RESEARCH

The Costs of Warfarin Underuse and Nonadherence in Patients with Atrial Fibrillation: A Commercial Insurer Perspective

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ABSTRACT

BACKGROUND: Atrial fibrillation (AF) imposes a substantial clinical and economic burden on the U.S. health care system. Despite national guidelines that recommend oral anticoagulation for stroke prevention, the literature consistently reports its underuse in AF patients with moderate to high stroke risk.

OBJECTIVE: To assess the economic burden of underuse and nonadherence of warfarin therapy among patients with nonvalvular AF in a commercially insured population.

METHODS: Claims data between January 2003 and December 2007 from the Thomson Reuters MarketScan Research Database were used. Patients diagnosed with nonvalvular AF who were continuously enrolled for at least 12 months prior to and 2 months following their diagnosis, who had a $CHADS_2$ score ≥2, and were not at high risk of bleeding (ATRIA score <5, $HEMORR_2HAGE$ score <4, and HAS-BLED score <3) at baseline were included. Patients were followed for up to 18 months after the AF diagnosis date to assess the level of warfarin utilization. Health care resource utilization and cost during follow-up among patients with the proportion of days covered (PDC) by warfarin >0.8 (high) and ≤0.8 (low) versus patients with no warfarin exposure were assessed. Multivariate negative binomial regressions and generalized linear models were used to estimate differences in resource utilization and cost, respectively.

RESULTS: Of the 13,289 subjects included in this analysis, 47% had no warfarin exposure; 31.5% had low PDC; and 21.5% had high PDC. The rates of ischemic stroke and transient ischemic attack (per 100 patient-years) were significantly lower for the groups that had high and low PDCs as compared with the group with no warfarin exposure ($P<0.001$). Multivariate analysis showed that patients with high PDC were 27% less likely ($P<0.001$) to incur hospitalizations, and 16% were less likely ($P=0.019$) to incur emergency room visits than patients who did not receive warfarin, but the differences between low PDC patients and no warfarin exposure were not significant. Although both low and high PDC were associated with lower all-cause inpatient cost ($P<0.001$), only high PDC was associated with a lower post-index all-cause total cost ($P<0.001$) compared with no warfarin exposure.

CONCLUSION: Our results confirm that underutilization and nonadherence of warfarin among nonvalvular AF patients is both prevalent and costly. Warfarin use among patients with moderate to high stroke risk and low to moderate bleed risk demonstrated a stroke benefit without a significant increase in intracranial hemorrhage. Adherence to oral anticoagulant therapy was associated with a significant reduction in inpatient service use and total health care cost. Improving adherence to oral anticoagulation is important to attaining the clinical and economic benefits of therapy.

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What is already known about this subject

- Atrial fibrillation (AF) is estimated to affect more than 3 million U.S. adults. It is associated with significant increase in the likelihood of stroke, resulting in a substantial clinical and economic burden.
- The efficacy of warfarin for stroke prevention in AF patients is well established, but the literature consistently shows that it is underused even in patients at high risk of stroke.
- Maintaining adherence to warfarin therapy is challenging. Previous data have shown that 1 in 4 AF patients discontinue warfarin therapy within the first year of receiving their initial prescriptions.

What this study adds

- High warfarin adherence (proportion of days covered >80%) was associated with fewer inpatient admissions and emergency room visits and lower total health care cost, compared with no use of warfarin at all. These data underscore the economic and clinical benefits of improving oral anticoagulant use in AF patients.

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, and it affects more than 3 million U.S. adults.[1] AF is responsible for 15% to 20% of all strokes[2] and confers almost 5 times the risk of stroke and 1.9 times the risk of death versus patients without AF.[2,3] Total direct cost related to AF treatment in the United States is reported to be more than $6 billion annually.[4] The overall economic burden of stroke from a societal perspective, including both direct and indirect costs, was estimated at $34.3 billion in 2008.[5] Direct cost of AF-related strokes was estimated to be approximately $8 billion.[6]

Clinical guidelines recommend the use of oral anticoagulants for long-term stroke prevention in AF patients who are at intermediate to high risk of stroke (i.e., $CHADS_2$ score >1), assuming patients are not at high bleeding risk.[7,8] However, studies have consistently reported that many patients who were eligible for oral anticoagulation did not receive warfarin. Zimetbaum et al. (2010)[9] report that only 42.1% of patients with a $CHADS_2$ score ≥3 received warfarin therapy, and according to a systematic literature review, less than 60% of patients with high stroke risk are on oral anticoagulant (OAC)

therapy.[10] Contributing further to AF morbidity and mortality is poor adherence with warfarin therapy and high discontinuation rates among those who received prescriptions.[11,12] According to a recent study of 4,188 Kaiser Permanente (U.S.) patients with AF, more than 1 in 4 patients (26%) starting on warfarin discontinued therapy in the first year despite a low overall hemorrhage rate (2.3% of patients).[13]

Suboptimal utilization of OACs can lead to higher health care cost associated with strokes that would be prevented by effective anticoagulation therapy. As oral anticoagulation is also associated with an increased risk of bleeding,[14] risk-benefit assessment is crucial in the anticoagulation treatment decision. Data on the economic impact of OAC underuse are limited. Based on decision-analytic modeling, Caro (2004)[6] estimated that optimizing INR (international normalized ratio) control among AF patients that received warfarin and increasing warfarin use in AF patients could result in a reduction of health care costs by $2.4 billion per year.[6]

The objective of this study was to estimate the economic burden from the payers perspective associated with suboptimal utilization of warfarin therapy in a commercially insured AF population with moderate to high stroke risk without contraindications for warfarin treatment. This study utilized medical claims data to identify clinical events and costs and prescription claims data to assess warfarin use, which provides a more precise estimate of the economic implications of warfarin underuse and nonadherence than previous economic modeling.

Methods

Study Design and Data Source

This study was a retrospective, observational, quasi-experimental study using de-identified health care claims data from the Thomson Reuters' MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases from January 2003 to December 2007. These databases include individual-level enrollment and cost data across inpatient, outpatient, and prescription drug services from 45 large employers, health plans, and government and public organizations. The MarketScan database has been used in published research conducted in AF patients previously.[9,15,16]

Study Population

The study sample consisted of adult incident AF patients who would be candidates for OAC. Specifically, AF was identified based on the presence of at least 2 medical claims with primary or secondary AF diagnoses (using the *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] diagnosis code 427.31) separated by at least 30 days and not more than 12 months, of which at least 1 claim was in the outpatient setting. The date of the first AF medical claim was defined as the AF index date. Patients were required to have been continuously enrolled in the health plan for at least 12 months prior to the AF index date and at least 2 months after the AF index date to be eligible for inclusion.

Eligible patients were required to have moderate to high stroke risk as assessed by a $CHADS_2$ score ≥ 2[17] and did not have high bleed risk as assessed by an ATRIA bleeding risk score <5,[18] the $HEMORR_2HAGES$ score <4,[19] or the HAS-BLED score <3.[20] ICD-9-CM codes associated with inpatient and outpatient medical claims in the 12-month pre-index period were used to determine baseline stroke and bleeding risk scores. Patients with ICD-9-CM codes corresponding to contraindications to warfarin, according to the package insert for Coumadin, as well as those presenting with valvular and transient AF were excluded (see Appendices). Patients with warfarin prescription claims or prothrombin/INR (PT/INR) claims in the 12 months prior to AF index date were also excluded.

