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Risk Factors for Symptomatic Atrial Fibrillation-Analysis of an Outpatient Database

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Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in practice and is the leading cause of debilitating strokes with significant economic burden. It is currently not known whether asymptomatic undiagnosed AF should be treated if detected by various screening methods. Currently United States guidelines have no recommendations to identify patients with asymptomatic undiagnosed AF due to lack of evidence. The American Heart Association Center for Health Technology & Innovation undertook a plan to identify tools in 3 phases that may be useful in improving outcomes in patients with undiagnosed AF. In phase I we sought to identify AF risk factors that can be used to develop a risk score to identify high-risk patients using a large commercial insurance dataset. The principal findings of this study show that individuals at high risk for AF are those of advance age, the presence of heart failure, coronary artery disease, hypertension, metabolic disorders, and hyperlipidemia. Our analysis also found that chronic respiratory failure was a significant risk factor for those over 65 years of age and chronic kidney disease for those less than 65 years of age.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in practice and is the leading cause of debilitating strokes[1], leading to significant economic burden[2]. While AF presently affects 2.7-6.1 million, it is expected to increase to 12.1 million by 2030.[1] AF may be asymptomatic and underdiagnosed with the first presentation being a stroke.[3] Studies estimate that 13% to 40% of patients with AF are undiagnosed.[4,5] Strokes associated with AF have worse outcomes resulting in larger cerebral infarct size, more hemorrhagic transformation, subsequent disabilities, and death.[6] Increasing awareness of AF by clinicians and patients may lead to an earlier diagnosis and treatment, resulting in fewer adverse health outcomes. However, the United States Preventive Task Force has stated there is insufficient evidence to endorse electrocardiographic (ECG) screening for AF. [7]

The American Heart Association's Center for Health Technology & Innovation undertook a plan to identify tools that may be useful in improving outcomes in patients with undiagnosed AF. The work plan consists of 3 phases. Phase I is to develop a predictive screening tool, using multivariate logistic regression to calculate the risk of developing AF. Phase II is to create and evaluate the use of the screening tool developed in Phase I to prospectively identify individuals at high risk for the onset of AF, as compared to usual care. Phase III will ask patients with newly diagnosed with AF to enroll in a study that would compare compliance with AF treatment in patients using a digital tracking device to usual care. The results of our analysis reported here are from phase I of the study. The aim of this analysis was to address the problem of undiagnosed AF in the US population by gaining a better understanding of the factors associated with AF.

We hypothesized that using a large population database could potentially identify clinically important risk factors associated with AF. The primary objective of this phase of the study was to identify patients at high risk for undiagnosed AF.

Methods

We performed a retrospective cohort study using a commercial dataset to identify risk factors that are associated with AF ICD diagnosis codes of 427.31.

Key Words
Atrial fibrillation, Left atrial appendage, Stroke.

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Data source

A commercial dataset representing over 50 health plans and self-insured employers, representing all 50 states and containing 535,499 records, including 4862 cases of AF from 2010-17 was used in this analysis. The dataset was cross-sectional, and all records were de-identified. The dataset included demographic data, including age and gender, frequency of 40 chronic conditions as identified by ICD codes, biometric measures, including height, weight, and blood pressure, and cost data, including pharmacy and total paid claims.

Calculations

To assess the risk of stroke in this patient population the $CHADS_2$ and CHA_2DS_2-VASc scores were calculated,[8] as well as the number of chronic conditions.

Statistical analysis

Statistical analysis was performed with SPSS version 25. Chi Square, binary logistic regression and hierarchical logistic regression were conducted to test the hypothesis that AF could be predicted from demographic, biometric, and claims data. Chronic conditions, including AF were coded as binary variables, Yes=1 and No=0. Frequencies, prevalence of AF and odds ratios were calculated from the binary variables. Frequencies of AF were calculated by $CHADS_2$ and CHA_2DS_2-VASc scores. Independent sample t-tests were calculated for height, weight, body mass index, systolic blood pressure, diastolic blood pressure, number of chronic conditions, age, total pharmacy cost, and lifetime paid claims, comparing cases with AF and cases without AF. Binary and hierarchical logistic regression was performed with AF as the dependent variable.

