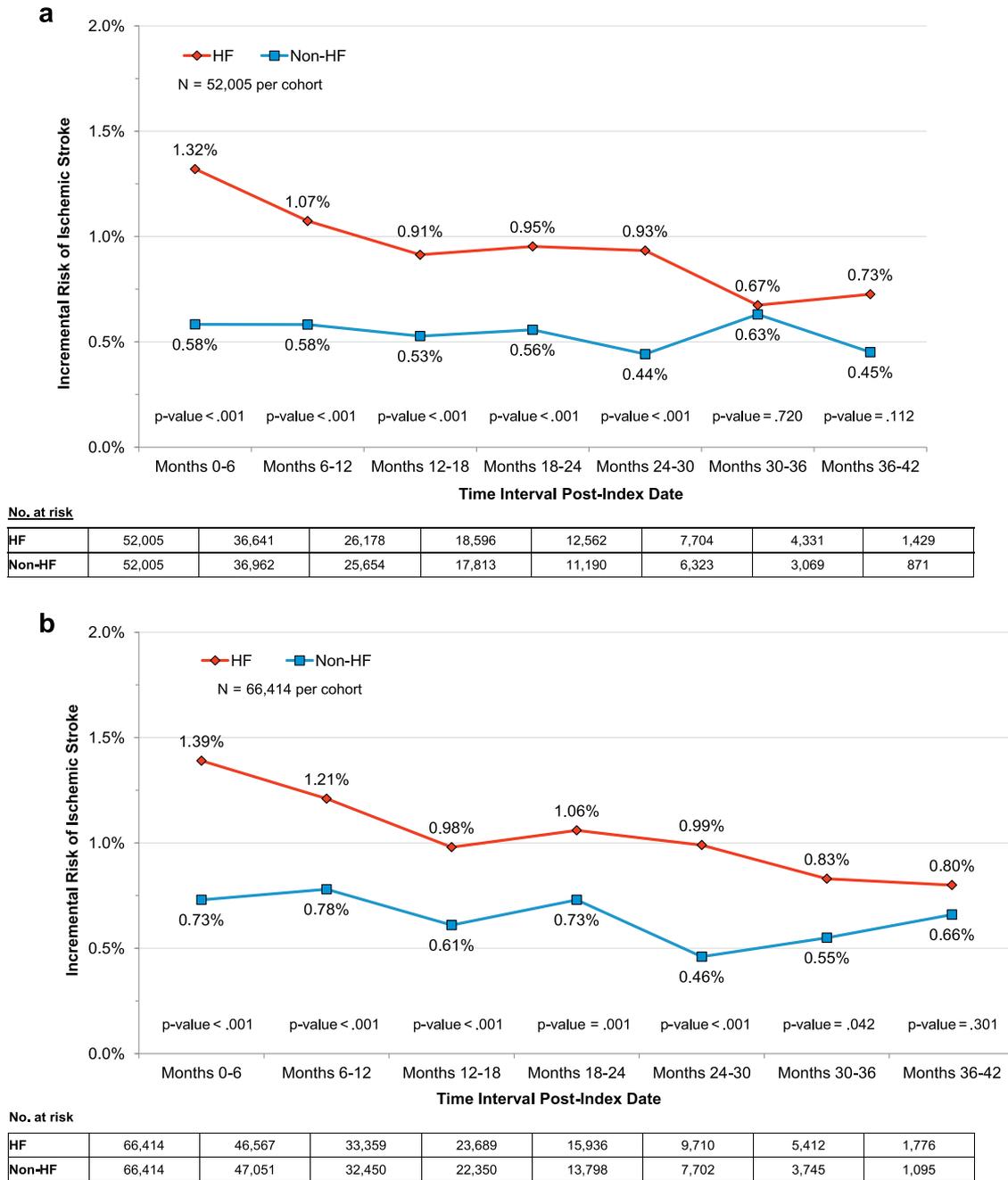


Fig. 2. a, Incremental risk of ischemic stroke in the HF- vs non-HF-matched cohorts, excluding individuals with AF at baseline. Legend *P* values corresponding to the difference in risk for HF vs non-HF patients at each time point are shown. b, Incremental risk of ischemic stroke in the HF- vs non-HF-matched cohorts. Abbreviations as in Table 2.

