Hospital Admissions, Costs, and 30-Day Readmissions Among Newly Diagnosed Nonvalvular Atrial Fibrillation Patients Treated with Dabigatran Etexilate or Warfarin

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ABSTRACT

BACKGROUND: Oral anticoagulation such as warfarin and dabigatran is indicated for atrial fibrillation (AF) patients at risk of ischemic stroke. Dabigatran etexilate was developed to address the limitations of warfarin, including the need for regular blood monitoring, which has the potential to lead to higher health care resource use, particularly in hospitalized patients.

OBJECTIVE: To evaluate whether hospitalization cost, length of hospital stay (LOS), likelihood of readmission within 30 days, and cost of readmissions differed across inpatient encounters among nonvalvular atrial fibrillation (NVAF) patients that were newly diagnosed and newly treated with either dabigatran or warfarin.

METHODS: A retrospective cohort study was conducted using IMS Health's Charge Detail Master (CDM) database. Hospitalizations were identified based on a primary or secondary AF diagnosis, dabigatran or warfarin use, and a discharge date from January 2011 through March 2012. The identified patients without valvular procedures and transient AF were required to have a minimum of 12 months of pharmacy and private practitioner records prior to the inpatient encounter to ensure that they were newly treated on dabigatran or warfarin. Propensity score matching was used to balance baseline characteristics between treatment cohorts. Outcomes assessed were LOS, 30-day readmissions, and costs. Because individual patients could have more than 1 hospital observation, generalized estimating equations (GEE) with a gamma distribution (log link) were used for the analysis of continuous outcome measures (e.g., LOS and costs) and a binomial distribution for dichotomous outcomes (hospital readmissions).

RESULTS: Two cohorts were propensity score matched (1:2) on demographic and clinical characteristics. The dabigatran cohort included 646 hospitalizations, and the warfarin cohort included 1,292 hospitalizations. Hospitalizations were on average 13% shorter (4.8 vs. 5.5 days, $P < 0.001$) and cost 12% less (\$14,794 vs. \$16,826, $P = 0.007$) when dabigatran was used versus warfarin. No differences in 30-day readmissions were observed.

CONCLUSIONS: Hospital encounters among newly diagnosed NVAF patients during which warfarin was initiated had longer lengths of stay and incurred higher costs than those during which dabigatran was initiated.

J Manag Care Spec Pharm. 2015;21(11):1039-53

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What is already known about this subject

- The Centers for Medicare & Medicaid Services and other payers are increasingly focused on reducing length of stay and readmission rates to improve quality of care and reduce cost.
- Warfarin has been the standard therapy for stroke prevention in nonvalvular atrial fibrillation (NVAF) patients but poses several clinical and administrative challenges in the management of these patients over time.

What this study adds

- This study used a geographically diverse sample of hospitalization encounters among newly diagnosed and newly treated NVAF patients on warfarin or dabigatran.
- Hospitalizations of NVAF patients newly diagnosed and started on treatment with dabigatran etexilate had shorter hospital stays and incurred lower total inpatient care costs than those patients initiated on warfarin.

Atrial fibrillation (AF) poses a substantial health care burden.¹⁻⁵ Since the risk of AF increases with age, the prevalence of the disease and costs of treatment in Western countries are projected to increase with the aging population.⁶ In hospitalized patients, the presence of AF is a significant driver of hospital cost.³ It has become increasingly important for decision makers to understand the health care utilization and costs that are associated with anticoagulation treatment options as their use relates to hospitalization and readmissions for better management of AF patients.

Anticoagulation is indicated for AF patients with moderate to high risk of ischemic stroke. Warfarin is an oral anticoagulant (OAC) therapy that has been shown to be effective in reducing the risk of stroke.⁷ It can be difficult to bring levels of warfarin to within therapeutic range and to maintain those levels, making international normalized ratio (INR) monitoring necessary.⁸ The limitations of warfarin are well known; in particular, the fluctuating levels of anticoagulation with a warfarin regimen may contribute to undertreatment.^{9,10} New OAC therapies, such as dabigatran etexilate, have been developed to address the limitations of warfarin therapy.

FIGURE 1 Schematic Representation of Study Design

AF = atrial fibrillation; DE = dabigatran etexilate; LOS = length of stay; NVAF = nonvalvular atrial fibrillation; W = warfarin.

Dabigatran etexilate is approved for the reduction of risk of stroke and systemic embolism in nonvalvular AF (NVAF).¹¹ Dabigatran does not interact with cytochrome P450 pathway drugs, and there is no requirement for INR monitoring. In a large, randomized phase III clinical study,^{12,13} rates of stroke, systemic embolism, and intracranial bleeding were significantly lower for dabigatran 150 milligrams (mg) twice daily compared with warfarin after a median 2-year follow-up. Similar efficacy was observed among patients new to warfarin treatment and with prior warfarin experience.^{14,15} Real-world clinical practice studies have shown that mortality, intracranial bleeding, and pulmonary embolism are lower with dabigatran compared with warfarin.¹⁶

Given the guidance from the Centers for Medicare & Medicaid Services (CMS), there are several national and regional initiatives underway to reduce unplanned all-cause readmissions.¹⁷ With an increasing incidence of NVAF and a growing interest in improving quality of care across the continuum of health care settings, it is pertinent for payers and providers to understand the association between OAC treatment choice on length of stay (LOS), readmission rates, and costs. There are currently no known published real-world studies comparing U.S. hospital utilization in newly diagnosed NVAF patients newly treated with warfarin or dabigatran. The current study assessed total inpatient care cost, LOS, 30-day readmissions, and associated readmission costs among newly diagnosed NVAF patients who were newly treated with dabigatran or warfarin.

Methods

Data Sources

We identified hospitalizations from a nationwide hospital operational records database (IMS Health Charge Detail

Master) consisting of approximately 400 facilities in the United States. Cost-to-charge ratios submitted to CMS were used to approximate hospitals' average actual costs of goods and services, which may be below or above the amounts charged for a specific item. Hospital records and pharmacy claims (National Council for Prescription Drug Programs) data were used to determine patients' prior exposure to study medications and medications related to major bleed risk. Hospital records and private practitioner claims (CMS-1500) data were used to classify inpatients with respect to history of AF diagnosis, prior cardiac valve procedures, comorbid conditions, and stroke or major bleed risks. Patient-level data in this study were de-identified. All databases utilized in this study were certified as being compliant with the Health Insurance Portability and Accountability Act; therefore institutional review board approval was not necessary.

Study Sample Identification

The study sample consisted of all hospitalizations with AF as a primary or secondary discharge diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] 427.31, atrial fibrillation), a discharge date between January 2011 and March 2012 and the use of either warfarin or dabigatran (see Appendix A for drug classification terms, available in online article). The earliest hospitalization identified became the index encounter. Ultimately, only encounters for patients newly diagnosed with AF and newly treated with either warfarin or dabigatran, based on observed data during the 12 months prior to admission, were included. The study design schematic and outcomes measured are shown in Figure 1. Figure 2 shows the selection criteria for the study samples.