Results

Descriptive statistics

[Table 1] provides a breakdown of cases with and without AF by gender and age. The total number and rate of AF was higher in males than in females. The rate of AF increased with age. [Figure 1] shows the age distribution of the patient population in the database. [Table 2] shows the distribution of the presence of AF with respect to sex and age.

There was a slight majority of male participants (n = 286,710; 53.4%) to female participants (n = 248,101; 46.2%). For the male participants, (n = 3,255; 1.14%) were coded YES for AF and (n = 283,455; 98.86%) were coded NO for AF. For the female participants, (n = 1,603; 0.65%) were coded YES for AF and (n = 246,496; 99.35%) were coded NO for AF. Overall for both genders, (n = 4,858; 0.91%) were coded YES for AF and (n = 529,963; 99.09%) were coded NO for AF.

Table 1: Frequency of AF by age and gender

Group	+ AF	-AF	Rate /1000
Male	3255	283455	.011
Female	1603	246498	.003
Age: 18-64	2488	466468	.005
Age: 65-74	1302	31724	.039
Age: ≥75	1403	11092	.112

Most participants were under the age of 65 years (n = 490,566; 91.6%). A clear minority of participants were age 65 years or older (n = 44,883; 8.4%). For the under age 65-year participants, (n = 2,353; 0.48%) were coded YES for AF and (n = 488,213; 99.5%) were coded NO for AF. For the age 65 years or older, (n = 2,509; 5.59%) were coded YES for AF and (n = 42,374; 94.41%) were coded NO for AF. Overall for both age groups, (n = 4,862; 0.91%) were coded YES for AF and (n = 530,587; 99.09%) were coded NO for AF.

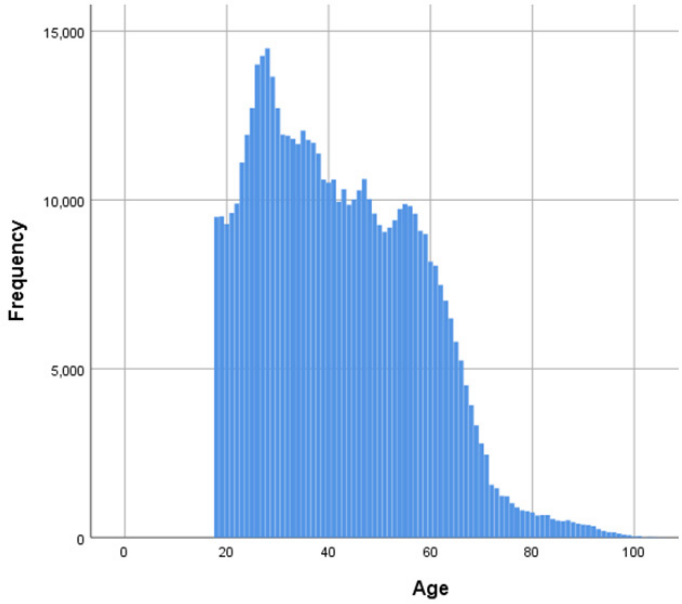

Figure 1: Age distribution of the patient population in the database.

Table 2: Distribution of age and sex in patients with AF.

	<65 years	≥65 years
Males	0.66%	7.03%
Females	0.28%	4.75%

Associated chronic conditions

The dataset included a total of 40 of the most common chronic conditions to look for possible trends. Metabolic disorders included unspecified metabolic conditions not including metabolic syndrome or diabetes. [Table 3] is a breakdown of each condition, including a 2X2 table of the presence or absence of AF and each chronic condition. From the table the rate of AF and each factor can be calculated, as well as the odds ratio. A Chi Square analysis was performed for each chronic condition to determine of there was a statistically significant relationship between AF and each chronic condition. The top 10 chronic conditions were used in the logistic regression model. Since age of a robust predictor of AF, and since this commercial dataset is heavily weighted to younger individuals, the rates, odds ratio and Chi Square were conducted for cases under age 65 and over age 65.