Finding that the consequences of HF on the risk of stroke can be observed over relatively long follow-up periods is also consistent with previous literature. For instance, in the population-based Olmstead County study, the cumulative 5-year risk of ischemic stroke after an initial HF diagnosis was nearly 3 times higher than that of the general population.²¹ Similarly, the Framingham Study reported a relative risk of stroke of 4.3 for patients with vs without cardiac failure after 2 years of follow-up. Thus, the results of the current study for the overall HF population not only support

these previous observations, but also suggest that these conclusions may hold true in patients with HF with sinus rhythm.

HF and AF are often co-prevalent because of common predisposing risk factors such as hypertension, coronary artery disease and structural heart disease, diabetes mellitus, and obesity. Data from clinical trials and registries have reported that 20%–30% of patients with HF also have AF; thus, the finding that 22% of patients with HF have concomitant AF at diagnosis is consistent with results of previous

studies.¹⁵ Therapeutic management of AF to reduce the incidence of stroke has included the vitamin K antagonist warfarin for >50 years. However, challenges inherent to warfarin therapy, including its narrow therapeutic range and food and drug interactions, were overcome with the development of the non-vitamin K antagonist oral anticoagulants (NOACs) rivaroxaban, apixaban, dabigatran, and edoxaban.²⁶ All of these NOACs have been approved by the US Food and Drug Administration to reduce the risk of stroke in patients with nonvalvular AF.¹⁶ The co-prevalence of AF and HF is high, but 70%–80% of patients with HF do not have AF. As shown in the current study, the risk of ischemic stroke remains high for this population without AF relative to that of matched controls without HF. Results from this study could aid ongoing efforts to assess the burden of ischemic stroke and identify patient populations suboptimally managed with current standard of care who may benefit from newer interventions, such as NOACs, to decrease the risk of ischemic stroke. Although warfarin and NOACs may be given to patients with AF, the benefit of these agents for patients with sinus rhythm has not been demonstrated. A meta-analysis comparing anticoagulation with warfarin to antiplatelet treatment in patients with HF with sinus rhythm demonstrated there was no improvement in the risk-benefit profile with warfarin treatment²⁷; however, that study did not include NOACs, which are known to have a risk-benefit profile different from that of warfarin. Although the contribution of AF to stroke risk is known, there are other stroke risk factors among patients with HF that could potentially be mitigated with anticoagulation therapy.²⁸ The first prospective study of a NOAC agent (ie, rivaroxaban) in patients with HF (ie, A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) is under way and expected to provide insights about safety and efficacy of this therapeutic class in the HF setting.²⁹

There are some limitations to the current study. First, a general limitation of observational studies is that

adjustment for potential confounders can be made only for observable factors. Second, the etiology of HF (eg, ejection fraction level) is unknown because of the nature of the data. ICD-9-CM codes were used to identify HF, AF, and ischemic stroke; these codes may not reflect confirmed clinical diagnoses and lack information to assess illness severity. Third, the association among HF, AF, and stroke risk is not necessarily causal in nature, which might increase difficulty identifying which prophylaxis strategies may have the highest success rate in lowering the incremental risk identified in the current study. Fourth, coding inaccuracies and missing data in the database could have occurred. Medical services obtained outside a patient's plan are not captured in a claims database and could contribute to misclassification. Fifth, the observational design of the study was susceptible to additional potential biases such as information or classification bias (eg, identification of false-positive or false-negative HF or ischemic stroke events). Sixth, this study focused on commercially insured patients and may not be fully representative of the general US population. Finally, AF was not treated as a time-varying covariate; thus, patients included in the HF without AF may have been subsequently diagnosed with AF. Despite these limitations, the current study adjusted for observed confounding factors through a matching technique to provide additional real-world data quantifying the impact of HF without AF on risks of ischemic stroke in the US population.

This analysis shows that, even in the absence of AF, HF is associated with a significant increase in risk of ischemic stroke compared with patients without HF. Moreover, the incremental risk of stroke associated with HF alone could be observed up to nearly 3 years after the initial HF diagnosis, and the highest incremental risk was observed within 12 months. Because the prevalence of HF without AF largely exceeds that of HF with AF, interventions that aim to decrease the risk and burden of ischemic stroke in patients with HF and sinus rhythm are needed. Moreover, further researches are warranted to determine whether stroke prophylaxis may also be beneficial in this population.