Key Variables of Interest

Warfarin exposure during the 18-month follow-up period after the AF index date was identified by the presence of outpatient prescription claims as well as the timing of PT/INR claims. Consistent with the algorithm validated by Go et al. (2003),[21] patients were considered to be continually on warfarin when the gaps between 2 prescription claims were ≤ 60 days apart. When the gaps between 2 prescription claims were >60 days apart, patients were considered to be continually on warfarin if there was a PT/INR claim every 42 days. If there was no PT/INR claim every 42 days, then patients were considered off warfarin from the thirty-first day after the end of the first prescription days of supply until the start of the next prescription fill date. The level of warfarin exposure for patients who had at least 1 warfarin prescription claim was assessed using proportion of days covered (PDC), calculated as the total days of supply associated with warfarin prescription claims during the follow-up period (less any overlapping days of supply) divided by the length of follow-up after the AF index date. The level of warfarin exposure was classified as high (PDC >0.8) and low (PDC ≤ 0.8), and patients who did not fill a warfarin prescription after the AF index date were considered to have a PDC $=0$ (no warfarin exposure). The use of the 0.8 cut point was based on conventions used in other conditions[22] and based on the distribution of PDC values of warfarin users in our sample to ensure there was an adequate number of subjects in each PDC group.

Health care resource utilization and costs during the follow-up period for the no warfarin exposure group (PDC $=0$) were compared with those with high and low PDC groups. Inpatient hospitalizations, length of stay (LOS), emergency room (ER) visits, and outpatient office visits during the 18-month period after the AF index date was assessed. All cost variables were evaluated from the payer perspective and were based on

TABLE 1 ICD-9-CM Codes for Stroke and Bleed Outcomes

Clinical Outcomes	ICD-9-CM Codes
Ischemic stroke	43.00-01, 433.10-11, 433.20-21, 433.30-31, 434.00-01, 434.10-11, 434.90-91, 436 (acute, ill-defined cerebrovascular disease)
Other thromboembolic events	444.0, 444.1, 444.21-22, 444.81, 444.89, 557.0, 557.1, 557.9
Intracranial hemorrhage	430, 431, 432.0, 432.1, 432.9 Note: all 5th digits 0-9 are searched for using the following traumatic ICH codes: 852.0, 852.2, 852.4, 853.0
Gastrointestinal hemorrhage	455.2, 455.5, 455.8, 456.0, 456.20, 459.0, 530.7, 530.82, 531.00-01, 531.20-21, 531.40-41, 531.60-61, 532.00-01, 532.20-21, 532.40-41, 532.60-61, 533.00-01, 533.20-21, 533.40-41, 533.60-61, 534.00-01, 534.20-21, 534.40-41, 534.60-61, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.0, 578.1, 578.9
Other bleeds	423.0 (hemopericardium) 593.81 (vascular disorders of kidney) 599.7 (hematuria) 719.11 (hemarthrosis: including fifth digits: 0-9) 784.7 (epistaxis) 784.8 (hemorrhage from throat; added December 4, 2000) 786.3 (hemoptysis)
Transient cerebral ischemia [112.]	435.0, 435.1, 435.2, 435.3, 435.8, 435.9

ICD-9-CM = International Classication of Diseases, Ninth Revision, Clinical Modification; ICH = intracranial hemorrhage.

amounts paid by the insurer to the provider (i.e., paid claims). Inpatient cost included services rendered during a hospital stay. Outpatient cost included physician office visits, hospital outpatient visits, ER visits, outpatient laboratory tests, medical procedures, and radiological exams, excluding outpatient prescription drug cost. Medical cost was defined as the total cost of all inpatient and outpatient medical services. Prescription drug cost included all outpatient pharmacy claims. Due to the variable length of follow-up for eligible study patients, cost measures were expressed on a per-patient per-month basis.

Ischemic stroke or bleeding events during the post-index period were assessed in each PDC group based on the presence of medical or inpatient claims with either a primary or secondary diagnosis (Table 1). Since the occurrence of strokes or bleeds may have resulted in the initiation or termination of warfarin therapy, which would influence warfarin exposure PDC levels, we censored the warfarin PDC calculation to either the day prior to the occurrence of such an event or at the end of the 18-month follow-up period, whichever occurred first.

Statistical Analyses

Descriptive analyses were used to compare baseline characteristics among patients at different PDC levels. A series of multivariate regressions were performed to examine the effect of warfarin exposure level on health care resource use and costs. Negative binomial regression was used to assess health care resource use variables and a generalized linear model (GLM) with gamma distribution and log link was used to assess cost outcomes based on the skewed distribution encountered in our data and previous modeling studies of cost.[23] When the proportion of patients with zero costs was >10%, two-part modeling using a preliminary logistic regression to obtain probabilities of incurring cost given the independent variables in the model, followed by a GLM on the subset of the population that incurred cost, was performed.

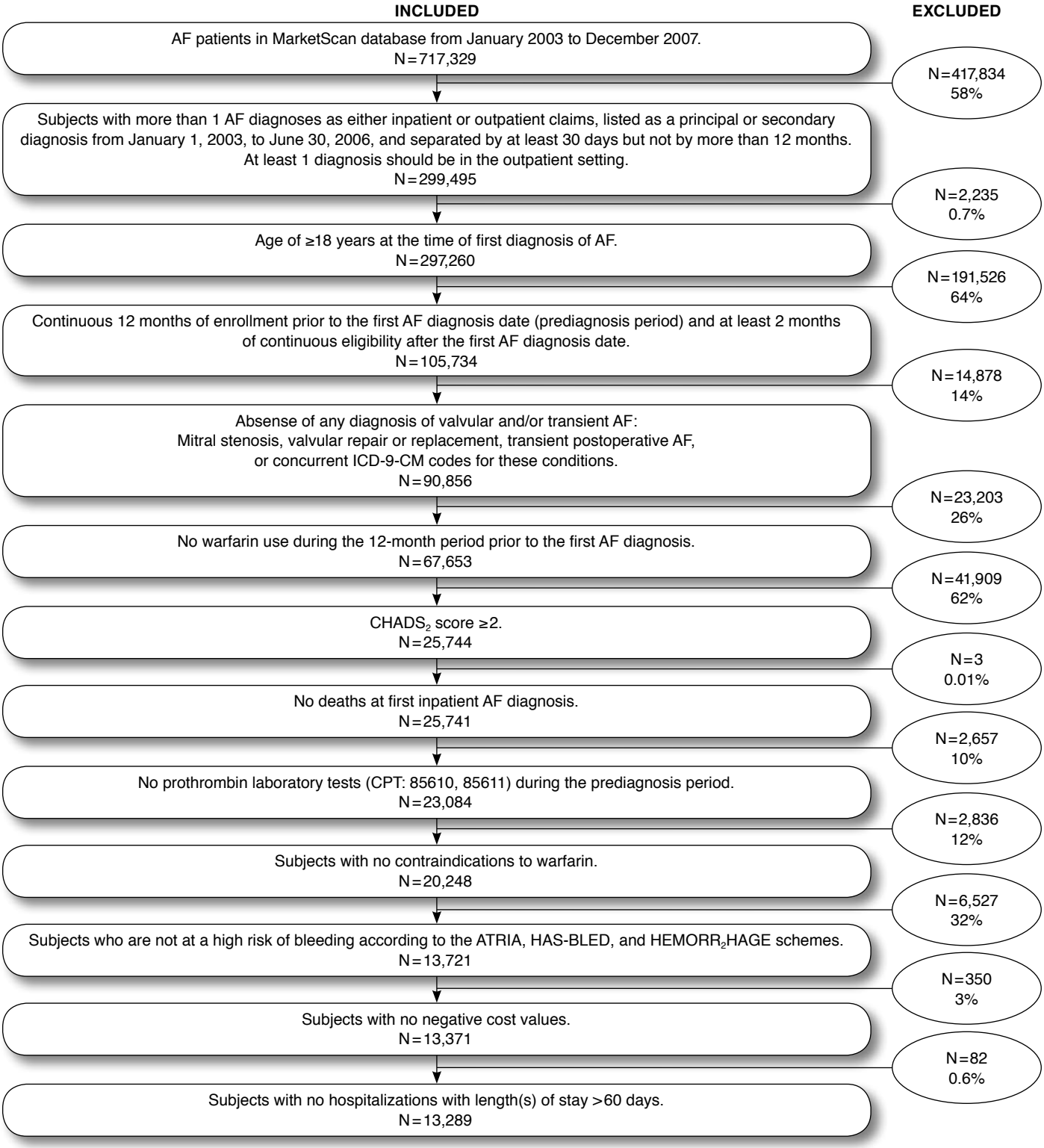
Covariates in the regression models included patient demographics, insurance type, comorbidities, stroke ($CHADS_2$) and bleed (ATRIA) risk factors, and pre-index measures of the same economic outcome variable under evaluation. Pre-index health care resource use and costs were identified by medical claims in the 12-month period before the AF index date. Comorbidities from the Elixhauser Comorbidity Index[24] were identified based on ICD-9-CM codes associated with inpatient and outpatient claims during the 12-month pre-index period. Due to a high degree of multicollinearity between ATRIA, $HEMORR_2HAGES$, and HAS-BLED bleeding risk scores (Pearson correlation coefficient = 0.6), we controlled for ATRIA bleeding risk score[13] in the models because the ATRIA risk factors can be more reliably defined using medical claims compared with the other indices. To account for variable follow-up time and to control its effect on cost variance, weights were determined based on the months of enrollment in the study divided by the study period (18 months) for each observation. All data management and analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Population Characteristics and Warfarin Utilization