$CHADS_2$ and CHA_2DS_2-VASc and AF. The $CHADS_2$ and CHA_2DS_2-VASc scores were calculated from the data. [Table 4] is a summary of the rate of AF by $CHADS_2$ scores, and [Table 5] is the summary of the rate of AF by CHA_2DS_2-VASc scores. In both scores the rate of AF increases with each level.

Table 3: Calculation of odds ratio and Chi Square for common chronic conditions for the total group.

Factor	+AF, + Factor	+AF, -Factor	-AF, + Factor	-AF, -Factor	Odds Ratio	Chi Square	P value
ADHD	26	4837	7148	524546	.394	23.9	<.05
Affective psychosis	33	4830	3073	528621	1.2	.848	NS
Alzheimer's	62	4801	236	531458	29.1	1314	<.05
Asthma	343	4520	14726	516968	2.6	323	<.05
Autism	0	4863	228	531466	.99	2.086	NS
Blood disorders	1428	3435	21495	510199	9.8	7555	<.05
Bronchopulm. dysplasia	0	4863	3	531691	.99	.027	NS
CAD	1652	3211	9675	522019	27.7	24105	<.05
CKD	638	4225	4064	537630	19.6	8468	<.05
COPD	690	4173	4547	527147	19.1	8864	<.05
Cancer	997	3866	16434	515260	8.0	4647	<.05
Cerebral palsy	1	4862	139	531555	.787	.058	NS
Chromosomal abnorm.	4	4859	161	531533	2.7	4.3	<.05
Chronic pain	317	4546	7089	524605	5.1	951	<.05
Chronic resp fail	227	4636	638	531056	40.7	6192	<.05
Heart failure	1354	3509	2902	528792	70.3	45630	<.05
Demyelinating diseases	16	4847	953	530741	1.8	5.9	<.05
Depression	257	4606	14358	517336	2.0	121	<.05
Developmental disorders	5	4858	308	531386	1.7	1.6	NS
Diabetes	1370	3493	28755	502939	6.8	4712	<.05
ESRD	154	4709	682	531012	25.4	2859	<.05
Eating disorders	39	4824	745	530949	5.7	144	<.05
HIV/AIDS	8	4855	341	531353	2.5	7.4	<.05
Hyperlipidemia	2717	2146	61692	470002	9.6	8939	<.05
Hypertension	3628	1235	70102	461592	19.3	15336	<.05
Immune disorders	48	4815	1006	530668	5.2	156	<.05
Inflammatory bowel dis	54	4809	2171	529523	2.7	57	<.05
Intellectual disabilities	2	4861	77	531617	2.8	2.3	NS
Liver diseases	289	4574	6625	525069	5.0	835	<.05
Lower back pain	825	4038	37016	494678	2.7	735	<.05
Metabolic disorders	3305	1558	76023	455671	12.7	11015	<.05
Metabolic syndrome	49	4814	1586	530108	3.4	79.8	<.05
Morbid obesity	420	4443	8780	522914	5.6	1395	<.05
Osteoarthritis	1072	3791	18686	513008	7.7	4664	<.05
Paralysis	82	4781	690	531004	13.1	812	<.05
Peripheral vascular dis	341	4522	2183	529511	18.2	4485	<.05
Rheumatoid Arthritis	98	4765	2480	529214	4.3	241.7	<.05
Sickle cell disease	1	4862	88	531606	1.2	.047	NS
Sleep apnea	1389	3474	23540	508154	8.6	6336	<.05
Stroke	1303	3850	9511	499791	17.8	13595	<.05

+AF indicates number of positive cases of atrial fibrillation, -AF indicates number of negative cases of atrial fibrillation, +Factor means the number of positive cases of condition listed on the left, - Factor means the number of negative cases of the condition listed on the left. ADHD = attention deficit and hyperactive disorder, CAD=coronary artery disease, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, ESRD=end stage renal disease.

Comparison of means

The dataset included a subset of continuous variables including body composition, blood pressure, number of chronic conditions and cost variables. [Table 6] shows the results of independent samples t-test comparing cases with AF to those without AF. While there was no difference in height or blood pressure, there were statistically significant differences in weight and body mass index. Individuals with AF were significantly older, had more chronic conditions and had higher medical and pharmacy costs than those without AF.

