RESEARCH

All-Cause and Bleeding-Related Health Care Costs in Warfarin-Treated Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND: Bleeding is a major complication of warfarin therapy. Assessing the cost of warfarin-associated bleeding may more fully describe the costs associated with warfarin use.

OBJECTIVE: To assess health care costs related to warfarin-associated bleeding in patients with newly diagnosed atrial fibrillation (AF).

METHODS: Medical and pharmacy claims were analyzed for patients with AF (ICD-9-CM code 427.31) in the Medstat MarketScan database from January 2003 to December 2007. Eligible patients had no warfarin pharmacy claim or AF diagnosis in the 4 months prior to AF index date, a warfarin pharmacy claim within 30 days of AF diagnosis, and 12 months follow-up data after the index warfarin claim. Subjects were categorized based on the first type of bleeding event observed during follow-up, and only bleeding events occurring within 30 days following a warfarin claim were considered. Intracranial hemorrhage (ICH) and gastrointestinal (GI) events were assessed based on primary or secondary ICD-9-CM codes, and major GI bleeding was defined as a GI bleed associated with hospitalization. Annual total all-cause allowed charges in patients with and without bleeding events after the index warfarin claim were compared using generalized linear model (GLM) regression with gamma distribution and log link, controlling for demographics, insurance status, and comorbidities. Costs for claims with a primary or secondary diagnosis of bleeding were calculated separately.

RESULTS: Of the 47,437 patients who were analyzed, 194 (0.4%) had an ICH, 919 (1.9%) had a major GI bleed, and 1,804 (3.8%) had a minor GI bleed within 30 days after a warfarin claim during follow-up. Compared with patients who had no bleeding events after a warfarin claim (n = 44,520, 93.9%) during the study period, patients with at least 1 bleeding event were older and had more comorbidities ($P < 0.01$). Patients with at least 1 ICH or major GI bleed had more all-cause hospitalizations ($P < 0.05$) and hospital days ($P < 0.01$) than patients without bleeding events. Patients with at least 1 ICH, major GI bleed, or minor GI bleed had more all-cause emergency room visits ($P < 0.01$) than patients without bleeding events. Mean (SD) unadjusted all-cause health care costs in the 12 months after the warfarin index claim were $41,903 ($56,654), $40,586 ($65,164), and $24,347 ($56,488) for patients with at least 1 ICH, major GI bleed, and minor GI bleed, respectively, compared with $24,129 ($36,425) for patients with no bleeding events. Claims with a primary or secondary diagnosis of bleeding accounted for 49.6%, 30.2%, and 2.6% of annual cost in patients with ICH, major GI bleeding, and minor GI bleeding, respectively. On average, 50.9%, 33.5%, and 10.8% of annual all-cause costs occurred within 30 days after the first ICH, major GI bleeding event, and minor GI bleeding event, respectively. GLM regression showed that annual all-cause costs were 64.4% and 49.0% higher ($P < 0.001$) for patients with ICH and major GI bleeding, respectively, than for patients with no bleeding events.

CONCLUSION: ICH and major GI bleeding associated with warfarin therapy are rare but costly.

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What is already known about this subject

- Warfarin is the primary oral anticoagulant currently recommended for the prevention of stroke for patients with atrial fibrillation (AF). Published evidence suggests that warfarin reduces the risk of stroke by approximately 64%.
- The narrow therapeutic window of warfarin may result in insufficient anticoagulation, which may lead to stroke or over anticoagulation, which can increase the risk of bleeding. The incidence of major bleeding in AF patients receiving adjusted-dose warfarin has been reported as 1.1%.
- Kim et al. (2010) reported an average cost of $10,819 per hospitalization for warfarin-related bleeding events in older community-dwelling adults receiving state-funded prescription drug assistance. However, data from the perspective of other health care payers or for other patient populations remain limited.

What this study adds

- Among warfarin-treated patients with AF, subjects who have major bleeding events incur significantly higher all-cause health care costs and resource utilization than similar patients with no bleeding events after controlling for demographics and comorbid conditions.
- Subjects with intracranial (IC) and major gastrointestinal (GI) bleeding had significantly more all-cause hospitalizations, hospital days, and emergency room (ER) visits than subjects with no bleeding events. Subjects with minor GI bleeding had significantly fewer hospitalizations annually but significantly more ER visits and office visits compared with subjects who had no bleeding events.
- The annual all-cause health care costs for patients with IC and major GI bleeds were 64.4% and 49.0% higher, respectively, than for patients with no bleeding events after controlling for demographic characteristics and comorbidities ($P < 0.001$). Unadjusted mean (SD) annual all-cause costs were $41,903 ($56,654) per patient with IC bleeding, $40,586 ($65,164) per patient with major GI bleeding, $24,347 ($56,488) per patient with minor GI bleeding, and $24,129 ($36,425) per patient without bleeding events.