The study sample consisted of 13,289 patients with a $CHADS_2$ score ≥2 and no obvious contraindication to warfarin (Figure 1). Nearly half of the patients (n = 6,253; 47%) did not receive warfarin, and only 21.5% (n = 2,852) of patients had a PDC > 0.80. Patients who did not receive warfarin were more likely to be ≥75 years of age, and they had a slightly higher $CHADS_2$ score (mean score = 2.37 vs. 2.33; $P < 0.001$) partly due to the higher prevalence of congestive heart failure than those who received warfarin. Patients who did not receive warfarin also had slightly higher bleeding risk on average as assessed by all 3 bleeding risk indices. Of the patients who did receive warfarin, 65% did so within 30 days of the index diagnosis. The mean follow-up time for patients not exposed to warfarin was 14.2 months, significantly lower compared with 15.6 months ($P < 0.001$) for patients who received warfarin (Table 2.1). There was a significantly greater proportion of high PDC patients with a history of bleeding compared with low PDC patients ($P < 0.05$; Table 2.2).

FIGURE 1 Patient Selection Flowchart



AF = atrial fibrillation; CPT = Current Procedural Terminology; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

TABLE 2.1 Summary Statistics: Demographics, Baseline Risk Factors, Comorbidities, and Insurance Type

Patient Characteristics	Exposed to Warfarin (PDC > 0) n (%)		Unexposed to Warfarin (PDC = 0) n (%)	
	7,036	(52.94)	6,253	(47.06)
Gender				
Female	3,612	(51.34)[a]	3,426	(54.79)
Age				
≥ 75 years	5,327	(75.71)[a]	5,093	(81.45)
Location[a]				
Northeast	607	(8.63)	451	(7.21)
North central	2,545	(36.17)	1,988	(31.79)
South	1,973	(28.04)	1,740	(27.83)
West	1,885	(26.79)	2,048	(32.75)
Unknown	26	(0.37)	26	(0.42)
$CHADS_2$ stroke risk factors				
CHF	1,473	(20.94)[a]	1,693	(27.08)
Hypertension	5,404	(76.81)[a]	4,575	(73.16)
Diabetes	2,538	(36.07)[a]	2,084	(33.33)
Prior stroke or TIA	782	(11.11)	665	(10.63)
ATRIA bleed risk factors				
Anemia	47	(0.67)[b]	66	(1.1)
Renal failure	26	(0.51)	32	(0.5)
History of bleeding	95	(1.35)	90	(1.4)
Top 5 comorbidities (other than those included in $CHADS_2$/ATRIA scales)				
Chronic pulmonary disease	1,612	(22.91)	1,376	(22.01)
Valvular disease	1,463	(20.79)[c]	1,187	(18.98)
Peripheral vascular disorders	758	(10.77)	720	(11.51)
Fluid electrolyte disorders	655	(9.31)[a]	701	(11.21)
Hypothyroidism	505	(7.18)[a]	550	(8.80)
Insurance type[a]				
Comprehensive insurance	3,860	(55.47)	3,105	(50.45)
EPO/POS/CDHP	257	(3.65)	110	(1.8)
HMO	1,596	(22.93)	1,743	(28.32)
PPO	1,323	(18.80)	1,196	(19.43)
Warfarin initiation				
Within 30 days of AF index diagnosis	4,573	(64.99)	-	
Risk scores	**Mean (SD)**	**Median (Range)**	**Mean (SD)**	**Median (Range)**
$CHADS_2$	2.33 (0.60)[a]	2 (2-6)	2.37 (0.64)	2 (2-6)
ATRIA	2.33 (0.93)[a]	3 (0-4)	2.42 (0.86)	3 (0-4)
$HEMORR_2HAGES$	1.87 (0.74)[a]	2 (0-3)	1.92 (0.73)	2 (0-3)
HAS-BLED	1.74 (0.45)[c]	2 (0-2)	1.72 (0.46)	2 (0-2)
Follow-up				
Months of follow-up, mean (SD)	15.6	(4.23)[a]	14.2	(5.08)

[a]*P* < 0.001, patients exposed to warfarin versus those who were not.
[b]*P* < 0.05, patients exposed to warfarin versus those who were not.
[c]*P* < 0.01, patients exposed to warfarin versus those who were not.
AF = atrial fibrillation; CDHP = consumer-directed health plan; CHF = congestive heart failure; EPO = exclusive provider organizations; HMO = health maintenance organization; PDC = proportion of days covered; POS = point of service; PPO = preferred provider organization; SD = standard deviation; TIA = transient ischemic attack.