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FIGURE 2 Flowchart Describing the Process of Sample Selection (Inclusion/Exclusion)

AF=atrial fibrillation; CMS=Centers for Medicare & Medicaid Services; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; NVAf=nonvalvular atrial fibrillation.

Hospitals reporting consistently between 1 month prior to admission through 1 month after discharge and that dispensed dabigatran and warfarin were included. Encounters recording multiple OAC treatments or for patients with concurrent or prior cardiac valve procedures (ICD-9-CM procedure codes 35.20, 35.22, 35.24, 35.26, and 35.28 or ICD-9-CM 394.0, mitral stenosis; history back to 2001) were excluded to avoid confounding of the outcomes assessment. To ensure inclusion of prior medication and diagnostic history, only encounters for patients with observable pharmacy database activity within the 12 months

prior to admission and more than 12 months before admission, as well as observable private practitioner database activity more than 6 months prior to admission were included. Hospitals also had to have submissions of their cost-to-charge ratios to CMS.

The subset of index encounters assessed for 30-day readmissions, adhering to the CMS Hospital Readmission Reduction Program inclusion criteria, were required to have AF as the primary diagnosis and not itself be a 30-day readmission from any prior hospitalization.¹⁸ Additionally, the subset of encounters were limited to those where the patient was alive upon

discharge and was discharged home or to another residence but not to an acute care facility. To assess broader impact, the analysis was not limited to those aged ≥ 65 years. The dabigatran and warfarin inpatient encounters were matched and further adjusted using multivariate regression.

Study Cohort Matching

Propensity score matching was used to minimize the potential impact of selection bias with matching hospital encounters in the dabigatran cohort with those from the warfarin cohort that shared similar demographic and clinical characteristics.¹⁹ Each hospital encounter in the dabigatran cohort was matched, without replacement, using a 1:2 “nearest neighbor matching” technique, with a caliper of 0.20 of the standard deviation of the estimated logit of the propensity score.^{20,21} During matching, dabigatran and warfarin encounters were required to either both qualify for the readmission analysis or both not qualify to ensure balance among the subset. The propensity score was computed using a logistic regression model that adjusted for covariates including age, gender, payer, diagnoses listed within a modified Deyo Charlson Comorbidity Index²²; CHADS₂ stroke risk (1 point each for congestive heart failure, hypertension, aged ≥ 75 years, and diabetes mellitus and 2 points for transient ischemic attack or stroke); HAS-BLED major bleed risk (1 point each for current or prior hypertension, kidney disease, liver disease, stroke, major bleeding event, or having a condition that predisposes to bleeding, medication use that predisposes to risk of bleeding, abnormal INR, alcohol abuse, and aged > 65 years); number of prior hospital encounters; hospital characteristics; and geography. The CHADS₂ calculator is widely used in the United States to estimate stroke risk.^{23,24} The HAS-BLED scoring system has proven predictive of intracranial bleed and of bleeding during bridging and has been validated against other risk scores.²⁵⁻²⁷

The success of propensity score matching was assessed by comparing the prematch and postmatch balance of identified covariates. The chi-square test was used for categorical variables. The Welch’s t-test was used for differences in means, assuming unequal variances. A standardized difference between the 2 cohorts (mean difference expressed as a percentage of the average standard deviation of the variable’s distribution across the dabigatran and warfarin cohorts) of < 10 was considered indicative of good balance.^{19,28} Propensity score matching was performed using The Comprehensive R Archive Network and the MatchIt package.²⁹

Outcome Measures

The inpatient encounters were assessed for total inpatient care cost, LOS, likelihood of readmission within 30 days, and the total cost of readmissions within 30 days. Costs were computed by multiplying the charges by the inpatient cost-to-charge ratio reported to CMS.

Multivariate Analysis

To account for non-normal distribution of outcomes and possible correlation between observations within the same hospital (clusters) across the study period and to further adjust for covariates that remained statistically different after matching, a generalized linear model (GLM) with a gamma distribution (log link) for analysis of LOS, hospital cost, and readmission cost, and binominal distribution for hospital readmission was used based on generalized estimating equations (GEE) methodology. Analyses were performed using The Comprehensive R Archive Network and an a priori statistical significance level of 0.05. The GLM fitted by GEE was conducted using the geepack package.³⁰

Results

Study Samples

There were 33,123 inpatient encounters in the dabigatran cohort and 267,348 in the warfarin cohort for which 3,195 and 28,086 encounters, respectively, met inclusion and exclusion criteria (Figure 2). The available unmatched subset of encounters for newly treated/newly diagnosed patients included 715 hospitalizations in the dabigatran cohort and 4,619 in the warfarin cohort. Matched samples included 646 hospitalizations in the dabigatran cohort and 1,292 in the warfarin cohort. Within the matched sample, there were 244 hospitalizations in the dabigatran cohort and 488 in the warfarin cohort that met the study criteria for assessment of readmissions within 30 days.

Demographics and Characteristics

Table 1 shows the pre- and postmatched characteristics of hospitalized patients by cohort. The postmatch cohorts were generally well balanced. Postmatch demographic characteristics including gender, age, and comorbidity covariates demonstrated nonsignificant differences at $P < 0.05$. The percentage of postmatched hospitalizations with a patient history of prior thromboembolism or prior coronary artery disease (see Appendix B for ICD-9-CM codes for these and other referenced diagnoses, available in online article) had persistent variance at $P < 0.05$ (Table 1).

Kernel density plots illustrated uniform and overlapping densities postmatching (data not shown). Standardized difference for all covariates used for propensity matching was $< 10\%$ after matching (data not shown).

The postmatched encounters had a mean patient age of 72 years at baseline ($P = 0.534$; 21% of dabigatran and 23% of warfarin patients were aged < 65 years). The female-to-male balance was 50% to 50% in the dabigatran cohort and 53% to 47% in the warfarin cohort ($P = 0.304$). Populations were predominantly composed of encounters from the southern region of the United States, which is the largest U.S. census region. In comparison with benchmark census data of nonfederal and nonstate U.S. hospital admissions by geographic region for the most recent annual reported numbers to their respective state

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TABLE 1 Demographics, Clinical Characteristics, and Hospital Characteristics for Matched Cohorts