Logistic Regression

Since the chronic conditions are binary factors (yes or no) simple binary logistic regression was used to determine the relationship between AF and each chronic condition [Table 7]. The highest Nagelkerke r squared is for the number of chronic conditions. Age, hypertension (HTN), coronary artery disease (CAD), congestive heart failure (CHF) and metabolic disorders had the highest Nagelkerke scores. Binary logistic regression was also performed on the under age 65 and over age 65 cohorts.

Table 4: CHADS2 score distribution of the patient population

$CHADS_2$	Total	%	AF	%	Rate/1000
0	415,583	80.8	874	0%	2.10
1	66,589	12.9	1,362	2%	20.45
2	22,089	4.3	1,078	5%	48.80
3	5,671	1.1	751	13%	132.43
4	3,136	.6	544	17%	173.47
5	1,110	.2	398	36%	358.56
6	268	.1	146	54%	544.78

CHADS2=CHADS2 score, Total: Number of cases in CHADS2 score, %: percentage of cases in CHADS2 score, AF=number of cases of atrial fibrillation, %=percentage of atrial fibrillation cases.

Table 5: CHA2DS2-VASc score distribution of the patient population

$CHA2DS_2$-VASc Score	Total	%	AF	%	Rate/1000
0	193,811	37.7	490	0%	2.53
1	241,617	47.0	964	0%	3.99
2	48,182	9.4	965	2%	20.03
3	19,012	3.7	838	4%	44.08
4	6,461	1.3	613	9%	94.88
5	2,902	.6	524	18%	180.57
6	1,511	.3	370	24%	244.87
7	663	.1	259	39%	390.65
8	237	.0	101	43%	426.16
9	39	.0	27	69%	692.31

Total: Number of cases in CHA2DS2VASc score, %: percentage of cases in CHA2DS2VASc score, AF=number of cases of atrial fibrillation, %=percentage of atrial fibrillation cases

A hierarchical logistic regression model was performed for the whole group [Table 8] and separately for the under 65 and over 65 cohorts. Variables selected for the logistic regression model were based on the variables with the top 10 odds ratios. Since age resulted in a higher Nagelkerke score than any of the chronic conditions it was added to the model.

CAD, HTN, CHF, chronic respiratory failure and age were common to all 3 models. Only CKD in the under 65 cohort and COPD in the over 65 cohort were added. Since age is in the model and the highest ROC and Nagelkerke r squared was achieved in the total group there appears to be no reason to have a separate predictive model for each age group.

Discussion

Our principal findings show that individuals at high risk for AF are those of advance age, the presence of CHF, CAD, HTN, metabolic disorders, and hyperlipidemia. Our analysis also found that chronic respiratory failure was a significant risk factor for those over 65 years of age and chronic kidney disease for those less than 65 years of age.

Risk scores for predicting AF have been developed by the Framingham Heart Study and Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)-AF consortium. The risk score was validated in different ethnic groups including whites, Hispanics and African Americans.[9] In a community-based cohort, the CHARGE-AF risk score was compared to the CHA_2DS2-VASc risk score and found to perform better at predicting AF.[10] In another AF risk score study COPD was found to be a significant risk factor in a Chinese population study. [11]

Table 6: Comparison of means for continuous variables

Factor	AF	N	Mean	SD	P value
Height	Yes	526	65.53	15.8	.105
	No	47285	64.48	14.9	
Weight	Yes	526	211.07	75.1	.000
	No	47285	182.37	62.0	
Body mass index	Yes	526	25.4	15.3	.000
	No	47285	22.0	13.8	
Systolic blood pressure	Yes	526	124.6	17.8	.896
	No	47285	122.1	34.1	
Diastolic blood pressure	Yes	526	77.4	11.3	.051
	No	47285	76.2	13.1	
# of chronic conditions	Yes	4863	5.64	2.9	.000
	No	531694	.8	1.5	
Age	Yes	4862	66.1	14.6	.000
	No	530587	42.0	15.4	
Total Rx cost	Yes	4852	9800.9	32100	.000
	No	417586	2578.9	15861	
Lifetime paid claims	Yes	4852	163592	70031	.000
	No	417586	46933	12007	

Awareness of this high-risk group can be a signal to primary care physicians to pay more attention to the possibility that these patients are at greater risk for AF and, in turn, for stroke. This predictive tool has the potential, following further validation, to assess large amounts of patient claims and electronic medical record data to identify patients in need for AF detection devices. An additional possible use of this data would be in risk stratifying corporate employees for proactive encouragement to establish a relationship, and to stay engaged with a primary care physician.