TABLE 2.2 Summary Statistics: Demographics, Baseline Risk Factors, Comorbidities, and Insurance Type: High and Low PDC

Patient Characteristics	High PDC (>0.8) n (%)		Low PDC (≤0.8) n (%)	
	2,852 (21.46% of total population)		4,184 (31.48% of total population)	
Gender				
Female	1,404	(49.23)[a]	2,208	(52.77)
Age				
≥ 75 years	2,074	(72.72)[b]	3,253	(77.75)
Location[b]				
Northeast	210	(7.36)	397	(9.49)
North central	946	(33.17)	1,599	(38.22)
South	826	(28.96)	1,147	(27.41)
West	860	(30.15)	1,025	(24.50)
Unknown	10	(0.35)	16	(0.38)
$CHADS_2$ stroke risk factors				
CHF	495	(17.36)[b]	978	(23.37)
Hypertension	2,221	(77.88)[c]	3,183	(76.08)
Diabetes	1,078	(37.80)[a]	1,460	(34.89)
Prior stroke or TIA	331	(11.61)	451	(10.78)
ATRIA bleed risk factors				
Anemia	20	(0.7)	27	(0.65)
Renal failure	15	(0.53)	21	(0.5)
History of bleeding	49	(1.72)[c]	46	(1.1)
Top 5 comorbidities (other than those included in $CHADS_2$/ATRIA scales)				
Chronic pulmonary disease	574	(20.13)[b]	1,038	(24.81)
Valvular disease	584	(20.48)	879	(21.01)
Peripheral vascular disorders	289	(10.13)	469	(11.21)
Fluid electrolyte disorders	262	(9.19)	393	(9.39)
Hypothyroidism	214	(7.5)	291	(6.96)
Insurance type[b]				
Comprehensive insurance	1,352	(47.79)	2,508	(60.73)
EPO/POS/CDHP	98	(3.46)	82	(1.98)
HMO	817	(28.88)	779	(18.86)
PPO	562	(19.87)	761	(18.43)
Follow-up				
Months of follow-up, mean (SD)	15.6	(4.27)	15.6	(4.19)

[a]*P* < 0.01, patients exposed to warfarin versus those who were not.
[b]*P* < 0.001, patients exposed to warfarin versus those who were not.
[c]*P* < 0.05, patients exposed to warfarin versus those who were not.
CDHP = consumer-directed health plan; CHF = congestive heart failure; EPO = exclusive provider organizations; HMO = health maintenance organization; PDC = proportion of days covered; POS = point of service; PPO = preferred provider organization; SD = standard deviation; TIA = transient ischemic attack.

Stroke and Bleed Rates

Patients who received warfarin had significantly lower rates of ischemic stroke and transient ischemic attack (TIA) compared with those without warfarin exposure during the study follow-up, and the rates were consistently lowest among patients with high warfarin PDC (all *P* values < 0.001; Table 3). Considering

TABLE 3 Stroke and Bleed Rates Across Warfarin Exposure Level Groups During the Follow-Up Period

	Unexposed to Warfarin (PDC = 0) n = 6,253		Low PDC (≤ 0.8) n = 4,184			High PDC (> 0.8) n = 2,852		
Group	n	Rate per 100 Person-Years	n	Rate per 100 Person-Years	*P* Value (Low vs. No Exposure)	n	Rate per 100 Person-Years	*P* Value (High vs. No Exposure)
Ischemic stroke	326	4.41	102	1.87	< 0.001	60	1.62	< 0.001
Transient ischemic attack	131	1.77	39	0.72	< 0.001	17	0.46	< 0.001
Intracranial bleed	40	0.54	32	0.59	0.449	24	0.65	0.285
Major GI bleed	104	1.41	110	2.02	0.001	61	1.65	0.115
Other bleed	16	0.22	13	0.29	0.602	13	0.35	0.116
Total bleeds	158	1.73	152	2.79	0.001	97	2.62	0.012

GI = gastrointestinal; PDC = proportion of days covered.

TABLE 4 Unadjusted Mean (SD) Utilization Across Warfarin Exposure Groups During the Pre- and Post-index Periods, Per Patient Per Month

	Unexposed to Warfarin (PDC = 0) n = 6,253			Low PDC (≤ 0.8) n = 4,184				High PDC (> 0.8) n = 2,852			
	Mean Pre-index Visits (SD)	Mean Post-index Visits (SD)	Difference in Post- and Pre-index Utilization	Mean Pre-index Visits (SD)	Mean Post-index Visits (SD)	Difference in Post- and Pre-index Utilization	*P* Value (Compared with No Exposure)	Mean Pre-index Visits (SD)	Mean Post-index Visits (SD)	Difference in Post- and Pre-index Utilization	*P* Value (Compared with No Exposure)
Inpatient encounters	0.064 (0.075)	0.088 (0.124)	0.024	0.073 (0.075)	0.091 (0.113)	0.018	0.352	0.071 (0.070)	0.063 (0.088)	-0.008	< 0.001
Outpatient encounters	1.449 (0.958)	2.195 (1.393)	0.746	1.421 (0.942)	2.595 (1.379)	1.174	< 0.001	1.334 (0.854)	2.816 (1.364)	1.482	< 0.001
ER encounters	0.078 (0.117)	0.121 (0.179)	0.043	0.075 (0.116)	0.128 (0.181)	0.053	< 0.001	0.060 (0.096)	0.093 (0.174)	0.033	0.004
LOS	0.298 (0.688)	0.393 (0.953)	0.095	0.276 (0.607)	0.381 (0.813)	0.105	0.673	0.223 (0.370)	0.212 (0.554)	-0.011	< 0.001

ER = emergency room; LOS = length of stay; PDC = proportion of days covered; SD = standard deviation.

all types of bleeding events (major, minor, and other), patients who received warfarin had a significantly higher bleeding rate than patients who did not receive warfarin ($P < 0.05$). There was no significant difference in the rate of intracranial hemorrhage between patients who received warfarin and patients who did not receive warfarin. However, the major gastrointestinal (GI) hemorrhage rate was significantly higher among patients with warfarin PDC ≤ 0.80 than patients who did not receive warfarin. The risk of major GI bleeding was similar between patients with high warfarin PDC and patients who did not receive warfarin.

Health Care Resource Utilization

Table 4 summarizes unadjusted health care service utilization differences between the pre-index and post-index follow-up period. Differences in post- and pre-index hospitalizations (-0.008 vs. 0.024; $P < 0.001$) and LOS (-0.011 vs. 0.095; $P < 0.001$) were significantly lower for the high warfarin PDC group compared with no warfarin. Increases in post-index outpatient encounters (from pre-index) were significantly greater for low (1.174 vs. 0.746; $P < 0.001$) and high warfarin (1.482 vs. 0.746; $P < 0.001$) PDC groups compared with the no exposure group. The increase in number of ER encounters between the pre- and post-index periods was significantly lower in the high PDC group (0.033 vs. 0.043; $P = 0.004$) and higher in the low PDC group (0.053 vs. 0.043; $P < 0.001$) compared with the group with no warfarin exposure.