	Dabigatran Etexilate		Warfarin		P Value ^a	Dabigatran Etexilate		Warfarin		P Value ^a
Number of unique hospitalizations	715		4,619			646		1,292		
Characteristics of Patients, n (%)	Prematch					Postmatch				
Age										
Mean [SD]	70.7	[11.7]	73.1	[10.6]	<0.001	71.7	[11.4]	72.1	[10.9]	0.534
≤ 59	109	(15)	527	(11)	<0.001	81	(13)	168	(13)	0.284
60-64	69	(10)	391	(9)		53	(8)	130	(10)	
65-69	115	(16)	542	(12)		102	(16)	157	(12)	
70-74	121	(17)	682	(15)		115	(18)	218	(17)	
75-79	106	(15)	909	(20)		103	(16)	223	(17)	
80-84	111	(16)	862	(19)		110	(17)	212	(16)	
85+	84	(12)	706	(15)		82	(13)	184	(14)	
Female	344	(48)	2,301	(50)	0.396	323	(50)	678	(53)	0.304
Payer type										
Commercial	192	(27)	899	(20)	<0.001	151	(23)	276	(21)	0.205
Medicare	484	(68)	3,340	(72)		461	(71)	925	(72)	
Medicaid	23	(3)	211	(5)		20	(3)	41	(3)	
Other/unspecified	16	(2)	169	(4)		14	(2)	50	(4)	
Atrial fibrillation was primary diagnosis (vs. secondary diagnosis)	317	(44)	1,000	(22)	<0.001	255	(40)	522	(40)	0.694
No prior atrial fibrillation diagnosis	715	(100)	4,619	(100)	NA	646	(100)	1,292	(100)	NA
Secondary drug (bridging agent)										
None (product only)	211	(30)	927	(20)	<0.001	167	(26)	307	(24)	0.313
With any bridging agent (LMWH/PS and/or UFH)	504	(70)	3,692	(80)		479	(74)	985	(76)	
Comorbidities during prior 12 months										
At least 1 condition as defined by Charlson Comorbidity Index	588	(82)	4,176	(90)	<0.001	552	(85)	1,120	(87)	0.455
AIDS/HIV	1	(0)	17	(0)	^b	1	(0)	5	(0)	^b
Cancer	111	(16)	902	(20)	0.011	107	(17)	237	(18)	0.334
Congestive heart failure	254	(36)	2,122	(46)	<0.001	239	(37)	489	(38)	0.715
Chronic pulmonary disease	224	(31)	1,718	(37)	0.002	208	(32)	469	(36)	0.074
Cerebral vascular disease	149	(21)	1,126	(24)	0.039	143	(22)	282	(22)	0.877
Dementia	23	(3)	256	(6)	0.009	22	(3)	65	(5)	0.103
Diabetes (with or without complication)	234	(33)	1,816	(39)	0.001	228	(35)	421	(33)	0.234
Metastatic carcinoma	11	(2)	136	(3)	0.034	11	(2)	29	(2)	0.429
Myocardial infarction	110	(15)	854	(19)	0.045	105	(16)	194	(15)	0.477
Liver disease (mild through severe)	22	(3)	143	(3)	0.978	20	(3)	32	(3)	0.426
Paraplegia and hemiplegia	19	(3)	186	(4)	0.076	19	(3)	39	(3)	0.925
Peptic ulcer disease	15	(2)	100	(2)	0.908	14	(2)	27	(2)	0.911
Peripheral vascular disease	79	(11)	682	(15)	0.008	79	(12)	167	(13)	0.664
Renal disease	111	(16)	1,260	(27)	<0.001	110	(17)	205	(16)	0.514
Rheumatologic disease	40	(6)	268	(6)	0.825	40	(6)	86	(7)	0.696
At least 1 condition from stroke risk calculations	673	(94)	4,478	(97)	<0.001	613	(95)	1,228	(95)	0.883
Congestive heart failure	255	(36)	2,107	(46)	<0.001	240	(37)	483	(37)	0.921
Left ventricular systolic dysfunction	55	(8)	526	(11)	0.003	52	(8)	115	(9)	0.529
Hypertension	608	(85)	4,059	(88)	0.033	554	(86)	1,118	(87)	0.641
Diabetes mellitus	234	(33)	1,824	(40)	0.001	228	(35)	424	(33)	0.277
Stroke/transient ischemic	190	(27)	1,336	(29)	0.196	182	(28)	336	(26)	0.309
Thromboembolism	17	(2)	939	(20)	<0.001	17	(3)	99	(8)	<0.001
Myocardial infarction	110	(15)	854	(19)	0.045	105	(16)	194	(15)	0.477
Coronary artery disease	276	(39)	2,277	(49)	<0.001	260	(40)	581	(45)	0.048
Peripheral artery disease	43	(6)	417	(9)	0.008	41	(6)	94	(7)	0.449
Risk for stroke										
Mean CHADS ₂ score ^c [SD]	2.5	[1.4]	2.8	[1.4]	<0.001	2.6	[1.4]	2.6	[1.3]	0.590
Mean CHADS ₂ -VASc score ^d [SD]	4.2	[1.9]	5.0	[1.8]	<0.001	4.4	[1.8]	4.5	[1.8]	0.266

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TABLE 1 Demographics, Clinical Characteristics and Hospital Characteristics for Matched Cohorts (continued)

	Dabigatran Etexilate		Warfarin		P Value ^a	Dabigatran Etexilate		Warfarin		P Value ^a
Characteristics of Patients, n (%)	Prematch					Postmatch				
Risk for major bleed, mean HAS-BLED score ^c [SD]	3.0	[1.2]	3.4	[1.2]	<0.001	3.1	[1.1]	3.0	[1.1]	0.092
Mean number of prior hospitalizations, all-cause, within 12 months [SD]	0.3	[0.7]	0.4	[0.9]	<0.001	0.3	[0.8]	0.3	[0.7]	0.514
Within study sample, which hospitalization is this for patient?										
1st	703	(98)	4,400	(95)	0.002	635	(98)	1,237	(96)	0.011
2nd	12	(2)	199	(4)		11	(2)	51	(4)	
3rd	0		19	(0)		0		4	(0)	
4th	0		1	(0)		0		0		
Characteristics of Hospitalization (unadjusted)	Prematch					Postmatch				
Mean length of stay [SD]	4.9	[4.9]	7.5	[6.8]	<0.001	5.2	[5.1]	6.1	[5.9]	<0.001
Mean days in ICU/CCU [SD]	1.0	[2.6]	2.0	[4.2]	<0.001	1.1	[2.7]	1.6	[3.6]	0.001
Mean unique days on drug [SD]	2.9	[2.8]	3.8	[3.3]	<0.001	3.0	[2.9]	3.4	[3.1]	0.005
Mean unique days on bridging agent ^f [SD]	2.1	[3.0]	4.0	[4.5]	<0.001	2.2	[3.1]	3.2	[3.7]	<0.001
Identified as “index” encounter for readmission subset analysis, ^g n (%)	303	(42)	934	(20)	<0.001	244	(38)	488	(38)	1.000
Characteristics of Hospitals, n (%)	Prematch					Postmatch				
U.S. Census divisions										
New England	3	(0)	112	(2)	<0.001	3	(1)	12	(1)	0.452
Middle Atlantic	79	(11)	496	(11)		70	(11)	122	(9)	
East North Central	41	(6)	291	(6)		39	(6)	83	(6)	
West North Central	55	(8)	569	(12)		55	(9)	84	(7)	
South Atlantic	265	(37)	1,505	(33)		239	(37)	476	(37)	
East South Central	45	(6)	267	(6)		43	(7)	93	(7)	
West South Central	103	(14)	505	(11)		87	(14)	184	(14)	
Mountain	22	(3)	219	(5)		22	(3)	32	(3)	
Pacific	102	(14)	655	(14)		88	(14)	206	(16)	
Number of beds										
1-199	164	(23)	1,035	(22)	<0.001	148	(23)	289	(22)	0.214
200-299	143	(20)	689	(15)		117	(18)	208	(16)	
300-499	240	(34)	1,824	(40)		226	(35)	508	(39)	
500+	119	(17)	580	(13)		107	(17)	205	(16)	
Unknown	49	(7)	491	(11)		48	(7)	82	(6)	
Location										
Urban	633	(89)	3,841	(83)	0.001	567	(88)	1,143	(89)	0.636
Rural	33	(5)	287	(6)		31	(5)	67	(5)	
Unknown	49	(7)	491	(11)		48	(7)	82	(6)	
Academic (vs. community)	281	(39)	1,950	(42)	0.141	265	(41)	556	(43)	0.398

