Individual and Combined Risk Factors for Incident Atrial Fibrillation and Incident Stroke: An Analysis of 3 Million At-Risk US Patients

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Background—The incremental effects of risk factor combinations for atrial fibrillation (AF) and stroke are incompletely understood. We sought to quantify the risks of incident AF and stroke for combinations of established risk factors in a large US sample.

Methods and Results—Patients with no evidence of AF or stroke in 2007 were stratified by combinations of the following risk factors: heart failure, hypertension, diabetes, age 65 to 74, age ≥75, coronary artery disease, and chronic kidney disease. Patients with ≥2 of the first 5 or ≥3 of the first 7, classified as "high-risk," and an age-matched sample of patients with fewer risk factors, classified as "low-risk," were followed over 2008–2010 for incident AF and stroke. Annualized incidence rates and risks were quantified for each combination of factors by using Cox regression. Annualized incidence rates for AF, stroke, and both were 3.59%, 3.27%, and 0.62% in 1 851 653 high-risk patients and 1.32%, 1.48%, and 0.18% in 1 156 221 low-risk patients, respectively. Among patients with 1 risk factor, those with age ≥75 had the highest hazards of incident AF and stroke (HR 9.2, 6.9). Among patients with 2 risk factors, those with age ≥75 and heart failure had the highest annualized incidence rates of AF and stroke (10.2%, 5.9%). The combination of age ≥75 and hypertension was prevalent and had the highest incidences of AF and stroke.

Conclusions—Adults with combinations of known risk factors are at increased risk of incident AF and stroke, but combinations of risk factors are not always additive. (*J Am Heart Assoc*. 2015;4:e001723 doi: 10.1161/JAHA.114.001723)

Key Words: atrial fibrillation • epidemiology • risk factors/global assessment • risk stratification • stroke

Atrial fibrillation (AF), the most common cardiac arrhythmia, is projected to affect nearly 3 million people in the United States by 2015.[1] AF increases stroke risk by 5-fold; this risk is further modified by the presence of other stroke risk factors.[2] Although oral anticoagulant drugs significantly reduce the risk of stroke in patients diagnosed with AF, it is not uncommon for AF to be detected only after the occurrence of a stroke, even when symptoms likely indicative of arrhythmias are present.[3–5]

While risk factors and risk stratification schemas for AF[6,7] and for stroke[7–11] have been reported from epidemiologic data, the assessment of risk based on specific combinations of known risk factors have not been previously reported. The incremental risks of various factors in different combinations may not be additive; thus, different combinations with the same number of risk factors may confer very different total risks for the development of AF or stroke. However, analyzing a large number of potential risk factor combinations requires a very large sample size and thus is not feasible with most sources of clinical data. Therefore, the objective of our study was to use a large healthcare claims database to quantify and stratify the total and incremental risks associated with combinations of risk factors for AF and stroke in a large sample of the US population.

Methods

Study Design

We conducted a retrospective cohort study by using health care claims data from the Truven Health MarketScan Commercial and Medicare Supplemental Databases (January 2007 to December 2010). These databases represent the health services of >180 million employees, dependents, and retirees in the United States with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans. These databases consist of fully integrated patient-level records that serve as the basis of

>350 peer-reviewed articles since 2000 and are fully HIPAA compliant.[12,13] In particular, these data have been used extensively for outcomes research related to AF and stroke risk.[14–17] A protocol describing the study objectives, criteria for patient selection, data elements of interest, and statistical methods was submitted to the New England Institutional Review Board (NEIRB) and exemption was obtained (NEIRB No. 12–388).
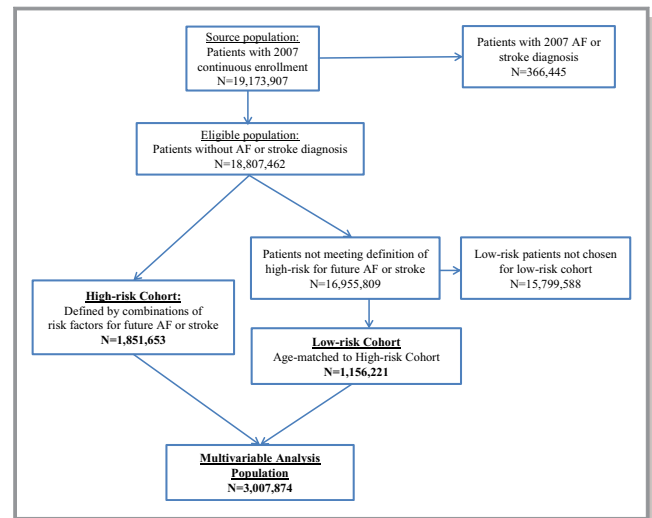
Study Population

The study population consisted of all patients in the MarketScan databases with continuous medical and pharmacy enrollment for the entire baseline calendar year of 2007 and with no record of AF or stroke diagnoses in either inpatient or outpatient claims during that time (Appendix S1). For the purposes of this study, stroke diagnoses included both ischemic and hemorrhagic strokes, as well as transient ischemic attack (TIA).