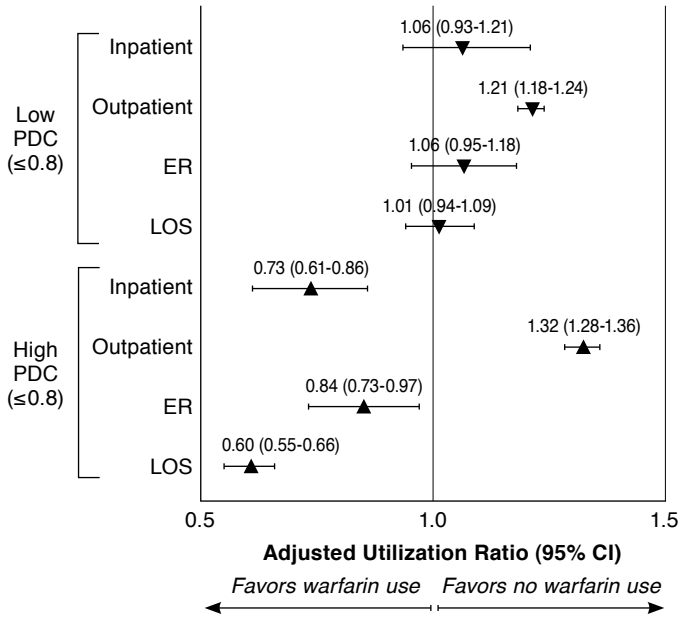
After controlling for covariates and baseline utilization, the high warfarin PDC group was associated with 27% fewer inpatient encounters ($P < 0.001$), 16% fewer ER visits ($P = 0.019$), and nearly a 40% reduction in the number of hospital days ($P < 0.001$) compared with patients who did not receive warfarin (Figure 2). In contrast, inpatient and ER services utilization were not significantly different between patients with low warfarin PDC and patients who did not receive warfarin. Patients who received warfarin, regardless of PDC level, had

TABLE 5 Unadjusted Mean (SD) Costs Across Warfarin Exposure Groups During the Pre- and Post-index Periods, Per Patient Per Month ($US)

	Unexposed to Warfarin (PDC = 0) n = 6,253			Low PDC (≤ 0.8) n = 4,184				High PDC (> 0.8) n = 2,852			
	Mean Pre-index Cost (SD)	Mean Post-index Cost (SD)	Difference in Post- and Pre-index Utilization	Mean Pre-index Cost (SD)	Mean Post-index Cost (SD)	Difference in Post- and Pre-index Utilization	*P* Value (Compared with No Exposure)	Mean Pre-index Cost (SD)	Mean Post-index Cost (SD)	Difference in Post- and Pre-index Utilization	*P* Value (Compared with No Exposure)
All-cause inpatient costs	180.69 (732.45)	314.15 (2,491.19)	133.46	184.86 (673.31)	273.57 (1,612.26)	104.46	0.477	213.46 (611.45)	228.91 (1,099.59)	15.45	0.002
Stroke-related	8.81 (113.12)	29.01 (629.13)	20.20	11.98 (146.28)	6.31 (90.73)	-5.67	0.002	19.77 (151.77)	8.63 (181.45)	-11.14	0.0006
Bleed-related	1.67 (30.94)	9.44 (267.89)	7.77	1.25 (36.27)	10.25 (272.14)	9	0.8	0.24 (11.44)	5.66 (62.94)	5.42	0.5
All-cause outpatient costs	122.63 (315.26)	309.94 (717.04)	187.31	123.2 (664.83)	278.15 (643.67)	154.94	0.028	120.24 (333.58)	242.18 (558.63)	121.94	< 0.001
Stroke-related	2.07 (22.25)	10.07 (83.31)	8.00	2.34 (17.09)	8.66 (109.07)	6.32	0.4	2.17 (15.18)	3.53 (26.84)	1.36	< 0.0001
Bleed-related	0.26 (5.68)	4.91 (50.78)	4.65	0.14 (3.35)	4.22 (44.88)	4.08	0.5	0.26 (3.93)	3.06 (21.52)	2.8	0.01
All-cause prescription drug costs	156.03 (215.14)	174.96 (242.15)	18.93	181.96 (198.51)	223.04 (215.77)	41.09	< 0.001	172.58 (207.89)	222.54 (216.82)	49.96	< 0.001
Total costs	459.35 (906.43)	799.06 (2,746.66)	339.71	490.02 (1,138.29)	790.52 (2,056.73)	300.49	0.392	506.28 (826.48)	693.63 (1,459.91)	187.35	< 0.001

PDC = proportion of days covered; SD = standard deviation.

FIGURE 2 Adjusted Utilization Ratios (95% CI): Post-index Resource Utilization Among Low (≤ 0.8) and High (> 0.8) PDC Warfarin Users Compared with Patients Who Did Not Receive Warfarin



CI = confidence interval; ER = emergency room; LOS = length of stay; PDC = proportion of days covered.

significantly more outpatient visits in the post-index period than patients who did not receive warfarin. Patients with low and high PDCs had 21% and 32% greater outpatient visits, respectively, during follow-up compared with those who did not receive warfarin ($P < 0.001$ for both).

Health Care Costs

Increases in pre- versus post-index period inpatient, outpatient, and total cost were significantly lower for the high PDC group, compared with the group with no warfarin exposure (15.45 vs. 133.46, $P = 0.002$; 121.94 vs. 187.31, $P < 0.001$; 187.35 vs. 339.71, $P < 0.001$, respectively). Patients with high PDC showed a decrease in stroke-related inpatient cost in the post-index period (-$11.14), significantly lower than patients with no warfarin use who showed an increase in these costs in the post-index period ($20.20; $P = 0.0006$). Additionally, outpatient stroke-related cost increases from the pre-index period were significantly lower for the high warfarin PDC group compared with patients with no warfarin exposure (1.36 vs. 8.00, $P < 0.0001$; Table 5).

Adjusted mean pharmacy cost was significantly higher for both patients with low (adjusted cost ratio = 1.08; $P < 0.001$) and high PDCs (adjusted cost ratio = 1.16; $P < 0.001$) than patients who did not receive warfarin (Table 6). After controlling for covariates and pre-index health care cost, adjusted mean all-cause inpatient (adjusted cost ratio = 0.88; $P < 0.001$), all-cause outpatient (adjusted cost ratio = 0.73; $P < 0.001$), and all-cause

TABLE 6 Generalized Linear Model Estimation of Adjusted Mean Monthly Cost During Study Follow-up Period[a]

Parameter	No Warfarin Exposure	Low PDC Warfarin Exposure		High PDC Warfarin Exposure		
	Mean Adjusted Cost Estimate $ (SD)	Exponentiated Coefficient/Cost Ratio (SD)	95% CI	Mean Adjusted Cost Estimate $ (SD)	Exponentiated Coefficient/Cost Ratio (SD)	95% CI	Mean Adjusted Cost Estimate $ (SD)
All-cause inpatient cost (in cases where inpatient admission cost was incurred)	870.79 (1.12)	0.90[b] (1.03)	0.85-0.95	781.88 (1.12)	0.88[b] (1.03)	0.82-0.94	763.34 (1.12)
All-cause outpatient cost	747.32 (1.11)	0.96 (1.02)	0.92-1.01	717.16 (1.11)	0.73[b] (1.03)	0.69-0.77	542.61 (1.12)
All-cause medical cost	1,304.53 (1.12)	0.97 (1.02)	0.93-1.02	1,269.65 (1.12)	0.72[b] (1.03)	0.68-0.76	937.30 (0.72)
Stroke-related medical cost (in cases where stroke-related medical cost was incurred)	140.56 (1.38)	0.52[b] (1.08)	0.45-0.61	73.16 (1.38)	0.40[b] (1.10)	0.33-0.48	56.22 (1.39)
Bleed-related medical cost (in cases where bleed-related medical cost was incurred)	33.61 (1.35)	1.05 (1.09)	0.89-1.24	35.39 (1.35)	0.78[c] (1.11)	0.65-0.95	26.37 (1.36)
Rx drug cost	183.46 (1.07)	1.08[b] (1.02)	1.05-1.12	199.02 (1.08)	1.16[b] (1.02)	1.12-1.20	213.24 (1.08)
Total cost	1,344.13 (1.09)	1.03 (1.02)	0.99-1.07	1,384.37 (1.09)	0.87[b] (1.02)	0.83-0.90	1,164.56 (1.09)