^aStatistical testing at alpha=0.05 level. Chi-square test for categorical variables. Welch 2 sample t-test for differences in means, assuming unequal variances.

^bIndicates that at least 1 cell had n<5, so statistical testing could not be confidently preformed.

^cOne point each for congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus; 2 points for transient ischemic attack or stroke.

^dOne point each for congestive heart failure or left ventricular systolic dysfunction; hypertension; diabetes mellitus; vascular disease (inclusive of coronary artery disease, pulmonary artery disease, or myocardial infarction); female gender; age between 65 and 74 years; 2 points each for transient ischemic attack or stroke or thromboembolism and age ≥75 years.

^eOne point each for current or prior hypertension; impaired kidney function (i.e., kidney disease); impaired liver function (i.e., liver disease); stroke, major bleeding event, or having condition that predisposes (i.e., bleeding diathesis); medication use that predisposes to risk of bleeding; abnormal INR (low detection rates in these data); alcohol abuse (low detection rates in these data); and age >65 years.

^fA bridging agent was considered as used regardless of the sequence of the bridging agent and the study drug during the encounter.

^gThis was an exact match criteria in the propensity score matching.

AF=atrial fibrillation; AIDS/HIV=acquired immune deficiency syndrome/human immunodeficiency virus; ICU/CCU=intensive care unit/critical care unit; INR=international normalized ratio; LMWH/PS=low molecular weight heparin/pentasaccharide; NA=not applicable; SD=standard deviation; UFH=unfractionated heparin.

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TABLE 2 Difference in Adjusted Average Length of Stay Between Dabigatran and Warfarin Treatment Groups

Explanatory Variables	Coefficient	Exp PE ^a	Standard Error	P Value ^b
Intercept	1.0325	2.81		
Treatment Group (reference: warfarin)				
Dabigatran etexilate	-0.1358	0.87	0.0369	<0.001
Use of bridging agent (LMWH and/or UFH; reference: no)	0.3816	1.46	0.0391	<0.001
Patient age (in years)	0.0022	1.00	0.0022	0.306
Female (reference: male)	0.0036	1.00	0.0380	0.924
Payer type (reference: commercial)				
Medicare	0.0973	1.10	0.0444	0.027
Medicaid	0.1468	1.16	0.0843	0.082
Other/unspecified	0.1725	1.19	0.2167	0.426
AF was primary diagnosis (reference: secondary diagnosis)	-0.5547	0.57	0.0420	<0.001
Comorbidities (excluding those used in stroke risk calculation)				
Cancer	-0.0659	0.94	0.0486	0.175
Chronic pulmonary disease	0.1919	1.21	0.0354	<0.001
Cerebral vascular disease	0.0513	1.05	0.0535	0.338
Dementia	0.1939	1.21	0.0943	0.040
Metastatic carcinoma	0.2189	1.24	0.1033	0.034
Liver disease (mild through severe)	0.3476	1.42	0.1090	0.001
Paraplegia and hemiplegia	0.2441	1.28	0.0873	0.005
Peptic ulcer disease	0.4098	1.51	0.1174	<0.001
Peripheral vascular disease	0.0314	1.03	0.0495	0.526
Renal disease	0.1404	1.15	0.0461	0.002
Rheumatologic disease	0.0463	1.05	0.0741	0.532
Left ventricular systolic dysfunction	0.0869	1.09	0.0560	0.120
Thromboembolism	0.1287	1.14	0.0642	0.045
Myocardial infarction	0.0317	1.03	0.0592	0.592
Coronary artery disease	-0.0389	0.96	0.0390	0.319
Peripheral artery disease	-0.1227	0.88	0.0668	0.066
Left ventricular systolic dysfunction	-0.0659	0.94	0.0486	0.176
CHADS₂ score^c (reference: 2 [moderate risk])				
0-1 (low risk)	-0.0255	0.97	0.0547	0.641
3-6 (high risk)	0.1341	1.14	0.0387	0.005
HAS-BLED score^d (reference: 2 [moderate risk])				
0-1 (low risk)	0.0651	1.07	0.0765	0.397
3-9 (high risk)	0.0099	1.01	0.0409	0.809
Number of prior hospitalizations	0.0562	1.06	0.0223	0.012
Hospitalization within matched study sample (reference: 1st)				
2nd	0.4376	1.55	0.0889	<0.001
3rd or greater	0.1201	1.13	0.2915	0.680
Stay include time in the ICU/CCU (reference: no)	0.2812	1.32	0.0597	<0.001
Hospital U.S. Census divisions (reference: Pacific)				
New England	-0.2156	0.81	0.1257	0.086
Middle Atlantic	0.0921	1.10	0.0641	0.151
East North Central	0.0137	1.01	0.0693	0.844
West North Central	-0.1916	0.83	0.0786	0.015
South Atlantic	-0.0127	0.99	0.0557	0.820
East South Central	-0.0975	0.91	0.1008	0.333
West South Central	-0.0778	0.93	0.0638	0.223
Mountain	-0.3743	0.69	0.0563	<0.001
Hospital bed size (reference: 300-499 beds)				
1-199 beds	-0.1069	0.90	0.0617	0.083
200-299 beds	0.1354	1.14	0.0562	0.016
500+ beds	0.0728	1.08	0.0506	0.150

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TABLE 2 Difference in Adjusted Average Length of Stay Between Dabigatran and Warfarin Treatment Groups (continued)

Explanatory Variables	Coefficient	Exp PE ^a	Standard Error	P Value ^b
Hospital location (reference: rural)				
Urban	0.0143	1.01	0.0656	0.828
Unknown	0.1082	1.11	0.0915	0.237
Hospital type (reference: community)				
Academic	0.1142	1.12	0.0498	0.022

^aThe multiplicative effect of this level versus the reference level (e.g., 1.46 is interpreted as 46% longer length of stay; 0.87 as 13% shorter length of stay).