Several studies are underway to determine if opportunistic AF detection leads to decreased strokes, heart failure and mortality. [12] Screening tools such as pulse palpation followed by ECG, sphygmomanometer with rhythm determinations and rhythm monitoring devices are being studied to identify patients with asymptomatic AF.[12] However, it has yet to be determined whether asymptomatic AF detected through opportunistic means such as implanted devices or screening studies should prompt the same treatment for symptomatic AF.[12] The AF Screen International Collaboration acknowledged that health resources vary widely between countries and health systems and thus AF screening should be both country- and health system-specific. Large randomized outcomes studies are needed to strengthen the evidence base of the value of detecting asymptomatic AF. Guidelines vary in their recommendations for opportunistic screening for AF. The European Society of Cardiology AF guidelines has a level IB recommendation for opportunistic screening for AF by pulse taking or ECG rhythm strip in patients >65 years of age as well as routine detections of atrial high rate episodes in patients with implanted devices. Further evaluation for treatment of AF is then recommended.[13] The American guidelines make no recommendations for opportunistic AF screening but consider it a priority for stroke prevention. Efforts are underway to provide randomized controlled trials to determine the value of opportunistic AF screening.

Table 7: Binary Logistic Regression for total group and common chronic conditions

Factor	Wald	Nagelkerke	OR	LL	UL	P value
ADHD	.22.298	.001	.394	.268	.580	.000
Affective psychosis	.846	.000	1.175	.833	1.658	.846
Alzheimer's	551.969	.005	29.082	21.954	38.527	.000
Asthma	299.409	.004	2.644	2.384	2.977	.000
Blood disorders	5036.616	.066	9.867	9.263	10.511	.000
CAD	10807.959	.130	27.759	26.073	29.544	.000
CKD	4315.374	.046	19.605	17.940	21.425	.000
COPD	4564.768	.049	19.169	17.595	20.884	.000
Cancer	3298.310	.042	8.086	7.529	8.683	.000
Chromosomal abnorm.	3.898	.000	2.718	1.007	7.332	.048
Chronic pain	765.563	.010	5.160	4.594	5.796	.000
Chronic respiratory failure	2220.662	.022	40.757	34.933	47.552	.000
Heart failure	13202.329	.148	70.311	65.391	75.601	.000
Demyelinating diseases	5.815	.000	1.838	1.121	3.016	.016
Depression	116.379	.002	2.010	1.771	20282	.000
Developmental disorders	1.621	.000	1.176	.734	4.298	.203
Diabetes	3521.769	.048	6.860	6.437	7.310	.000
ESRD	1282.070	.013	25.463	21.328	30.400	.000
Eating disorders	112.783	.001	5.762	4.171	7.960	.000
HIV/AIDS	6.939	.000	2.568	1.273	5.179	.008
Hyperlipidemia	6026.756	.103	9.646	9.109	10.214	.000
Hypertension	7964.790	.177	19.343	18.125	20.643	.000
Immune disorders	125.030	.002	5.259	3.931	7.035	.000
Inflammatory bowel disorder	52.901	.001	2.739	1.572	3.593	.000
Intellectual disabilities	2.124	.000	2.841	.698	11.566	.145
Liver diseases	677.300	.009	5.008	4.435	5.654	.000
Lower back pain	677.651	.010	2.730	2.531	2.945	.000
Metabolic disorders	6736.697	.135	12.715	11.966	13.511	.000
Metabolic syndrome	70.554	.001	3.402	2.557	4.527	.000
Morbid obesity	1097.189	.014	5.630	5.083	6.236	.000
Osteoarthritis	3354.483	.043	7.763	7.243	8.321	.000
Paralysis	480.473	.005	13.199	10.480	16.624	.000
Peripheral vascular disease	2337.602	.024	18.291	16.258	20.579	.000
Rheumatoid Arthritis	202.197	.003	4.389	3.579	5.381	.000
Sleep apnea	4414.928	.059	8.0631	8.099	9.198	.000
Gender	352.507	.007	.565	.532	.600	.000
Age	9395.060	.192	1.091	1.089	1.093	.000
Age group	7409.449	.118	12.285	11.603	13.007	.000
Chronic conditions	16330.588	.319	1.856	1.839	1.874	.000
$CHADS_2$	15633.265	.234	3.301	2.959	3.063	.000
$CHA2DS_2$-VASc	13933.352	.211	2.358	2.325	2.392	.000