[a]*All models were adjusted for previous resource use, gender, age, region, insurance carrier, ATRIA score, $CHADS_2$ score, and comorbidities.*

[b]*$P < 0.001$, patients with low or high warfarin exposure versus those with no exposure.*

[c]*$P < 0.05$, patients with low or high warfarin exposure versus those with no exposure.*

CI = confidence interval; PDC = proportion of days covered; Rx = prescription; SD = standard deviation.

medical (adjusted cost ratio = 0.72; $P < 0.001$) costs were significantly lower in patients with high warfarin PDC than patients who did not receive warfarin. Stroke-related medical cost was 60% lower (adjusted cost ratio = 0.40; $P < 0.001$) and bleed-related medical cost was 22% lower (adjusted cost ratio = 0.78; $P < 0.05$) for patients with high warfarin PDC compared with those with no warfarin exposure. Patients with low warfarin PDC had significantly lower mean adjusted all-cause inpatient cost (adjusted cost ratio = 0.90; $P < 0.001$) but similar all-cause outpatient cost (adjusted cost ratio = 0.96; $P = 0.09$) and all-cause medical cost (adjusted cost ratio = 0.97; $P = 0.27$) compared with patients who did not receive warfarin. Stroke-related medical cost was 48% lower for patients with low warfarin PDC compared with patients with no warfarin exposure. Overall, total health care costs were 13% lower for patients with high PDC ($P < 0.001$) but similar for patients with low PDC compared with patients who did not receive warfarin.

Discussion

Our study found that only 53% of patients with moderate to high risk of stroke and not at high bleeding risk received warfarin therapy. Even among patients who received warfarin, only 40% were adherent to warfarin with a PDC > 0.80. Previous studies using administrative claims and patient registries have found warfarin underuse to be a prevalent problem in AF patients[9,10] and that maintaining optimal INR control[25] and minimizing unintended discontinuation of warfarin therapy to be a significant challenge among patients who had received warfarin therapy.[13,26] Our study represents one of the first attempts to estimate the economic burden associated with warfarin underuse and nonadherence. Although AF patients who received warfarin had higher pharmacy cost and incurred more outpatient visits, adherence to OAC therapy resulted in fewer inpatient admissions and ER visits, leading to significant reductions in total health care cost. Greater adherence as measured by PDC, compared with no use, clearly shows beneficial economic results in terms of lower total, inpatient, and outpatient costs during follow-up. Ischemic stroke rates for the low and high warfarin exposure groups were significantly lower than the no warfarin exposure group. However, there was not a significant difference in the ischemic strokes rates between the high and low warfarin PDC groups. While there was a greater rate of GI bleeds among the low PDC group compared with those not taking warfarin ($P = 0.001$), we did not find a significant difference between the high PDC and no warfarin group. This observation may be explained through a widely established association between poor adherence to warfarin and unstable INR, which has been shown to increase bleeding risk.[13,20] This relationship between poor adherence and bleeding risk may also explain the significantly greater number of observed ER encounters for the low PDC group.

The findings of our study should be viewed in light of several limitations. First, although the study used a large nationally representative database of patients recently diagnosed with AF, it may be subject to selection bias. The MarketScan database under-represents the U.S. Medicare population, a dominant patient segment in AF. Additionally, in working with large sample sizes, observed differences may be statistically significant but clinically irrelevant. For example, our observed baseline difference in the $CHADS_2$ score (mean score = 2.33 vs. 2.37; $P < 0.001$) between patients that used and did not use warfarin may not translate to notable clinical difference in stroke risk. Patients were required to have at least 2 months of continuous eligibility after the AF index date. Patients who died within 2 months of the index AF diagnosis were not included in the study. By excluding patients who may have died from stroke or intracranial bleeding, the study can potentially over- or underestimate the cost of warfarin underutilization. Second, as with other retrospective claims data analysis, adherence in this study was measured by prescription claim records. In the absence of additional clinical information, we were unable to determine how well patients follow the instructions given by their health care providers and if discontinuation of warfarin therapy is medically necessary. Third, we defined eligibility of OAC therapy using $CHADS_2$ and published bleeding risk algorithms. Although the $CHADS_2$ score has been available and validated for stroke risk stratification, it remains unclear to what extent it has been routinely used in clinical practice to guide anticoagulation decisions. Current treatment guidelines for anticoagulation do not specify a standard instrument that should be used for bleeding risk assessment.[8] Limited data exist on how well these bleeding risk scores can predict bleeding in clinical practice and to facilitate risk-benefit assessment of OAC treatment decisions. More data on the validity of these scores in clinical practice are needed.

This study identifies a significant economic and clinical burden driven by previously established warfarin underutilization among patients with AF. These findings reveal a missed opportunity to reduce costs by avoiding strokes that can be effectively prevented by OAC therapy. The results underscore the need for actions by health insurers and policy makers to develop programs to overcome these challenges in prescribing OAC therapy.

Conclusion

The economic implications of underutilizing warfarin in nearly half of the commercially insured nonvalvular AF population are significant. Adherence in terms of greater warfarin exposure was shown to reduce health care resource use as well as overall health care cost. Given the chronic nature of AF, improving adherence is critical to attaining the clinical and economic benefits of OAC therapy.

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DISCLOSURES

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Concept and design were performed by Casciano, Kwong, Dotiwala, and Martin. Data were collected by Martin, Casciano, Moore, and Dotiwala and interpreted by Dotiwala, Casciano, Martin, Kwong, and Szamreta. The manuscript was written by Casciano, Dotiwala, Kwong, and Martin and was revised by Casciano with the help of Dotiwala, Martin, and Kwong.

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APPENDIX A ICD-9-CM Diagnoses for Excluding Patients with Valvular Disease