^bGeneralized linear model with gamma distribution (log link), fitted by generalized estimating equations performed using The Comprehensive R Archive Network geepack package.

^cOne point each for congestive heart failure, hypertension, age ≥ 75 years, and diabetes mellitus; 2 points for transient ischemic attack or stroke.

^dOne point each for current or prior hypertension; impaired kidney function (i.e., kidney disease); impaired liver function (i.e., liver disease); stroke, major bleeding event, or having condition that predisposes (i.e., bleeding diathesis); medication use that predisposes to risk of bleeding; abnormal INR (low detection rates in these data); alcohol abuse (low detection rates in these data); and age > 65 years.

AF = atrial fibrillation; Exp PE = exponentiated parameter estimate; ICU/CCU = intensive care unit/critical care unit; INR = international normalized ratio; LMWH/PS = low molecular weight heparin/pentasaccharide; UFH = unfractionated heparin.

health departments,³¹ our study's representation of inpatient admissions, while balanced within the study, is more heavily weighted towards the South (58% vs. 39%) and slightly under-representative of the Northeast and Midwest (11% vs. 19% and 13% vs. 23%, respectively). This study's hospitals consisted primarily of urban community hospitals with up to 500 beds. Medicare was the primary payer for most study encounters (71% dabigatran and 72% warfarin).

AF was the primary diagnosis in 40% of each cohort ($P=0.694$). Prevalent comorbidities among patients in both populations included hypertension (86% dabigatran; 87% warfarin; $P=0.641$), coronary artery disease (40% dabigatran; 45% warfarin; $P=0.480$), congestive heart failure (37% dabigatran; 38% warfarin; $P=0.715$), chronic pulmonary disease (32% dabigatran; 36% warfarin; $P=0.074$), diabetes mellitus (35% dabigatran; 33% warfarin; $P=0.234$), and stroke/transient ischemic attack (28% dabigatran; 26% warfarin; $P=0.310$). For both cohorts, the median HAS-BLED scores were 3, median CHADS₂ scores were 2, and median CHA₂DS₂-VASc scores were 4. Bridging agents (see Appendix C for definition, available in online article) were used in 74% of encounters in the dabigatran cohort and 76% in the warfarin cohort ($P=0.313$).

Hospital Length of Stay and Total Hospital Costs

After accounting for the effects of the covariates, encounters initiating with dabigatran had an adjusted average LOS 13% shorter compared with those initiating with warfarin (4.8 days vs. 5.5 days, $P<0.001$; Table 2). Table 2 indicates the effect of other variables, adjusted for the influence of covariates including drug exposure, on LOS. Controlling for all the covariates (Table 3), the estimated total inpatient care costs of dabigatran-treated encounters was 12% lower than warfarin-treated encounters (\$14,794 vs. \$16,826, $P=0.007$). Table 3 shows the effect of other variables, adjusted for the influence of covariates including drug exposure, on total inpatient care costs.

Proportion of Hospital Readmissions and Costs of Readmission

A subset of encounters qualified for analysis of 30-day hospital readmissions ($n=244$ in the dabigatran cohort and $n=488$ in the warfarin cohort). There were 31 dabigatran and 72 warfarin index encounters with at least 1 subsequent hospitalization within 30 days from discharge. The results of the readmission analyses are presented in Table 4.

Hospitalizations in the U.S. Census Mountain geographic area ($n=9$ dabigatran and 13 warfarin) were excluded in the assessment of readmission likelihood, since none represented readmissions, and their inclusion would impact proper development of the model coefficients. The estimated percentage of readmissions adjusted by covariates was similar in the 2 cohorts: 13.1% and 13.3% in the dabigatran and warfarin cohorts, respectively (odds ratio=0.987, 95% confidence interval=0.65-1.49, $P=0.951$). Not many variables included in the model are associated with significant influence on the likelihood of a hospital readmission (Table 4). Those that do should be considered within the limits of the sample representation (i.e., only 3% [$n=17$] of the matched dabigatran and 8% [$n=99$] of the matched warfarin patients had a history of thromboembolism).

Table 5 shows the adjusted average inpatient care cost for the index encounter and all readmissions within 30 days following discharge from the index encounter among the subset of hospitalizations with at least 1 readmission. Among this subset of 31 dabigatran and 72 warfarin hospitalizations, the index hospitalization costs and the readmission costs were not statistically different between the dabigatran and warfarin cohorts (index costs: \$9,803 vs. \$9,755, respectively, with difference of \$48, $P=0.944$; readmission costs: \$10,403 vs. \$11,911, respectively, with difference of \$1,507, $P=0.375$).

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TABLE 3 Difference in Adjusted Total Inpatient Care Cost Between Dabigatran and Warfarin Treatment Groups