Appendix

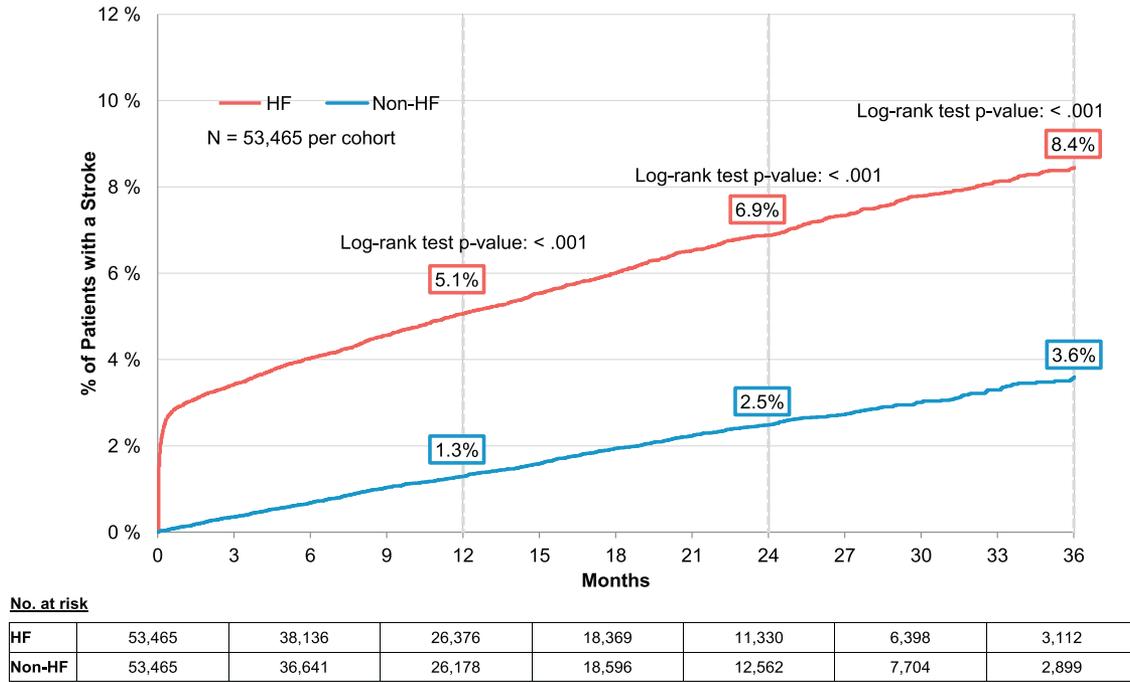


Fig. A1. Kaplan-Meier rates of ischemic stroke in the HF- and non-HF-matched cohorts without AF, including individuals with ischemic stroke within 14 days of index date.

Table A1. Demographic and Clinical Characteristics of Patients With Recent HF Diagnosis and Without AF Including Individuals with Ischemic Stroke within 14 Days of Index Date—Unmatched and Matched Cohorts

| Characteristics | Unmatched Cohorts | | | Matched Cohorts* | | |
|-------------------------------|---------------------------|--------------------------------|-----------------|---------------------------|-------------------------------|-----------------|
| | HF Cohort (N = 53,465) | Non-HF Cohort (N = 893,795) | Std Diff (%) | HF Cohort (N = 53,465) | Non-HF Cohort (N = 53,465) | Std Diff (%) |
| <i>Matching factors</i> | | | | | | |
| Demographics† | | | | | | |
| Age, y, mean [median (SD)] | 68.4 [69] (15.4) | 58.5 [64] (20.1) | 55.2 | 68.4 [69] (15.4) | 69.0 [71] (15.3) | 3.8 |
| Gender, female, n (%) | 26,740 (50.0) | 488,975 (54.7) | 9.4 | 26,740 (50.0) | 26,780 (50.1) | 0.1 |
| Region, n (%)† | | | | | | |
| South | 17,649 (33.0) | 299,451 (33.5) | 1.0 | 17,649 (33.0) | 17,525 (32.8) | 0.5 |
| North central | 15,092 (28.2) | 212,132 (23.7) | 10.2 | 15,092 (28.2) | 14,906 (27.9) | 0.8 |
| Northeast | 11,399 (21.3) | 180,571 (20.2) | 2.8 | 11,399 (21.3) | 11,590 (21.7) | 0.9 |
| West | 8,223 (15.4) | 180,416 (20.2) | 12.6 | 8,223 (15.4) | 8,378 (15.7) | 0.8 |
| Unknown | 1,102 (2.1) | 21,225 (2.4) | 2.1 | 1,102 (2.1) | 1,066 (2.0) | 0.5 |
| Payment type, n (%)† | | | | | | |
| Commercial | 22,894 (42.8) | 457,678 (51.2) | 16.8 | 22,894 (42.8) | 22,156 (41.4) | 2.8 |
| Medicare | 30,571 (57.2) | 436,117 (48.8) | 16.8 | 30,571 (57.2) | 31,309 (58.6) | 2.8 |
| Insurance type, n (%)† | | | | | | |
| PPO | 25,040 (46.8) | 488,743 (54.7) | 15.7 | 25,040 (46.8) | 24,919 (46.6) | 0.5 |
| HMO | 5,419 (10.1) | 103,056 (11.5) | 4.5 | 5,419 (10.1) | 5,562 (10.4) | 0.9 |
| Comprehensive | 15,591 (29.2) | 153,536 (17.2) | 28.4 | 15,591 (29.2) | 15,635 (29.2) | 0.2 |
| POS | 2,746 (5.1) | 39,942 (4.5) | 3.1 | 2,746 (5.1) | 2,750 (5.1) | 0.0 |
| CDHP | 1,378 (2.6) | 24,167 (2.7) | 0.8 | 1,378 (2.6) | 1,328 (2.5) | 0.6 |
| EPO | 586 (1.1) | 13,195 (1.5) | 3.4 | 586 (1.1) | 596 (1.1) | 0.2 |
| POS capitated | 115 (0.2) | 3,081 (0.3) | 2.5 | 115 (0.2) | 117 (0.2) | 0.1 |
| HDHP | 743 (1.4) | 21,771 (2.4) | 7.6 | 743 (1.4) | 691 (1.3) | 0.8 |
| Not specified | 1,847 (3.5) | 46,304 (5.2) | 8.5 | 1,847 (3.5) | 1,867 (3.5) | 0.2 |