The study cohort was classified according to the following 7 epidemiologically determined risk factors known to be associated with AF and/or stroke: (1) heart failure, (2) hypertension, (3) diabetes, (4) age ≥65 to 74 years, (5) age ≥75 years, (6) coronary artery disease (CAD), and (7) chronic kidney disease (CKD).[18] Baseline risk factors were identified by using claims data from calendar year of 2007 (Appendix S2). Any patient with ≥2 of the first 5 risk factors or ≥3 of any of the 7 risk factors was defined as high risk for future AF or stroke and was assigned to the high-risk cohort. These 7 factors were selected based on epidemiologic data and previous risk prediction models for AF[1,6,7,19–21] and for stroke.[8,9,22,23] The threshold of 2 or 3 factors corresponds roughly with pre-2014 guidelines for oral anticoagulation of AF patients with high risk of stroke.[24] To create a low-risk cohort for comparison, a random-number generator was used to draw samples of patients in a 1:1 ratio from among the patients with lower risk profiles, matched by age group to the high-risk cohort (Figure 1).

All patients in the high-risk and age-matched low-risk cohorts were included in the multivariable analysis population (Figure 1). Each patient in this population, regardless of risk cohort designation, was further classified by their distinct combination of the 7 baseline risk factors, by using a categorical variable with 96 values to represent the full spectrum of mutually exclusive and collectively exhaustive risk factor combinations.

Identification of Outcomes

The outcomes for this study were incident AF and incident stroke (ischemic, hemorrhagic, and TIA), as defined with *International Classification of Diseases, Ninth Revision* (ICD-9)

Figure 1. Study population. The eligible population included 18.8 million patients without AF or stroke diagnoses in 2007. From these, a high-risk cohort of 1.85 million patients and an age-matched low-risk cohort of 1.16 million patients were identified and included in our study. The multivariable analysis population included both the high-risk and the age-matched low-risk cohort, totaling ≈3.01 million patients. AF indicates atrial fibrillation.

diagnosis codes (Appendix S1). Diagnoses of AF and stroke were tracked for patients with continuous enrollment extending through any portion of calendar years 2008–2010. Incidence rates during the 3 years of follow-up were calculated and annualized for the entire population by dividing the total counts of patients with each event by the sum of patient-years to the first of either the patient's index event or enrollment censoring date. Annualized incidence rates were calculated for the high-risk and low-risk cohorts, for each combination of sex and age group (ages 0 to 17, 18 to 34, 35 to 44, 45 to 54, 55 to 64, 65 to 74, and ≥75 years), as well as for each of the 96 risk factor combinations in the multivariable analysis population.

Statistical Analysis

We calculated hazard ratios (HRs) for incident AF and incident stroke during the 3-year follow-up period from January 1, 2008, to December 31, 2010, by using Cox regression models. All patients with enrollment through December 31, 2010, were censored as of that date. For each end point (AF or stroke/TIA), 2 models were constructed. All analyses were performed with SAS Version 9.2 (SAS Institute).

The first set of Cox regression models used individual baseline risks as predictor variables, such that HRs for each risk could be calculated, with adjustment for all remaining risks and other baseline characteristics. Values for individual baseline predictor variables were obtained from the claims

databases. Predictor variables were age group, sex, geographic region, comorbid conditions (heart failure, hypertension, diabetes, CAD, CKD, and sleep apnea, identified based on ICD-9 codes and prescription medications as described in Appendix S2), symptoms (chest pain, palpitations, dizziness, tachycardia, and respiratory abnormalities, identified based on ICD-9 codes as described in Appendix S3), baseline medication use, and use of internal cardiac devices (pacemaker, implantable cardioverter-defibrillator, implantable loop recorder) or external electrocardiographic monitoring (Holter, external loop monitor, mobile cardiac outpatient telemetry). In addition to these predictors, the stroke model adjusted for oral anticoagulation use >14 days before stroke event or censoring date and for the diagnosis of incident AF before or concurrent with stroke event. Patients with none of the studied risk factors were used as the reference group.

The second set of multivariable models evaluated the incremental impact of individual risks within risk factor combinations. This was accomplished by creating Cox regression models for AF and stroke that used a single categorical predictor variable denoting each patient's mutually exclusive and collectively exhaustive risk factor combination. Patients with none of the studied risk factors were used as the reference group for this model.

Results

Patient Population

Of the 19 173 907 patients in the source population with continuous medical and pharmacy enrollment throughout 2007 in the Truven Health MarketScan Commercial and Medicare Supplemental Databases, 366 445 (1.9%) were excluded based on a diagnosis of AF and/or stroke at baseline. From the remaining population of 18 807 462 patients, a high-risk cohort of 1 851 653 (9.8%) patients was identified. A total of 1 156 221 lower-risk patients were randomly selected from within each age group to match the age distribution of the high-risk cohort. The sampling ratio was 1:1 except in age groups ≥65 years, where age itself was a predefined risk factor and thus fewer low-risk patients were available. The combined multivariable analysis population consisted of 3 007 874 patients (Figure 1). Baseline characteristics of the overall analysis population and the 2 risk cohorts are summarized in Table 1. Among the high-risk patients, the most prevalent risk factors were hypertension (95.3%), diabetes (52.9%), and age ≥65 years (66.0%). Only a small proportion of patients with symptoms commonly associated with cardiac arrhythmias had external cardiac monitoring, regardless of risk cohort designation (Table 1). There are additional baseline characteristics in Appendix S4.