Explanatory Variables	Coefficient	Exp PE ^a	Standard Error	P Value ^b
Intercept	10.4068	33,084.49		
Treatment Group (reference: warfarin)				
Dabigatran etexilate	-0.1287	0.88	0.0480	0.007
Use of bridging agent (LMWH and/or UFH; reference: no)	0.5371	1.71	0.0420	<0.001
Patient age (in years)	-0.0072	0.99	0.0023	0.001
Female (reference: male)	-0.0770	0.93	0.0418	0.065
Payer type (reference: commercial)				
Medicare	0.1344	1.14	0.0591	0.023
Medicaid	0.0625	1.06	0.1018	0.540
Other/unspecified	-0.0725	0.93	0.2440	0.766
AF was primary diagnosis (reference: secondary diagnosis)	-0.7836	0.46	0.0518	<0.001
Comorbidities (excluding those used in stroke risk calculation)				
Cancer	-0.0021	1.00	0.0470	0.964
Chronic pulmonary disease	0.1654	1.18	0.0379	<0.001
Cerebral vascular disease	-0.0060	0.99	0.0604	0.921
Dementia	-0.0145	0.99	0.0796	0.856
Metastatic carcinoma	-0.0133	0.99	0.1075	0.902
Liver disease (mild through severe)	0.2488	1.28	0.1348	0.065
Paraplegia and hemiplegia	0.2434	1.28	0.1142	0.033
Peptic ulcer disease	0.5914	1.81	0.1942	0.002
Peripheral vascular disease	-0.0532	0.95	0.0527	0.313
Renal disease	0.0747	1.08	0.0564	0.186
Rheumatologic disease	0.0581	1.06	0.0769	0.450
Left ventricular systolic dysfunction	0.1441	1.15	0.0787	0.067
Thromboembolism	-0.0363	0.96	0.0785	0.643
Myocardial infarction	0.1788	1.20	0.0649	0.006
Coronary artery disease	0.0434	1.04	0.0467	0.353
Peripheral artery disease	0.0829	1.09	0.0768	0.281
CHADS₂ score^c (reference: 2 [moderate risk])				
0-1 (low risk)	0.0427	1.04	0.0652	0.513
3-6 (high risk)	0.1147	1.12	0.0470	0.015
HAS-BLED score^d (reference: 2 [moderate risk])				
0-1 (low risk)	-0.0351	0.97	0.0990	0.723
3-9 (high risk)	0.0121	1.01	0.0471	0.798
Number of prior hospitalizations	0.0139	1.01	0.0239	0.562
Hospitalization within matched study sample (reference: 1st)				
2nd	-0.2307	0.79	0.0777	0.003
3rd or greater	0.1400	1.15	0.3051	0.646
Hospital U.S. Census divisions (reference: Pacific)				
New England	-0.1290	0.88	0.3531	0.715
Middle Atlantic	-0.1393	0.87	0.1238	0.261
East North Central	-0.5131	0.60	0.0833	<0.001
West North Central	-0.2284	0.80	0.1551	0.141
South Atlantic	-0.4457	0.64	0.0900	<0.001
East South Central	-0.8217	0.44	0.1038	<0.001
West South Central	-0.7246	0.48	0.1128	<0.001
Mountain	-0.3108	0.73	0.0912	0.001
Hospital bed size (reference: 300-499 beds)				
1-199 beds	0.0234	1.02	0.0856	0.785
200-299 beds	0.1022	1.11	0.0956	0.285
500+ beds	0.3108	1.36	0.0894	0.001

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TABLE 3 Difference in Adjusted Total Inpatient Care Cost Between Dabigatran and Warfarin Treatment Groups (continued)

Explanatory Variables	Coefficient	Exp PE ^a	Standard Error	P Value ^b
Hospital location (reference: rural)				
Urban	-0.3411	0.71	0.0970	<0.001
Unknown	0.2487	1.28	0.1695	0.142
Hospital type (reference: community)				
Academic	0.1886	1.21	0.0779	0.016

^aThe multiplicative effect of this level versus the reference level (e.g., 1.04 is interpreted as 4% higher total health care costs; 0.69 as 31% lower total health care costs).

^bGeneralized linear model with gamma distribution (log link), fitted by generalized estimating equations performed using The Comprehensive R Archive Network geepack package.

^cOne point each for congestive heart failure, hypertension, age ≥ 75 years, and diabetes mellitus; 2 points for transient ischemic attack or stroke.

^dOne point each for current or prior hypertension; impaired kidney function (i.e., kidney disease); impaired liver function (i.e., liver disease); stroke, major bleeding event, or having condition that predisposes (i.e., bleeding diathesis); medication use that predisposes to risk of bleeding; abnormal INR (low detection rates in these data); alcohol abuse (low detection rates in these data); and age > 65 years.

AF=atrial fibrillation; Exp PE=exponentiated parameter estimate; INR=international normalized ratio; LMWH/PS=low molecular weight heparin/pentasaccharide; UFH=unfractionated heparin.

Discussion

This study was based on a national multipayer dataset for analyses of real-world use of dabigatran and warfarin in a geographically dispersed sample of hospitals. Patients with newly diagnosed AF account for a significant portion of hospitalizations due to dysrhythmias in the United States.^{2,3} The study encounters included only newly diagnosed/newly treated NVAF patients to reduce the possibility of biased estimates from the limited control for length of treatment time or switching of treatments. The demographics and clinical history of the sample were similar to those among the U.S. general population with newly diagnosed AF and with emergency department patients presenting with recent onset AF in Italy.^{32,33} Interestingly, both of these studies reported undertreatment with anticoagulation therapy in up to 25% of patients at high risk of stroke, highlighting that appropriate anticoagulation management remains a worldwide problem.

The total inpatient care costs finding in the current study are comparable with other studies. According to Coyne et al. (2006), the typical AF hospitalization cost in 2001 using 2005 U.S. dollars was \$8,371 (total of \$2.93 billion for 350,000 hospitalizations with AF as the primary diagnosis).³ Our study's higher cost estimates (\$14,794 and \$16,826) are based on costs of actual hospital resources (vs. payments), include primary and secondary AF diagnosed encounters of only newly diagnosed patients, and were based on 2011-2012 data and U.S. dollars. Results using this study's data and replication of methods with the exception of propensity score matching confirmed the results of lower costs (by \$4,240) among the dabigatran cohort. While cost-effectiveness does not always translate to a lower cost solution, several studies have identified dabigatran to be a cost-effective alternative. For instance, a cost-effectiveness analysis model showed dabigatran 150 mg twice daily to be a cost-effective alternative to INR-adjusted warfarin for patients aged ≥ 65 years.³⁴ A decision analysis model of dabigatran cost

effectiveness versus warfarin stratified results by INR control, stroke risk, and bleeding risk and showed that dabigatran 150 mg twice daily was cost-effective for patients with high stroke and hemorrhage risk.³⁵ Freeman et al. (2010) used a Markovian analytical model to assess costs and reported that dabigatran could be a cost-effective alternative to warfarin in patients aged ≥ 65 years at increased risk for stroke.³⁶ These studies in tandem with our results suggest that dabigatran use is cost-effective and a lower cost option for OAC therapy. Additional studies should be conducted to validate this.

Patients receiving dabigatran may not need bridging agents because of a rapid onset of action and predictable pharmacokinetics; however, the findings indicated nearly three quarters of the unmatched and matched dabigatran etexilate cohort (71% and 74%, respectively) were observed receiving bridging agents during hospitalization. This contributed significantly to the cost in the dabigatran cohort. Other than intended warfarin use, predictors of bridging are not well defined for newly diagnosed/newly treated NVAF patients, and use of bridging agents remains a challenge in AF patients.³⁷ One study found that among diagnosed AF patients undergoing temporary interruption of anticoagulation therapy for invasive procedures, bridging agents were used inappropriately in more than 50% of patients at low thromboembolic risk.³⁸ Patients hospitalized with a primary or secondary discharge diagnosis of NVAF have also been shown to have increased LOS when bridging agents are used.³⁹ Therefore, including bridging agents as a covariate in the present analysis was done as a reflection of observed, real-world clinical practice.