OR=Odds ratio, LL=lower limit of the odds ratio, UL=upper limit of the odds ratio, ADHD = attention deficit and hyperactive disorder, CAD=coronary artery disease, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, ESRD=end stage renal disease.

For the next phase of our study, we plan to develop and use the predictive screening tool using the high-risk conditions to see if this would predict the presence of asymptomatic AF in patients in different populations and other databases. In addition, we will need to evaluate the risk of stroke and thromboembolism in patients with asymptomatic subclinical AF since this is not yet known. The threshold amount of AF that should be treated with anticoagulation in these patients is not yet universally established.

Limitations

There are several limitations in our study. The commercial dataset is derived from specific codes of the diseases entered by healthcare providers and errors from incorrect coding from misclassification of diseases may be possible. Another limitation was that the accuracy of the diagnosis of AF was not verified by cardiologists. We assume the patients in the dataset were symptomatic, as asymptomatic diagnosis is unlikely with the exception of occasional incidental diagnosis in a routine visit with an observation such as an irregular pulse. Our study

Table 8: Hierarchical logistic regression total group

Factor	Wald	Nagelkerke	Odds Ratio	95% CI	ROC
Heart failure	13202.329	0.148	70.31	65.40-75.60	0.636
CAD	10807.959	0.13	27.76	26.07-29.54	0.661
Hypertension	7964.79	0.177	19.34	18.13-20.64	0.807
Metabolic disorders	6736.697	0.135	12.72	11.97-13.51	0.768
Hyperlipidemia	6026.756	0.103	9.65	9.109-10.21	0.721
Age	9395.06	0.192	1.10	1.089-1.093	0.798

strength is the large cohort of a diverse population in terms of sex and age. Because the database consists only of patients known to have been diagnosed with AF, the findings of AF markers in this report may or may not hold for undiagnosed AF. Other considerations such as treatment for hypertension or slower ventricular rate that may reduce symptoms must be taken into account, and thus further validation is needed.

Disclosures

Dr. Waldo has received consulting fees/honoraria from Biosense Webster, AtriCure, Milestone Pharmaceuticals, Cardiac Insight, Correvio Pharms, Pfizer, Bristol-Myers Squibb; Dr. Naccarelli has received consulting fees/honoraria from Acesion, Glaxo-Smith-Kline, Janssen, Milestone, Omecos, and Sanofi; Dr. Albert has received funding from the NIH (R01 HL116690; Dr. Turkhia has received grants from Janssen, AstraZeneca, Veterans Health Administration, Boehringer Ingelheim, Cardiva Medical, Bristol Myers-Squibb, and the American Heart Association, and consulting fees/honoraria from Medtronic, AliveCor, Abbott, Precision Health Economics, Zipline Medical, IBeat, and iRrythm. The remaining authors have no disclosures.

Conclusions

This analysis demonstrates that individuals at risk for AF can be identified from the general population with the use of a predictive algorithm. Increasing age and the presence of heart failure, coronary artery disease, hypertension, metabolic disorders, and hyperlipidemia represent this high-risk group. Respiratory failure and chronic kidney disease may also identify certain age groups at risk for AF. Awareness of this high-risk group can be a signal to primary care physicians to pay more attention to the possibility that these patients are at greater risk for AF, and, in turn, for stroke. With further validation, this predictive tool can be used to determine the need for AF detection devices, clinical decision-support tools and appropriate treatment plans.

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