Annualized Incidence Rates and Risk Cohorts

Risk cohort designation, based on our risk stratification scheme of baseline risk factors, differentiated patients with high-risk for incident AF, incident stroke, or both AF and stroke from low-risk patients. The annualized incidence rates for AF alone, stroke alone, and both AF and stroke were 3.59%, 3.27%, and 0.62% for the high-risk cohort and 1.32%, 1.48%, and 0.18%, respectively, for the low-risk cohort (Table 2).

Annualized Incidence Rates Stratified by Age, Sex, and Risk Cohort Designation

In the multivariable analysis population, composed of both the high- and low-risk cohorts, annualized AF and stroke rates were stratified by combination of age group, sex, and high-/low-risk cohort. Among these combinations, rates of incident AF and incident stroke appeared to increase exponentially with each age group, regardless of sex or risk cohort stratification (Figure 2A and 2B). Annualized incidence rates for AF were higher in men than in women in all age groups, except in the 0 to 17 age group, where the incidence rates in both men and women were very low (Figure 2A). However, annualized incidence rates for stroke were similar across the sexes (Figure 2B).

Relationship Between Incident AF and Incident Stroke in Patients Diagnosed With Both Incident AF and Incident Stroke in the Follow-up Period

In the combined population, 158 020 patients were diagnosed with stroke in the follow-up period. Diagnoses of incident AF were also reported for 28 395 (18%) of these patients with incident stroke. Among the patients with diagnoses of both AF and stroke in the follow-up period, diagnosis of incident AF was most commonly within 14 days of stroke diagnosis, followed by >14 days after stroke diagnosis, and was least likely to occur >14 days before stroke diagnosis (Figure 3).

Hazard Ratios of Individual Risk Factors for Incident AF and for Incident Stroke Based on Multivariable Analysis

In the first multivariable Cox regression models, HRs for incident AF and for incident stroke were calculated by using individual risk factors as independent variables. As summarized in Table 3, the risk for incident AF and for incident stroke both increased exponentially with age. Male sex was a significant predictor of incident AF but not of stroke.

Table 1. Baseline Characteristics of Analysis Population: High-Risk Cohort and Low-Risk Cohort as Well as Combined Population for Multivariable Analysis

Baseline Characteristics	High-Risk Cohort (n=1 851 653), No. (%)	Low-Risk Cohort (n=1 156 221), No. (%)	Combined Population (N=3 007 874), No. (%)
Age group, y			
0 to 17	1304 (0.1)	1304 (0.1)	2608 (0.1)
18 to 34	20 463 (1.1)	20 463 (1.8)	40 926 (1.4)
35 to 44	67 962 (3.7)	67 962 (5.9)	135 924 (4.5)
45 to 54	205 934 (11.1)	205 934 (17.8)	411 868 (13.7)
55 to 64	333 810 (18.0)	333 810 (28.9)	667 620 (22.2)
65 to 74	643 258 (34.7)	319 014 (27.6)	962 272 (32.0)
≥75	578 922 (31.3)	207 734 (18.0)	786 656 (26.2)
Sex			
Male	862 486 (46.6)	556 212 (48.1)	1 418 698 (47.2)
Female	989 167 (53.4)	600 009 (51.9)	1 589 176 (52.8)
Comorbid conditions used for risk stratification			
Heart failure	138 746 (7.5)	505 (0.0)	139 251 (4.6)
Hypertension	1 764 318 (95.3)	186 868 (16.2)	1 951 186 (64.9)
Diabetes	978 724 (52.9)	28 295 (2.5)	1 007 019 (33.5)
Coronary artery disease	331 185 (17.9)	43 649 (3.8)	374 834 (12.5)
Chronic kidney disease	93 034 (5.0)	6058 (0.5)	99 092 (3.3)
Comorbid condition not used for risk stratification			
Sleep apnea	107 000 (5.8)	26 691 (2.3)	133 691 (4.4)
Symptoms			
Any symptom	517 646 (28.0)	153 721 (13.3)	671 367 (22.3)
Chest pain	312 300 (16.9)	86 924 (7.5)	399 224 (13.3)
Dizziness	87 437 (4.7)	27 982 (2.4)	115 419 (3.8)
Palpitations	49 033 (2.7)	17 374 (1.5)	66 407 (2.2)
Tachycardia unspecified	15 641 (0.8)	3295 (0.3)	18 936 (0.6)
Shortness of breath	165 614 (8.9)	34 918 (3.0)	200 532 (6.7)
Respiratory—other	104 711 (5.7)	23 084 (2.0)	127 795 (4.2)
Respiratory—unspecified	10 836 (0.6)	2476 (0.2)	13 312 (0.4)
External cardiac monitoring			
Overall	27 303 (1.5)	6140 (0.5)	33 443 (1.1)
Among patients with any symptom	22 433 (4.3)	5046 (3.3)	27 479 (4.1)

Baseline characteristics are based on records from the Truven Health MarketScan® Commercial and Medicare Supplemental Databases from the calendar year of 2007. y indicates years.

Comorbid conditions and symptoms each individually conferred modest but significant risks for incident AF as well as stroke. In the stroke model, diagnosis of incident AF >14 days before or within 14 days of the censoring date (the first of a stroke event or end of follow-up) dramatically increased risks of stroke, whereas oral anticoagulation use >14 days before the censoring date significantly decreased risks for stroke.