We found that dabigatran relative to warfarin was associated with a shorter LOS for inpatient encounters, which is consistent with the study by Tan et al. (2007) that demonstrated longer LOS for AF patients newly started versus not initiated on warfarin while in the hospital.⁴⁰ Thirty percent of patients had delayed discharges attributed to initiation of warfarin, for a

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TABLE 4 Difference in Adjusted Hospital Readmission Rate Between Dabigatran and Warfarin Treatment Groups

Explanatory Variables	Coefficient	Standard Error	P Value ^a	Odds Ratio
Intercept	-2.5046	0.08		
Treatment Group (reference: warfarin)				
Dabigatran etexilate	-0.0129	0.21	0.951	0.99
Use of bridging agent (LMWH and/or UFH; reference: no)	0.3109	0.37	0.395	1.36
Patient age (in years)	0.0028	0.01	0.844	1.00
Female (reference: male)	0.4567	0.27	0.094	1.58
Payer type (reference: commercial)				
Medicare	0.1041	0.35	0.763	1.11
Medicaid	0.6944	0.63	0.269	2.00
Other/unspecified	0.8188	1.20	0.496	2.27
Comorbidities (excluding those used in stroke risk calculation)				
Cancer	0.4350	0.25	0.086	1.54
Chronic pulmonary disease	0.0988	0.23	0.661	1.10
Cerebral vascular disease	-0.3507	0.38	0.350	0.70
Dementia	0.0207	0.61	0.973	1.02
Metastatic carcinoma	-0.2988	1.13	0.792	0.74
Liver disease (mild through severe)	-1.0234	1.10	0.354	0.36
Paraplegia and hemiplegia	1.4393	1.13	0.204	4.22
Peptic ulcer disease	-9.2118	1.28	<0.001	<0.01
Peripheral vascular disease	-0.0735	0.47	0.876	0.93
Renal disease	0.1695	0.36	0.640	1.18
Rheumatologic disease	-0.2899	0.51	0.569	0.75
Left ventricular systolic dysfunction	-0.0439	0.51	0.932	0.96
Thromboembolism	1.5718	0.53	0.003	4.82
Myocardial infarction	0.2084	0.38	0.587	1.23
Coronary artery disease	0.0641	0.27	0.809	1.07
Peripheral artery disease	-0.4257	0.65	0.513	0.65
CHADS ₂ score ^b (reference: 2 [moderate risk])				
0-1 (low risk)	-0.0593	0.27	0.827	0.94
3-6 (high risk)	0.2707	0.28	0.340	1.31
HAS-BLED score ^c (reference: 2 [moderate risk])				
0-1 (low risk)	-0.2080	0.49	0.673	0.81
3-9 (high risk)	0.3301	0.29	0.263	1.39
Number of prior hospitalizations	-0.1601	0.33	0.630	0.85
Stay include time in the ICU/CCU (reference: no)	0.5457	0.25	0.030	1.73
Hospital U.S. Census divisions (reference: Pacific)				
New England	1.9841	0.49	<0.001	7.27
Middle Atlantic	0.0420	0.45	0.926	1.04
East North Central	0.1676	0.46	0.717	1.18
West North Central	-0.0209	0.49	0.966	0.98
South Atlantic	-0.2324	0.30	0.441	0.79
East South Central	-0.3914	0.51	0.444	0.68
West South Central	-0.1847	0.44	0.673	0.83
Mountain	Insufficient data ^d			
Hospital bed size (reference: 300-499 beds)				
1-199 beds	-0.0930	0.31	0.763	-0.09
200-299 beds	0.1084	0.44	0.806	0.11
500+ beds	-0.4856	0.42	0.250	-0.49
Hospital location (reference: rural)				
Urban	-0.4439	0.45	0.325	0.64
Unknown	-0.7643	0.70	0.276	0.47
Hospital type (reference: community)				
Academic	-0.3420	0.29	0.244	0.71

^aGeneralized linear model with binomial distribution, fitted by generalized estimating equations performed using The Comprehensive R Archive Network geepack package.

^bOne point each for congestive heart failure, hypertension, age ≥ 75 years, and diabetes mellitus; 2 points for transient ischemic attack or stroke.

^cOne point each for current or prior hypertension; impaired kidney function (i.e., kidney disease); impaired liver function (i.e., liver disease); stroke, major bleeding event, or having condition that predisposes (i.e., bleeding diathesis); medication use that predisposes to risk of bleeding; abnormal INR (low detection rates in these data); alcohol abuse (low detection rates in these data); and age > 65 years.

^dThe 22 patients from the Mountain Census Division were removed from the sample as none were readmitted; retaining them was mathematically skewing the model betas.

AF = atrial fibrillation; ICU/CCU = intensive care unit/critical care unit; INR = international normalized ratio; LMWH/PS = low molecular weight heparin/pentasaccharide; UFH = unfractionated heparin.

TABLE 5 Adjusted Average Inpatient Care Costs for Index Encounter and All Readmissions During 30 Days Postdischarge Between Dabigatran and Warfarin Treatment Groups

Measure	Dabigatran Etexilate Adjusted ^a Average Value	Warfarin Adjusted ^a Average Value	Difference (Dabigatran Minus Warfarin)	P Value ^b
Index encounter inpatient care costs, \$ (n)	9,803 (244)	9,755 (488)	48	0.944
All inpatient care costs from readmissions within 30 days of discharge of index encounter, \$ (n)	10,403 (31)	11,911 (72)	-1,507	0.375

^aAdjusted values were estimated using a generalized linear model with gamma distribution, fitted by generalized estimating equations performed using The Comprehensive R Archive Network geepack package.

^bStatistical testing at alpha=0.05 level. Welch 2 sample t-test for differences in means, assuming unequal variances.

combined 17% of delayed days. Additional hospitalization time required for patients treated with warfarin may be driven by the need to titrate to the correct dose determined by monitoring the patient's INR.

For the subset of hospitalizations analyzed for readmission within 30 days, rates of readmission and total readmission costs were similar between the cohorts. In current literature, readmission rates are reported to be lower when discharged patients have follow-up visits with physicians within 30 days of discharge.⁴¹ Our study did not account for follow-up care to a practitioner or, for warfarin, to an anticoagulation clinic for dose monitoring. If either cohort had a greater compliance with therapy after discharge or higher proportion that followed up with a clinic or physician, this could be insightful in interpreting our results that readmission rates and costs were similar for encounters involving dabigatran and warfarin.

Limitations

Despite the strength of the methodological approaches and analyses in this large retrospective, observational study, there are certain limitations. Charges modified by cost-to-charge ratios estimated the cost of hospital resources used but may over- or underrepresent the actual amount reimbursed by payers. Since clinical characteristics were determined using ICD-9-CM diagnosis codes on nondiagnostic claims, errors from coding inaccuracies could not be ruled out. Abnormal INR and alcohol abuse, 2 elements in HAS-BLED, may be underdetected using only diagnostic codes. The primary diagnosis was assumed to be consistent with the principal diagnosis reported. The analysis could not identify nor correct for data entry errors at the site of care. Finally, given the data used for this study, we could not assess compliance with anticoagulation therapy among each group or follow up with INR monitoring among the warfarin cohort. However, despite these limitations, the study presented hospitalized cohorts that were well matched with respect to demographics and medical history and identified how attributes among similar populations given different therapies might impact hospital utilization.