Measure	ICD-9-CM Code
Closed heart valvotomy, unspecified valve	35
Closed heart valvotomy, aortic valve	35.01
Closed heart valvotomy, mitral valve	35.02
Closed heart valvotomy, pulmonary valve	35.03
Closed heart valvotomy, tricuspid valve	35.04
Open heart valvuloplasty of unspecified valve, without replacement	35.1
Open heart valvuloplasty of aortic valve, without replacement	35.11
Open heart valvuloplasty of mitral valve, without replacement	35.12
Open heart valvuloplasty of pulmonary valve, without replacement	35.13
Open heart valvuloplasty of tricuspid valve, without replacement	35.14
Replacement of unspecified heart valve	35.2
Replacement of aortic valve with tissue graft	35.21
Other replacement of aortic valve	35.22
Replacement of mitral valve with tissue graft	35.23
Other replacement of mitral valve	35.24
Replacement of pulmonary valve with tissue graft	35.25
Other replacement of pulmonary valve	35.26
Replacement of tricuspid valve with tissue graft	35.27
Other replacement of tricuspid valve	35.28
Mitral stenosis	394
Mitral stenosis with insufficiency	394.2
Mitral valve stenosis and aortic valve stenosis	396
Mitral valve stenosis and aortic valve insufficiency	396.1
Multiple involvement of mitral and aortic valves	396.8
Organ or tissue replaced by transplant	V42
Heart valve	V42.2
Organ or tissue replaced by other means	V43 O
Heart valve	V43.3
Operations of structures adjacent to heart valves	35.3
Operations on papillary muscle	35.31
Operations on chordae tendinaea	35.32
Annuloplasty	35.33
Infundibulectomy	35.34
Operations on trabeculae carness cordis	35.35
Operations on other structures adjacent to valves of heart	35.39
Production of septal defect in heart	35.4
Enlargement of existing atrial septal defect	35.41
Creation of septal defect in heart	35.42
Repair of atrial and ventricular septa with prosthesis	35.5
Repair of unspecified septal defect of heart with prosthesis	35.5
Repair of atrial septal defect with prosthesis open technique	35.51
Repair of atrial septal defect with prosthesis, closed technique	35.52
Repair of ventricular septal defect with prosthesis	35.53
Repair of endocardial cushion defect with prosthesis	35.54
Repair of atrial and ventricular septa with tissue graft	35.6
Repair of unspecified septol defect of heart with tissue graft	35.6
Repair of atrial septal detect with tissue graft	35.61
Repair of ventricular septal defect with tissue graft	35.62
Repair of endocardial cushion defect with tissue graft	35.63
Other and unspecified repair of unspecified specific defect of heart	35.7
Other and unspecified repair of atrial septal defect	35.71
Other and unspecified repair of ventricular septal defect	35.72
Other and unspecified repair of endocardial cushion defect	35.73
Bypass anastomosis for heart revascularization	36.1
Aortocoronary bypass of one coronary artery	36.11
Aortocoronary bypass of two coronary arteries	36.12
Aortocoronary bypass of three coronary arteries	36.13
Aortocoronary bypass of four or more coronary arteries	36.14
Single internal mammory-coronary artery bypass	36.15
Double internal mammary-coronary artery bypass	36.16
Abdominal-coronary artery bypass	36.17
Other bypass anastomosis for heart revascularization	36.19
Cardiotomy and pericardiotomy	37.1
incision of heart, not otherwise specified	37.1
Cardiotomy	37.11
Pericardiotomy	37.12
Periocardiectomy and excision of lesion of heart	37.3
Pericardiotomy	37.31
Excision of aneurysm of heart	37.32
Excision el destruction of other lesion or tissue of heart	37.33
Repair of heart and pericardium	37.4

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

APPENDIX B ICD-9-CM Codes Used to Identify Contraindication to Warfarin

Measure	ICD-9-CM Code
Pregnancy	V22.0-.2 650
Blood dyscrasias	289.9
Recent or complicated surgery of: CNS Eye	 V58.72 V45.6
Trauma surgery resulting in large open surface area	V58.43
Bleeding tendencies associated with active ulceration or overt bleeding of: Gastrointestinal/Genito-Urinary/Respiratory tract	578.9 627.1
Cerebrovascular hemorrhage	430 431 432.0, .1, .9
Aneurysm-cerebral	437.3
Dissecting aorta	441.00-.03
Pericarditis and pericardial effusion	420.0 420.9 423.9
Bacterial endocarditis	421.0
Threatened abortion	640.0
Eclampsia/pre-eclampsia	642.4 642.6 642.7
Hypersensitivity to warfarin	995.27
History of cirrhosis	571.5 571.2
Hepatitis	571.40 571.41
Seizure disorder	345.8 345.9 780.39
Previous intracranial hemmorhage	432.9
Diagnostic spinal tap/other diagnostic procedure	03.31 03.32 03.39
Alcohol-related disorders	Same codes as Appendix E

Measure	ICD-9-CM Code
Acquired immunodeficiency syndrome (human immunodeficiency virus infection)	042 0420 0421 0422 0429 0430 0431 0432 0433 0439 0440 0449 079.53 279.10 279.19 795.71 795.8 V08
Dementia	294.10 294.11
Liver disease	571.5 572.0 572.1 572.2 572.3 572.8 789.5 789.59 570 571.6 571.8 571.9 573.0 573.4 573.8 573.9 782.4 789.1 790.4 790.5 794.8 V427

CNS = central nervous system; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

APPENDIX C ICD-9-CM Diagnoses for $CHADS_2$ Stroke Risk Factors

Prior stroke	433.xx-434.xx
Transient cerebral ischemia	435.0, 435.1, 435.2, 435.3, 435.8, 435.9
Hypertension	401.xx-405.xx
Diabetes	250.0x-250.8x
Expanded diabetes	249.xx, 250.9x, 790.2, 790.21, 790.22, 790.29, 791.5, 791.6
Heart failure	398.91, 402.01, 402.11, 402.91, 428.0x-428.9x, 518.4

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

APPENDIX D ICD-9-CM Diagnoses for *ATRIA* Bleeding Risk Factors

Description	ICD-9-CM Code
Anemia	
Acute posthemorrhagic anemia	285.1
Sickle cell anemia	282.41, 282.42, 282.5, 282.60, 282.61, 282.62, 282.63, 282.64, 282.68, 282.69
Deficiency and other anemia	
Iron deficiency anemia	280.1, 280.8, 280.9
Other deficiency anemia	281.0, 281.1, 281.2, 281.3, 281.4, 281.8, 281.9
Aplastic anemia	284.0, 284.01, 284.09, 284.1, 284.8, 284.81, 284.89, 284.9
Chronic blood loss anemia	280.0
Acquired hemolytic anemia	283.0, 283.1, 283.10, 283.11, 283.19, 283.2, 283.9
Other specified anemia	282.0, 282.1, 282.2, 282.3, 282.4, 282.49, 282.7, 282.8, 282.9, 284.2, 285.0, 285.21, 285.22, 285.29, 285.8
Anemia; unspecified	285.9
Renal failure	
Acute and unspecified renal failure	
Acute renal failure	584.5, 584.6, 584.7, 584.8, 584.9
Unspecified renal failure	586
Chronic renal failure	585, 585.3, 585.4, 585.5, 585.6, 585.9, 792.5, V42.0, V45.1, V45.11, V45.12, V56.0, V56.1, V56.2, V56.31, V56.32, V56.8
History of any bleeding	
Prior intracranial hHemorrhage	430.xx, 431.xx, 432.x, 852.0x, 852.2x, 852.4x, 853.0x
Prior gastrointestinal hemorrhage	
Internal hemorrhoids with other complication	455.2
External hemorrhoids with other complication	455.5
Unspecified hemorrhoids with other complication	455.8
Esophageal varicies with bleeding	456.0
Esophageal varicies in diseases classified elsewhere with bleeding	456.20
Hemorrhage, unspecified	459.0
Gastroesophageal laceration-hemorrhage syndrome	530.7
Esophageal hemorrhage	530.82
Acute gastric ulcer with hemorrhage without mention of obstruction	531.00
Acute gastric ulcer with hemorrhage with obstruction	531.01
Acute gastric ulcer with hemorrhage and perforation without mention of obstruction	531.20
Acute gastric ulcer with hemorrhage and perforation with obstruction	531.21
Chronic or unspecified gastric ulcer with hemorrhage without mention of obstruction	531.40
Chronic or unspecified gastric ulcer with hemorrhage with obstruction	531.41
Chronic or unspecified gastric ulcer with hemorrhage and perforation without mention of obstruction	531.60
Chronic or unspecified duodenal ulcer with hemorrhage and perforation with obstruction	531.61
Acute peptic ulcer, site unspecified, with hemorrhage without mention of obstruction	533.00
Acute peptic ulcer, site unspecified, with hemorrhage with obstruction	533.01
Acute peptic ulcer, site unspecified, with hemorrhage and perforation without mention of obstruction	533.20
Acute peptic ulcer, site unspecified, with hemorrhage and perforation with obstruction	533.21
Chronic or unspecified peptic ulcer, site unspecified, with hemorrhage without mention of obstruction	533.40
Chronic or unspecified peptic ulcer, site unspecified, with hemorrhage with obstruction	533.41
Chronic or unspecified peptic ulcer, site unspecified, with hemorrhage and perforation	533.61
Acute gastrojejunal ulcer with hemorrhage without mention of obstruction	534.00
Acute gastrojejunal ulcer with hemorrhage with obstruction	534.01
Acute gastrojejunal ulcer with hemorrhage and perforation without mention of obstruction	534.20
Acute gastrojejunal ulcer with hemorrhage and perforation with obstruction	534.21
Chronic or unspecified gastrojejunal ulcer with hemorrhage without mention of obstruction	534.40
Chronic or unspecified gastrojejunal ulcer with hemorrhage with obstruction	534.41