Annualized Incidence Rates and Hazard Ratios of Unique Risk Combinations for Incident AF and for Incident Stroke

Annualized risks were calculated for each mutually exclusive and collectively exhaustive combination of risk factors. Hazard ratios were calculated separately for incident AF and stroke for each of the 96 unique risk factor combinations by

Table 2. Annualized Incidence of Atrial Fibrillation, Stroke, and Both Atrial Fibrillation and Stroke

| Event Category (2008–2010)	High-Risk Cohort (n=1 851 653)		Low-Risk Cohort (n=1 156 221)		Combined Population (N=3 007 874)	
Annualized Incidence	Patients	Rate/y	Patients	Rate/y	Patients	Rate/y
Atrial fibrillation	134 495	3.59%	31 246	1.32%	165 741	2.71%
Stroke	123 053	3.27%	34 967	1.48%	158 020	2.58%
Both atrial fibrillation and stroke	23 971	0.62%	4424	0.18%	28 395	0.45%

Annualized incidence rate is derived by dividing patient counts by total patient-years.

using Cox regression models with a single predictor variable that categorized patients according to their baseline combination. Patients with none of the studied risk factors were used as the reference group. Annualized incidence rates, HRs, *p*-value levels, event counts, and sample sizes for all 96 risk factor combinations are summarized in Table 4. The most prevalent high-risk combinations were hypertension plus age 65 to 74 and hypertension plus diabetes.

Annualized rates of AF and stroke diagnoses among patients with no risk factors were 0.35% and 0.49%, respectively, while rates ranged from 0.65% to 3.34% for those with single risk factors (Figure 4). Among patients with a single risk factor, patients with age ≥75 had the highest risks of AF (annualized incidence rate of 3.25%, HR 9.2) and highest risks of stroke (annualized incidence rate of 3.34%, HR 6.9) (Figure 4 and Table 4). Among patients with 2 risk factors, those with age ≥75 in combination with HF had the highest annualized incidence rate for AF and for stroke (10.2% and 5.9%, respectively), and the annualized incidence rates for AF were supra-additive (exceeding summation of 3.2% for age ≥75 alone and 1.7% for heart failure alone) (Table 4). The estimate of excess risk attributable to the interaction of these 2 risk factors is 5.3%, which is highly statistically significant due to the large sample sizes within each of these risk factor cohorts.

As illustrated in Table 4, risks for incident AF and for incident stroke did not increase linearly with the number of risk factors, and not all risk factor combinations conferred equal risks. Combinations inclusive of heart failure, hypertension, or age ≥75 appear to confer the highest risks for incident AF or incident stroke among 2–, 3–, 4–, 5–, or 6–risk factor combinations. The single risk factor of age ≥75 conferred greater risks for incident AF and for incident stroke than did 2–risk factor combinations of hypertension with age 65 to 74, or diabetes with age, or hypertension with diabetes. Similarly, among the 2–risk factor combinations, the combination group with age ≥75 and hypertension had greater risks
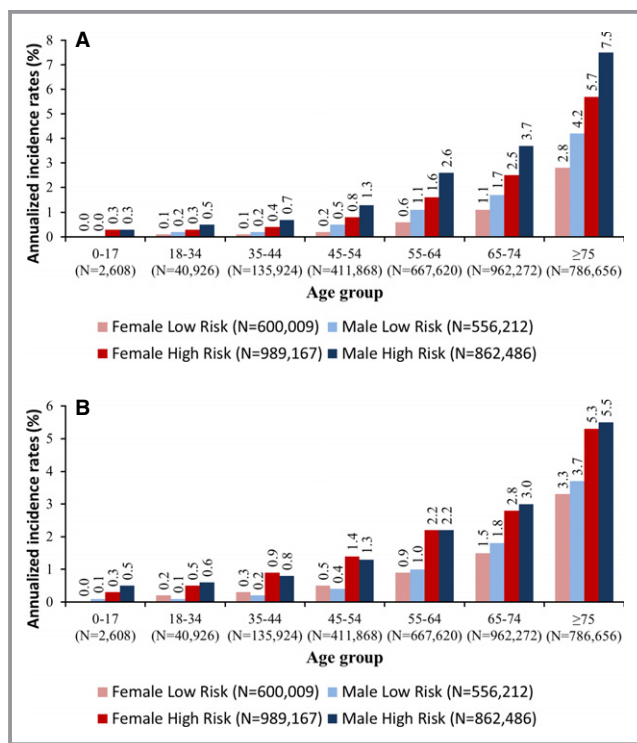
Figure 2. A, Annualized incidence rates of atrial fibrillation stratified by age, sex, and risk cohort, unadjusted, 2008–2011. B, Annualized incidence rates of stroke stratified by age, sex, and risk cohort, unadjusted, 2008–2011.
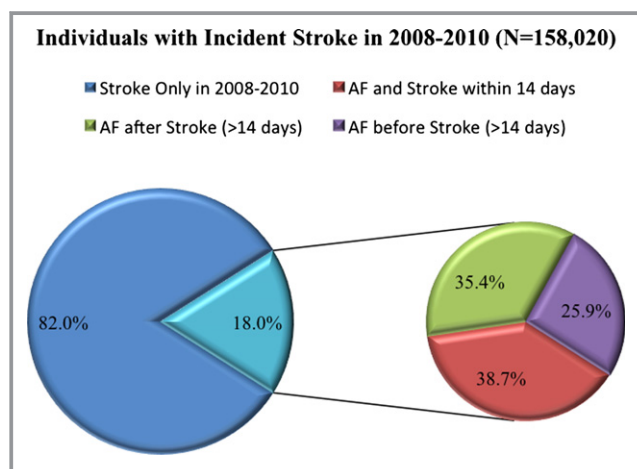
Figure 3. Timing of diagnosis of incident AF in relation to diagnosis of incident stroke. Of those with diagnosis of both incident AF and incident stroke in, diagnosis of AF was most commonly within 14 days of diagnosis of incident stroke. AF indicates atrial fibrillation.