(continued)

Table A1 (Continued)

| Characteristics | Unmatched Cohorts | | | Matched Cohorts* | | |
|---|---------------------------|--------------------------------|-----------------|---------------------------|-------------------------------|-----------------|
| | HF Cohort (N = 53,465) | Non-HF Cohort (N = 893,795) | Std Diff (%) | HF Cohort (N = 53,465) | Non-HF Cohort (N = 53,465) | Std Diff (%) |
| Year of index date, n (%)[†] | | | | | | |
| 2011 | 8774 (16.4) | 270,455 (30.3) | 32.7 | 8774 (16.4) | 8805 (16.5) | 0.2 |
| 2012 | 16,360 (30.6) | 292,657 (32.7) | 4.6 | 16,360 (30.6) | 16,500 (30.9) | 0.6 |
| 2013 | 13,525 (25.3) | 162,861 (18.2) | 17.1 | 13,525 (25.3) | 13,748 (25.7) | 1.0 |
| 2014 | 12,271 (23.0) | 138,008 (15.4) | 19.1 | 12,271 (23.0) | 12,060 (22.6) | 0.9 |
| 2015 | 2535 (4.7) | 29,814 (3.3) | 7.1 | 2535 (4.7) | 2352 (4.4) | 1.6 |
| Comorbidity index scores, mean [median] (SD)[‡] | | | | | | |
| Quan-Charlson comorbidity index | 2.5 [2] (2.5) | 0.9 [0] (1.6) | 77.0 | 2.5 [2] (2.5) | 2.3 [2] (2.6) | 6.8 |
| CHA ₂ DS ₂ -VAsC score | 3.0 [3] (1.8) | 2.0 [2] (1.6) | 64.2 | 3.0 [3] (1.8) | 3.0 [3] (1.9) | 0.8 |
| HAS-BLED score | 1.8 [2] (1.2) | 1.1 [1] (1.0) | 60.2 | 1.8 [2] (1.2) | 1.7 [2] (1.2) | 1.4 |
| Atrial fibrillation, n (%)[‡] | 0 (0.0) | 0 (0.0) | 0.0 | 0 (0.0) | 0 (0.0) | 0.0 |
| Stroke risk factors, n (%)[‡] | | | | | | |
| Hypertension | 39,186 (73.3) | 359,798 (40.3) | 66.7 | 39,186 (73.3) | 39,596 (74.1) | 1.7 |
| Hyperlipidemia | 29,623 (55.4) | 324,856 (36.3) | 38.3 | 29,623 (55.4) | 29,700 (55.6) | 0.3 |
| Diabetes | 19,321 (36.1) | 130,579 (14.6) | 49.5 | 19,321 (36.1) | 18,997 (35.5) | 1.3 |
| COPD | 10,158 (19.0) | 46,418 (5.2) | 42.3 | 10,158 (19.0) | 9434 (17.6) | 3.5 |
| Cerebrovascular accident (stroke/TIA) | 8640 (16.2) | 50,022 (5.6) | 33.9 | 8640 (16.2) | 8196 (15.3) | 2.3 |
| Depression | 7112 (13.3) | 68,569 (7.7) | 18.4 | 7112 (13.3) | 6730 (12.6) | 2.1 |
| Obesity | 6774 (12.7) | 46,603 (5.2) | 26.1 | 6774 (12.7) | 6508 (12.2) | 1.5 |
| Previous VTE | 3000 (5.6) | 12,416 (1.4) | 23.0 | 3000 (5.6) | 2488 (4.7) | 4.3 |
| Myocardial infarction | 2620 (4.9) | 4735 (0.5) | 26.9 | 2620 (4.9) | 1672 (3.1) | 9.0 |
| Acute coronary syndrome | 2433 (4.6) | 6383 (0.7) | 24.0 | 2433 (4.6) | 1743 (3.3) | 6.7 |
| Family history of CVD | 457 (0.9) | 5560 (0.6) | 2.7 | 457 (0.9) | 417 (0.8) | 0.8 |
| Health care resource utilization, mean [median] (SD)[‡] | | | | | | |
| Hospitalizations | 0.48 [0] (0.9) | 0.13 [0] (0.4) | 48.4 | 0.48 [0] (0.9) | 0.38 [0] (0.8) | 11.0 |