APPENDIX D ICD-9-CM Diagnoses for ATRIA Bleeding Risk Factors *(continued)*

Description	ICD-9-CM Code
Chronic or unspecified gastrojejunal ulcer with hemorrhage and perforation with obstruction	534.61
Acute gastritis with hemorrhage	535.01
Atrophic gastritis with hemorrhage	535.11
Gastric mucosal hypertrophy with hemorrhage	535.21
Alcoholic gastritis with hemorrhage	535.31
Other specified gastritis with hemorrhage	535.41
Unspecified gastritis and gastroduodenitis with hemorrhage	535.51
Duodenitis with hemorrhage	535.61
Angiodysplasia of stomach and duodenum with hemorrhage (added December 4, 2000)	537.83
Diverticulosis of small intestine with hemorrhage	562.02
Diverticulitis of small intestine with hemorrhage	562.03
Diverticulosis of colon with hemorrhage	562.12
Diverticulitis of colon with hemorrhage	562.13
Hemoperitoneum (nontraumatic)	568.81
Hemorrhage of rectum and anus	569.3
Angiodysplasia of intestine with hemorrhage	569.85
Gastrointestinal hemorrhage	578
Hematemesis	578.0
Blood in stool	578.1
Hemorrhage of gastrointestinal tract, unspecified	578.9
Other prior hemorrhage	
Hemopericardium	423.0
Hemorrhage, unspecified	459.0
Vascular disorders of the kidney	593.81
Hemarthrosis	719.1
Hemarthrosis: site unspecified	719.10
Hemarthrosis: shoulder region	719.11
Hemarthrosis: upper arm	719.12
Hemarthrosis: forearm	719.13
Hemarthrosis: hand	719.14
Hemarthrosis: pelvic region and thigh	719.15
Hemarthrosis: lower leg	719.16
Hemarthrosis: ankle and foot	719.17
Hemarthrosis: other specified sites	719.18
Hemarthrosis: multiple sites	719.19
Epistaxis	784.7
Hemorrhage from throat (added December 4, 2000)	784.8
Hemoptysis	786.3
Hematuria	599.7

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

APPENDIX E ICD-9-CM Diagnoses for HEMORR$_2$HAGES Bleeding Risk Factors

Description	ICD-9-CM Code
Anemia	Same codes as used in the ATRIA risk scheme (Appendix D)
Ethanol abuse	291.0, 291.1, 291.2, 291.3, 291.4, 291.5, 291.8, 291.81, 291.82, 291.89, 291.9, 303.00, 0301, 303.02, 303.03, 303.90, 303.91, 303.92, 0393, 305.00, 305.01, 305.02, 305.03, 760.71, 980.0
Prior bleed	Same codes as used in the ATRIA risk scheme (Appendix D)
Hypertension	Same codes as used in the CHADS$_2$ risk scheme (Appendix C)
Stroke	Same codes as used in the CHADS$_2$ risk scheme (Appendix C)
Hepatic or renal disease	
Acute renal failure	584.5, 584.6, 584.7, 584.8, 584.9
Unspecified renal failure	586
Chronic renal failure	585, 585.3, 585.4, 585.5, 585.6, 585.9, 792.5, V42.0, V45.1, V45.11, V45.12, V56.0, V56.1, V56.2, V56.31 V56.32, V56.8
Cirrhosis of liver without mention of alcohol	571.5
Liver abscess and sequelae of chronic liver disease	572.0, 572.1, 572.2, 572.3, 572.4, 572.8
Ascites	789.5, 789.59
Other and unspecified liver disorders	570, 571.6, 571.8, 571.9, 573.0, 573.4, 573.8, 573.9, 782.4, 789.1, 790.4, 790.5, 794.8, V42.7
Reduced platelet function	
Thrombocytopenia	287.3, 287.30, 287.31, 287.32, 287.33, 287.39, 287.4, 287.49, 287.5, 289.84
Malignancy	153.0-229.9
Genetic factors	Not available in the dataset so will be scored as 0.
Excessive fall risk	
Delirium dementia and amnestic and other cognitive disorders	290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 290.8, 290.9, 293.0, 293.1, 294.0, 294.1, 294.10, 294.11, 294.8, 294.9, 310.0, 310.2, 310.8, 310.9, 331.0, 331.1, 331.11, 331.19, 331.2, 331.8, 797
Schizophrenia and other psychotic disorders	293.81, 293.82, 295.00, 295.01, 295.02, 295.03, 295.04, 295.05, 295.10, 295.11, 295.12, 295.13, 295.14, 295.15, 295.20, 295.21, 295.22, 295.23, 295.24, 295.2, 295.30, 295.31, 295.32, 295.33, 295.34, 295.35, 295.40, 295.41, 295.42, 295.43, 295.44, 295.45, 295.50, 295.51, 295.52, 295.53, 295.54, 295.55, 295.60, 295.61, 295.62, 295.63, 295.64, 295.65, 295.70, 295.71, 295.72, 295.73, 295.74, 295.75, 295.80, 295.81, 295.82, 295.83, 295.84, 295.85, 295.90, 295.91, 295.92, 295.93, 295.94, 295.95, 297.0, 297.1, 297.2, 297.3, 297.8, 297.9, 298.0, 298.1, 298.2, 298.3, 298.4, 298.8, 298.9

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

APPENDIX F ICD-9-CM Diagnoses for HAS-BLED Bleeding Risk Factors

Hypertension	Same codes as used in the CHADS$_2$ risk scheme (Appendix C)
Ethanol abuse	Same codes as used in HEMORR$_2$HAGE risk scheme (Appendix E)
Stroke	Same codes as used in the CHADS$_2$ risk scheme (Appendix C)
Prior bleed	Same codes as used in the ATRIA risk scheme (Appendix D), also including anemia codes
LABILE INRs	Not available in the data; will be assumed to be 0 for all patients
Abnormal renal or liver function	Same codes as used in HEMORR$_2$HAGE risk scheme (Appendix E)

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; INR = international normalized rate.