Table 3. Multivariable Hazard Ratios of Individual Risk Factors for Incident Atrial Fibrillation (AF) or Incident Stroke Based on Cox Regression Models

	AF*		Stroke*†	
	Hazard Ratio	P Value	Hazard Ratio	P Value
Predictor variable				
Age group, y (reference = 18 to 34 years)				
35 to 44	1.30	0.0010	1.54	<0.0001
45 to 54	2.40	<0.0001	2.41	<0.0001
55 to 64	4.65	<0.0001	3.99	<0.0001
65 to 74	8.19	<0.0001	6.56	<0.0001
≥75	16.37	<0.0001	10.82	<0.0001
Sex (reference = Female)				
Male	1.32	<0.0001	0.99	0.0765
Comorbid conditions used for risk stratification of cohorts, 2007 (reference=no)				
Heart failure	1.72	<0.0001	1.23	<0.0001
Hypertension	1.31	<0.0001	1.24	<0.0001
Diabetes	1.11	<0.0001	1.25	<0.0001
Coronary artery disease	1.21	<0.0001	1.04	<0.0001
Chronic kidney disease	1.23	<0.0001	1.26	<0.0001
Comorbid condition not used for risk stratification of cohorts, 2007 (reference=no)				
Sleep apnea	1.21	<0.0001	1.14	<0.0001
Symptoms				
Chest pain	1.01	0.0411	1.27	<0.0001
Dizziness	1.07	<0.0001	1.40	<0.0001
Palpitations	1.46	<0.0001	1.07	<0.0001
Tachycardia unspecified	1.19	<0.0001	1.13	<0.0001
Shortness of breath	1.16	<0.0001	1.13	<0.0001
Respiratory—other	1.01	<0.0001	1.12	<0.0001
Respiratory—unspecified	1.09	0.6292	1.09	0.0033
Indicators of stroke timing† (reference=no)				
AF event >14 d before stroke event	—	—	16.2	<0.0001
AF event within 14 d of stroke event	—	—	21.9	<0.0001
Oral anticoagulation use >14 d before stroke event	—	—	0.6	<0.0001

d indicates days; y, years.

*Estimates for each risk factor were adjusted for geographic region, medications, and use of internal/external electrocardiographic recording devices, in addition to all other risk factors shown in the table.

†Stroke model also included indicators of stroke timing.

for incident AF and for incident stroke than 3–risk factor combinations of hypertension with CAD and age 65 to 74 or hypertension with diabetes and age 65 to 74, or hypertension with diabetes and CAD.

Furthermore, the prevalence of risk factor combinations in the population at baseline contributes to overall incidences of AF and stroke. Because age ≥75 was a prevalent risk factor, patients with age ≥75, as a single risk factor or in combination with additional risk factors, accounted for large numbers of AF

and stroke events. In particular, the combination of age ≥75 and hypertension (298 560 patients) had the highest absolute numbers of incident AF (32 268 diagnoses, HR 14.83) and incident stroke (28 968 diagnoses, HR 9.64) events.

The HRs computed in this analysis used the healthiest cohort (ie, patients with no risk factors) as the reference group. However, because all of these ratios were computed by using the same reference, the HR for any risk cohort compared with any other risk cohort can be estimated from

Table 4. Annualized Incidence Rates and HRs of All Unique Risk Combinations for Incident AF and for Incident Stroke