Conclusions

The length of stay was longer and total inpatient care costs were higher for hospitalizations of newly diagnosed NVAF patients initiated on warfarin as compared with those initiated on dabigatran. The estimated readmission rates and associated inpatient care costs of 30-day readmissions among dabigatran and warfarin groups were similar.

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DISCLOSURES

This study and preparation of the manuscript were supported by Boehringer Ingelheim Pharmaceuticals. At the time of this study, Fonseca and Hess were employees of IMS Health, a company that received funding to support the conduct of this study and development of the manuscript. Sander and Ghosh are employees of Boehringer Ingelheim Pharmaceuticals.

Study concept and design were created by Fonseca, Sander, and Hess. Data interpretation was contributed by Fonseca and Hess, along with Sander and Ghosh. The manuscript was written primarily by Fonseca and Hess, with assistance from Sander and Ghosh, and revised by Fonseca, Ghosh, Sander, and Hess.

ACKNOWLEDGMENTS

We acknowledge Patrice C. Ferriola, PhD (KZE PharmAssociates), for assistance with writing this manuscript, and Max Manzi for his assistance with code development and data extraction; all prior acknowledged work was funded by IMS Health. We also acknowledge David R. Walker, PhD, an employee at Boehringer Ingelheim Pharmaceuticals during the conduct of the study analyses, for his assistance in study design and interpretation.

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APPENDIX A List of Oral Anticoagulants and Corresponding Drug Classification

Study Drug	First 10 Digits of GPI ^a	Drug Note Terms ^b
Dabigatran etexilate	83-33-70-30-20	dabigatran, dabigatran etexilate, pradaxa, dabigat, dabigatran etexilate mesylate
Warfarin	83-20-00-30-20	warfarin sodium, warfarin, coumadin, jantoven

^aGPI is a 14-digit drug classification system maintained by Medi-Span. The first 10 digits represent drug group-subclass-name-extension. The remaining 4 digits represent dosage form-strength.

^bWhile GPI-10s were used to search the pharmacy claims database, the data source—hospital Charge Detail Masters—used for hospitalizations contains drug notes and not specific drug codes. Additional drug note terms were used (e.g., common misspellings).

GPI = Generic Product Identifier.

APPENDIX B ICD-9-CM Codes Used to Identify Conditions Reported in Results Section

Medical Condition	ICD-9-CM Code	Description
Thromboembolism	444*	arterial embolism and thrombosis
	445*	atheroembolism
	415.1*	pulmonary embolism and infarction
	449*	septic arterial embolism
	451*	phlebitis and thrombophlebitis
	452*	portal vein thrombosis
	453*	other venous embolism and thrombosis
Coronary artery disease	411.8*	other acute and subacute forms of ischemic heart disease
	413*	angina pectoris
	414.0*	coronary atherosclerosis
Hypertension	401*	essential hypertension
	402*	hypertensive heart disease
	403*	hypertensive chronic kidney disease
	404*	hypertensive heart and chronic kidney disease
	405*	secondary hypertension
Congestive heart failure ^a	398.91	rheumatic heart failure (congestive)
	402.01	malignant hypertensive heart disease with heart failure
	402.11	benign hypertensive heart disease with heart failure
	402.91	unspecified hypertensive heart disease with heart failure
	404.01	hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
	404.03	hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease
	404.11	hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
	404.13	hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
	404.91	hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
	404.93	hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
	425.4	other primary cardiomyopathies
	425.5	alcoholic cardiomyopathy
	425.7	nutritional and metabolic cardiomyopathy
	425.8	cardiomyopathy in other diseases classified elsewhere
	425.9	secondary cardiomyopathy, unspecified
	428*	heart failure
Chronic pulmonary disease	490*	bronchitis, not specified as acute or chronic
	491*	chronic bronchitis
	492*	emphysema
	493*	asthma
	494*	bronchiectasis
	495*	extrinsic allergic alveolitis

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APPENDIX B ICD-9-CM Codes Used to Identify Conditions Reported in Results Section (continued)

Medical Condition	ICD-9-CM Code	Description
Chronic pulmonary disease	496*	chronic airway obstruction, not elsewhere classified
	500*	coal workers' pneumoconiosis
	501*	asbestosis
	502*	pneumoconiosis due to other silica or silicates
	503*	pneumoconiosis due to other inorganic dust
	504*	pneumonopathy due to inhalation of other dust
	505*	pneumoconiosis, unspecified
	506.4	chronic respiratory conditions due to fumes and vapors
Diabetes mellitus ^b	249*	secondary diabetes mellitus
	250*	diabetes mellitus
	362.0*	diabetic retinopathy
	366.41	diabetic cataract
	V12.21	personal history of gestational diabetes
	V58.67	long-term (current) use of insulin
	V65.46	encounter for insulin pump training
Stroke/TIA	430*	subarachnoid hemorrhage
	431*	intracerebral hemorrhage
	432*	other and unspecified intracranial hemorrhage
	433*	occlusion and stenosis of precerebral arteries
	434*	occlusion of cerebral arteries
	435*	transient cerebral ischemia
	436*	acute but ill-defined cerebrovascular disease
	437.1	other generalized ischemic cerebrovascular disease
	438*	late effects of cerebrovascular disease
	997.02	iatrogenic cerebrovascular infarction or hemorrhage
	V12.54	personal history of TIA and cerebral infarction without residual deficits

^aThis congestive heart failure definition is used in the Charlson Comorbidity Index. The stroke risk definition does not include the codes 402.01-404.93 but does include additional codes 425.0-425.3, 674.5, 674.53, and 674.54.

^bThis diabetes mellitus definition is for stroke risk. The Charlson Comorbidity Index definition²⁴ is limited to 249* and 250*.

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; TIA = transient ischemic attack.

APPENDIX C List of Bridging Agents and Corresponding Drug Note Terms

Bridging Agent Group	Drugs	Drug Note Terms ^a
Low molecular weight heparin/pentasaccharide	fondaparinux	fondaparinux, fondaparinux sodium, Arixtra
	enoxaparin	enoxaparin, enox, Lovenox
	dalteparin	dalteparin, daltep, Fragmin
		nondrug specific reference to low molecular weight heparin/pentasaccharide
Unfractionated heparin	heparin	Heparin, Hep, Heparin Lock, Beef Heparin, Heparin (porcine), Heparin sodium

^aThe data source—hospital Charge Detail Masters—used to assess hospitalizations contains drug notes and not specific NDC numbers or HCPCS codes. Additional drug note terms were used (e.g., common misspellings).

HCPCS = Healthcare Common Procedure Coding System; NDC = National Drug Code.