| ER visits | 0.94 [0] (1.9) | 0.37 [0] (1.0) | 36.9 | 0.94 [0] (1.9) | 0.79 [0] (1.9) | 7.8 |
| Outpatient visits | 26.4 [19] (29.0) | 14.3 [9] (17.1) | 50.8 | 26.4 [19] (29.0) | 24.7 [18] (25.6) | 6.4 |
| Health care cost, \$US 2015 mean (SD)[‡] | | | | | | |
| Total health care cost | \$36,755 (165,016) | \$11,127 (28,860) | 21.6 | \$36,755 (165,016) | \$29,050 (62,128) | 6.2 |
| Hospitalizations | \$12,680 (44,622) | \$2677 (15,205) | 30.0 | \$12,680 (44,622) | \$9309 (33,463) | 8.5 |
| ER visits | \$1661 (5603) | \$598 (2757) | 24.1 | \$1661 (5603) | \$1435 (5674) | 4.0 |
| Outpatient visits | \$15,005 (53,105) | \$5356 (18,251) | 24.3 | \$15,005 (53,105) | \$12,309 (39,962) | 5.7 |
| Pharmacy | \$4993 (11,943) | \$1975 (5872) | 32.1 | \$4993 (11,943) | \$4,404 (12,416) | 4.8 |
| Non-matching factors | | | | | | |
| Observation period, days, mean [median] (SD)[§] | 469.6 [379] (370.6) | 472.1 [374] (377.5) | 0.6 | 469.6 [379] (370.6) | 449.6 [364] (341.7) | 5.6 |
| Type of index visit, n (%)[†] | | | | | | |
| Hospitalization | 20,987 (39.3) | - | - | 20,987 (39.3) | - | - |
| ER visit | 5419 (10.1) | - | - | 5419 (10.1) | - | - |
| Outpatient visit | 25,046 (46.8) | - | - | 25,046 (46.8) | - | - |
| Other visit | 2013 (3.8) | - | - | 2013 (3.8) | - | - |

CDHP, consumer directed health plan; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; EPO, exclusive provider organization; ER, emergency room; HDHP, high-deductible health plan; HF, heart failure; HMO, health maintenance organization; POS, point-of-service; PPO, preferred provider organization; SD, standard deviation; Std diff, standardized difference; TIA, transient ischemic attack; VTE, venous thromboembolism.

*Patients with HF were matched 1:1 with patients without HF using propensity score calipers of 5%. Variables assessed at the index date (unless otherwise indicated) used in the propensity score calculation included: age, gender, region, payment type, insurance type, year, atrial fibrillation during baseline, baseline risk factors for stroke, Quan-Charlson comorbidity index during baseline, CHA₂DS₂-VAsC score during baseline, HAS-BLED score during baseline, and baseline health care resource utilization and costs.

[†]Evaluated at the index date.

[‡]Evaluated during the 18 month baseline period.

[§]Period ends at the earliest of end of data availability or end of continuous health plan enrollment.

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