Risk Factors	Sample Size (2007)	Stroke Incidence			AF Incidence		
		Diagnoses (2008–10)	Annualized Rate[†] (%/year)	HR[‡]	Diagnoses (2008–10)	Annualized Rate[†] (%/year)	HR[‡]
Cohort with no risk factors							
None	409 074	3969	0.5	Ref	2900	0.4	Ref
Cohorts with single risk factors							
Age 65 to 74	305 984	10 898	1.6	3.3****	8840	1.3	3.7****
Age 75+	195 120	13 294	3.3	6.9****	12 958	3.2	9.2****
HTN	168 932	3336	1.0	2.1****	3114	0.9	2.6****
Diabetes	27 025	525	1.0	2.0****	346	0.6	1.8****
CAD	4134	123	1.6	3.3****	89	1.1	3.2****
CKD	563	19	1.8	3.6****	9	0.8	2.3*
HF	414	17	2.2	4.5****	13	1.7	4.7****
Cohorts with 2 risk factors							
HTN+diabetes	490 924	13 036	1.3	2.8****	9640	1.0	2.8****
HTN+age 65 to 74	338 402	17 071	2.3	4.7****	17 666	2.4	6.8****
HTN+age 75+	298 560	28 968	4.7	9.6****	32 268	5.3	14.8****
Diabetes+age 65 to 74	41 697	2243	2.4	5.0****	1600	1.7	4.9****
Diabetes+age 75+	25 025	2480	4.8	9.9****	2138	4.1	11.6****
HF+HTN	17 427	682	2.1	4.4****	1181	3.8	10.6****
HTN+CAD	15 835	555	1.9	4.0****	594	2.1	5.8****
CAD+age 65 to 74	11 679	657	2.7	5.5****	693	2.8	8.0****
CAD+age 75+	10 885	1147	5.3	10.8****	1281	5.9	16.7****
HF+age 75+	3672	342	5.9	12.1****	565	10.2	28.6****
HTN+CKD	2101	93	2.4	4.8****	63	1.6	4.5****
CKD+age 75+	1729	174	5.4	11.1****	206	6.5	18.2****
HF+diabetes	1443	57	2.2	4.5****	62	2.4	6.8****
CKD+age 65 to 74	1351	90	3.2	6.6****	95	3.4	9.5****
HF+age 65 to 74	1279	92	3.7	7.6****	133	5.5	15.4****
Diabetes+CAD	1005	54	3.0	6.2****	30	1.6	4.6****
Diabetes+CKD	265	14	3.0	6.2****	12	2.6	7.2****
HF+CAD	76	2	1.5	3.0	2	1.5	4.2*
CAD+CKD	35	0	0.0	0.0	1	1.7	4.7
HF+CKD	14	0	0.0	0.0	0	0.0	0.0
Cohorts with 3 risk factors							
HTN+diabetes+age 65 to 74	114 730	7711	3.1	6.4****	7270	2.9	8.2****
HTN+diabetes+age 75+	79 597	8805	5.4	11.1****	9217	5.7	16.0****
HTN+CAD+age 75+	65 200	7660	5.8	11.9****	9995	7.8	21.8****
HTN+diabetes+CAD	62 433	2976	2.6	5.4****	2779	2.4	6.9****
HTN+CAD+age 65 to 74	61 478	4471	3.4	7.1****	5490	4.3	12.0****
HTN+diabetes+CKD	16 380	942	3.1	6.4****	733	2.4	6.8****
HF+HTN+age 75+	16 339	1961	7.0	14.4****	3255	12.4	34.8****
HTN+CKD+age 75+	11 641	1337	5.9	12.2****	1545	6.9	19.5****

Table 4. Continued

Risk Factors	Sample Size (2007)	Stroke Incidence			AF Incidence		
		Diagnoses (2008–10)	Annualized Rate[†] (%/year)	HR[‡]	Diagnoses (2008–10)	Annualized Rate[†] (%/year)	HR[‡]
HF+HTN+diabetes	9708	618	3.6	7.5****	787	4.7	13.1****
HF+HTN+CAD	8643	446	3.0	6.2****	782	5.4	15.1****
HTN+CKD+age 65 to 74	7918	637	3.8	7.9****	583	3.5	9.8****
HF+HTN+age 65 to 74	6657	568	4.3	8.8****	988	7.8	21.8****
Diabetes+CAD+age 65 to 74	3551	293	3.9	8.1****	261	3.5	9.9****
Diabetes+CAD+age 75+	2889	350	6.1	12.5****	411	7.2	20.3****
HTN+CAD+CKD	2675	170	3.7	7.7****	166	3.6	10.2****
HF+HTN+CKD	1367	115	5.2	10.7****	118	5.3	14.9****
HF+diabetes+age 75+	1135	119	6.4	13.2****	176	9.8	27.5****
HF+CAD+age 75+	1029	131	8.0	16.4****	206	13.4	37.5****
Diabetes+CKD+age 65 to 74	830	82	4.9	10.1****	77	4.6	13.0****
Diabetes+CKD+age 75+	792	102	6.9	14.2****	91	6.1	17.1****
HF+diabetes+age 65 to 74	567	59	5.5	11.3****	90	8.8	24.8****
HF+CAD+age 65 to 74	379	22	3.0	6.2****	49	7.1	20.0****
HF+diabetes+CAD	353	28	4.7	9.6****	29	4.7	13.3****
CAD+CKD+age 75+	289	33	6.4	13.2****	41	8.2	23.2****
HF+CKD+age 75+	233	31	10.5	21.7****	38	13.4	37.2****
Diabetes+CAD+CKD	222	15	4.1	8.4****	12	3.2	9.1****
CAD+CKD+age 65 to 74	139	9	3.1	6.3****	15	5.4	15.1****
HF+diabetes+CKD	114	8	4.7	9.6****	15	8.7	24.3****
HF+CKD+age 65 to 74	48	3	4.0	8.2***	4	5.5	15.3****
HF+CAD+CKD	33	4	7.4	15.2****	7	15.0	41.9****
Cohorts with 4 risk factors							
HTN+diabetes+CAD+age 65 to 74	31 774	2940	4.4	9.1****	3273	4.9	13.9****
HTN+diabetes+CAD+age 75+	24 614	3271	6.7	13.7****	3871	8.0	22.6****
HF+HTN+CAD+age 75+	11 270	1538	7.8	16.0****	2640	14.4	40.5****
HF+HTN+diabetes+CAD	7886	608	4.7	9.6****	870	6.8	19.1****
HF+HTN+diabetes+age 75+	7243	1026	8.4	17.2****	1494	12.7	35.7****
HTN+diabetes+CKD+age 65 to 74	7161	732	5.0	10.2****	692	4.7	13.2****
HTN+diabetes+CKD+age 75+	6189	844	7.1	14.7****	868	7.4	20.8****
HF+HTN+CAD+age 65 to 74	5399	556	5.2	10.8****	948	9.4	26.5****
HF+HTN+diabetes+age 65 to 74	4801	523	5.6	11.5****	769	8.5	24.0****
HTN+diabetes+CAD+CKD	4384	396	5.3	10.9****	350	4.6	13.0****
HTN+CAD+CKD+age 75+	4212	574	7.2	14.8****	745	9.6	27.0****
HTN+CAD+CKD+age 65 to 74	2333	250	5.2	10.7****	287	6.1	17.1****
HF+HTN+diabetes+CKD	2304	212	5.9	12.1****	237	6.6	18.6****
HF+HTN+CKD+age 75+	2059	250	7.9	16.3****	430	14.5	40.5****
HF+HTN+CKD+age 65 to 74	697	82	6.7	13.7****	118	10.0	28.0****
HF+HTN+CAD+CKD	693	59	5.7	11.7****	102	10.5	29.5****
HF+diabetes+CAD+age 75+	421	68	10.8	22.2****	84	13.4	37.4****

Table 4. Continued

Risk Factors	Sample Size (2007)	Stroke Incidence			AF Incidence		
		Diagnoses (2008–10)	Annualized Rate[†] (%/year)	HR[‡]	Diagnoses (2008–10)	Annualized Rate[†] (%/year)	HR[‡]
HF+diabetes+CAD+age 65 to 74	260	31	6.5	13.4****	41	8.9	24.9****
Diabetes+CAD+CKD+age 75+	188	29	7.9	16.3****	24	6.6	18.6****
Diabetes+CAD+CKD+age 65 to 74	178	17	5.1	10.5****	24	7.5	21.1****
HF+diabetes+CKD+age 75+	145	12	6.0	12.4****	29	15.3	42.8****
HF+CAD+CKD+age 75+	97	2	1.5	3.0	25	21.5	60.0****
HF+diabetes+CKD+age 65 to 74	80	5	3.9	8.0****	21	18.2	51.0****
HF+diabetes+CAD+CKD	69	5	5.2	10.8****	9	9.9	27.7****
HF+CAD+CKD+age 65 to 74	29	0	0.0	0.0	5	12.6	35.2****
Cohorts with 5 risk factors							
HF+HTN+diabetes+CAD+age 75+	6526	1000	8.9	18.4****	1434	13.4	37.7****
HF+HTN+diabetes+CAD+age 65 to 74	5308	675	6.7	13.8****	995	10.3	29.0****
HTN+diabetes+CAD+CKD+age 65 to 74	3330	408	6.2	12.7****	450	6.8	19.2****
HTN+diabetes+CAD+CKD+age 75+	3172	443	7.4	15.3****	647	11.3	31.8****
HF+HTN+diabetes+CAD+CKD	2415	272	8.0	16.4****	314	9.2	25.7****
HF+HTN+CAD+CKD+age 75+	2038	295	9.5	19.5****	473	16.3	45.7****
HF+HTN+diabetes+CKD+age 75+	1875	278	9.7	20.0****	404	14.9	41.7****
HF+HTN+diabetes+CKD+age 65 to 74	1429	195	7.9	16.2****	250	10.3	28.8****
HF+HTN+CAD+CKD+age 65 to 74	694	81	6.8	14.0****	145	13.1	36.7****
HF+diabetes+CAD+CKD+age 75+	90	14	10.6	21.9****	24	19.1	53.4****
HF+diabetes+CAD+CKD+age 65 to 74	59	5	6.0	12.3****	10	14.2	39.5****
Cohort with 6 risk factors							
HF+HTN+diabetes+CAD+CKD+age 75+	2382	369	10.3	21.3****	510	15.0	41.9****
HF+HTN+diabetes+CAD+CKD+age 65 to 74	2051	311	9.2	18.9****	400	12.1	34.0****

Each section is displayed in descending order of HR for AF or stroke. HR indicates hazard ratio; AF, atrial fibrillation; HTN, hypertension; CAD, coronary artery disease; CKD, chronic kidney disease; HF, heart failure.
[†]Unadjusted annualized incidence rate.
[‡]HRs were calculated by using the second Cox regression model with mutually exclusive and collectively exhaustive risk factor combination as a predictor and patients with none of the studied risk factors were used as the reference group.
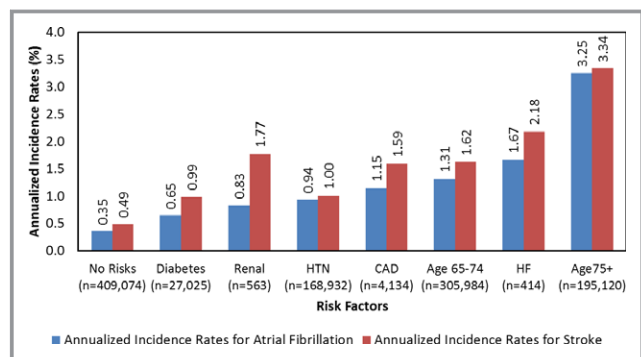*$P<0.05$, **$P<0.01$, ***$P<0.001$, ****$P<0.0001$.

Figure 4. Annualized incidence rates of AF and stroke diagnoses for patients with no risk factors or a single risk factor. AF indicates atrial fibrillation; CAD, coronary artery disease; HF, heart failure; HTN, hypertension.

the results in Table 4 by simply dividing the HR for the cohort of interest by the HR for the reference group of interest. For instance, if it is more desirable to compare the stroke risk for a patient of age 65 to 74 with diabetes to a patient of the same age without diabetes, the HR associated with the added risk of diabetes could be calculated as 5.0/3.3=1.5.

Discussion

In this study of >3 million US patients, for the first time, we quantified the separate and combinatorial effects of individual risk factors for incident AF and incident stroke by using a large claims database. In our stratification system, patients classified as high risk based on the presence of a combination of heart failure, hypertension, diabetes, advanced age (65 to

74 or ≥75 years), CAD, and CKD were indeed at higher risk for incident AF and incident stroke. These findings are consistent with epidemiologic data and previous risk prediction models for AF[1,6,7,19–21] and for stroke,[8,9,22,23] validating the concept that comorbidities determined from a claims database may provide reasonably accurate risk prediction.

Male sex was a significant predictor of incident AF in our study. This is consistent with published data from the Framingham Heart Study,[6] the Atherosclerosis Risk in Communities Study,[23] and the Cardiovascular Health Study.[20] Sex was not, however, a significant predictor of all-cause stroke in our study. This is not inconsistent with published data; although existing models (CHA$_2$DS$_2$-VASc, Framingham Heart Study) have demonstrated an independent association between female sex and stroke in the particular setting of AF, sex is not an independent predictor of all-cause stroke in the Framingham Heart Study model.[22]

The large size of our sample provided statistical power to compare risks associated with specific factors, not only in isolation but also in various combinations. With this approach, we demonstrated that not all risk factors—or risk factor combinations—are "created equal." Age ≥75 was the single most important risk factor for both incident AF and incident stroke, whether in isolation or in combination with other factors. Combinations of risk factors that included heart failure, hypertension, or age ≥75 conferred the highest risk for incident AF and incident stroke. Furthermore, we showed that risk factors are not simply additive—despite the convenience of certain existing models, 1 plus 1 does not always equal 2. For example, when combined, the risks of age ≥75 and heart failure were supra-additive, exceeding the sum of the risks associated with each factor in isolation.

The most recently revised AF guideline from the American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society highlights clinical risk factors associated with increased risks for AF but has not incorporated risk assessment schema for the identification and management of patients at risk for AF.[25] As the management of common cardiovascular conditions (eg, heart failure and ischemic heart disease) has moved to a stratified approach, based on risk level, we anticipate the management of AF and stroke to follow this similarly expanded framework. Observations from our study have relevant implications with respect to risk stratification of the population.

First, our data underscore the importance of age ≥75, especially when combined with hypertension, as a prevalent and high-risk combination for both incident AF and incident stroke. In this particularly vulnerable and prevalent cohort, more proactive measures to screen for incident AF and other modifiable risk factors may be warranted. The use of longer-term, external electrocardiographic monitoring devices could provide a particular benefit in this population, especially if symptoms are present. Given that AF is underdiagnosed and may even present as incident stroke,[26] earlier identification of subclinical AF in this high-risk cohort may permit earlier introduction of preventive measures, such as thromboprophylaxis where indicated. The value and optimal methodology for screening for AF in this cohort are incompletely understood and require further study.

Second, our data challenge the present paradigm of risk prediction by addition, rather than combination. There is a need to develop new risk predictive models that account for the observed differential effects of specific combinations of risk factors. The ubiquity of computing and, increasingly, smartphone-based applications in modern medicine lowers the bar for clinical application of a more sophisticated combinatorial model. Such a combinatorial model could potentially offer a more individualized and accurate risk prediction for a given patient, with direct implications for consideration of more intensive monitoring and the use of preventive interventions.

Limitations to our study include its retrospective design and its reliance on claims data. ICD-9 codes were used to ascertain diagnoses of AF and stroke, as well as risk factors and symptoms. There was likely variation in levels of arrhythmia monitoring and follow-up. In view of the acknowledged underdiagnosis of AF in the literature,[26] ICD-9 coding used in our study may have underestimated the true incidence of AF. Similarly, patient risks could be underestimated, though this would have a conservative dampening effect on the risk differentials. Finally, MarketScan data consist only of insured patients and so are not representative of the uninsured population in the United States. Acknowledging these limitations, our study had multiple strengths, including its large, real-world sample and novel combinatorial approach. These advantages permit an important contribution to the body of literature on the prediction of AF and stroke and prompt new directions in public health strategies and research. Further, the annualized risks of AF and stroke associated with specific combinations of risk factors in our study provide clinicians with concrete estimates for individual patients in the clinic.

Conclusion

Adults with combinations of heart failure, hypertension, diabetes, advanced age (65 to 74 or ≥75), CAD, and CKD are at increased risks of incident AF and incident stroke. Risks associated with combinations of risk factors are not always additive. Rather, certain combinations of risk factors are associated with substantially higher risks of incident AF and incident stroke. The combination of age ≥75 and hypertension in particular is both prevalent and high risk, contributing substantially to the incidence of AF and the incidence of stroke, thus constituting an important target for more active monitoring and prevention.

Disclosures

Dr. Chyou has no relationships relevant to the contents of this article to disclose. Dr. Hunter is an employee of CTI Clinical Trial and Consulting Services, which provides consulting services to Medtronic, plc. Ms. Mollenkopf is an employee of Medtronic, plc. Dr. Turakhia is a consultant to Medtronic, plc and St. Jude Medical, Inc and has received honoraria for speaking from St. Jude Medical, Inc and Boston Scientific. Dr. Reynolds is a consultant to Medtronic, plc.

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