Atrial fibrillation (AF) is a chronic disorder estimated to affect nearly 2.3 million people in the United States and 4.5 million people in the European Union.[1,2] AF is more prevalent in men than in women at all ages,[2-5] and the median age of patients with AF is approximately 72 years.[6] The prevalence of AF increases substantially with age, and the number of people with this disorder will increase substantially in the United States over the next few decades to more than 10 million by 2050.[7]

AF carries a 4-fold increase in the risk of stroke,[8-10] accounts for 15% of all strokes in the United States,[9] and is therefore associated with a substantially increased risk recurrence compared with other etiologies of stroke.[11] Therefore, the primary objective of treating AF patients with anticoagulant therapy is to reduce the risk of stroke. The 2008 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommend calculating each individual's stroke risk to identify patients who are at higher risk and who may benefit most from anticoagulation therapy.[6] Oral anticoagulant therapy is generally recommended for the prevention of stroke in patients with a moderate to high risk of stroke and not at high bleeding risk.[1] Despite the established efficacy of warfarin in stroke prevention, this therapy is also associated with increased bleeding risk. Concern over excessive bleeding has been cited as a primary reason for not receiving anticoagulation therapy.[12]

Despite concerns over bleeding associated with anticoagulation therapy, little is known about the cost associated with intracranial (IC) and major or minor gastrointestinal (GI) bleeding among patients receiving oral anticoagulant therapy. A recent study by Mercaldi et al. (2011) assessed the effectiveness of warfarin and its impact on medical costs among Medicare patients with nonvalvular AF.[13] The authors reported that use of warfarin was independently associated with lower total medical costs, averaging $9,836 per patient per year. The authors reported an average cost of $39,943 per year among patients with nonvalvular AF and major bleeding events; however, that analysis was not limited to those receiving oral anticoagulation therapy. Other studies assessing the cost of warfarin-associated bleeding have been limited to special populations and economic modeling of hypothetical cohorts of warfarin-treated patients based on clinical trial data.[14-17] Moreover, estimates of nonmajor bleeding have not been well described previously.

With increased focus on reducing health care costs, there is interest in evaluating the costs associated with bleeding events related to anticoagulant therapy in patients with AF. The primary purpose of this study was to assess the all-cause annual health care costs among warfarin-treated patients with AF, comparing patients with IC and major or minor GI bleeding events versus patients without bleeding events based on a retrospective analysis of a large health plan database. The secondary purpose of this study was to assess the costs associated with health care claims for IC and major or minor GI bleeding events.

Methods

Data Source

A retrospective cohort study was conducted utilizing the Thomson Reuters Medstat MarketScan Commercial Claims & Encounters and Medicare Supplemental & Coordination of Benefits database (Thomson Reuters, Chicago, IL). The database is fully compliant with the Health Insurance Portability and Accountability Act (HIPAA) privacy rules and consists of integrated enrollment history, medical, and pharmacy claims data for more than 94 million patients receiving commercial health insurance benefits through employers. In the Medstat Marketscan database, hospitalizations are categorized based on revenue codes; emergency room (ER) visits are categorized based on place of service, procedure codes, and service type; and office visits are categorized based on procedure codes. The Medstat Marketscan database has been used previously for research projects aimed at understanding the costs and patterns of medication utilization in patients with AF.[18-22] The study was reviewed and approved by the Institutional Review Board at the University of Utah.

Study Sample

The study sample consisted of adults aged 18 years or older with a first diagnosis of AF, identified by a medical claim associated with a primary or secondary diagnosis of *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) code 427.31, between January 1, 2003, and December 31, 2007. Subjects were eligible for inclusion if they had at least 17 months (4 months pre- and 13 months post-AF diagnosis date) of continuous eligibility for medical and pharmacy services. Subjects who died within 13 months of diagnosis of AF were excluded from this analysis. Subjects with either a medical claim with an AF diagnosis or a warfarin claim during the 4 months before the AF diagnosis date were excluded from the analysis; these patients were excluded to maximize the probability of including newly diagnosed subjects with AF and to maximize the likelihood that observed bleeding events were due to warfarin use measured during the study period. Only subjects with the first warfarin claim within 30 days of the index AF diagnosis were eligible for inclusion in this study. The 30-day rule was imposed to maximize the likelihood that study subjects were receiving warfarin therapy for stroke prevention.

The warfarin start date was the date of the first warfarin claim after the index diagnosis of AF within the study period. Subjects who met all the inclusion criteria were followed for 12 months after their warfarin start date to assess the presence of major GI, major IC, and minor GI bleeding events as identified by medical claims associated with the corresponding ICD-9-CM codes as primary or secondary diagnosis (Table 1,

TABLE 1 ICD-9-CM Codes for Atrial Fibrillation and Gastrointestinal and Intracranial Bleeding Events

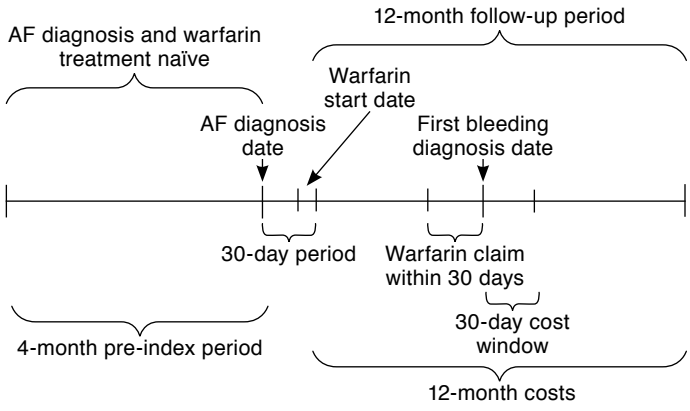
Diagnosis	ICD-9-CM Codes
Atrial fibrillation	427.31
Gastrointestinal bleeding event[a]	530.82, 531.2, 531.4, 531.6, 532.2, 532.4, 532.6, 533.2, 533.4, 533.6, 534.2, 534.4, 534.6, 535.x1, 537.83, 562.02, 562.03, 562.12, 562.13, 569.3 or 578.x
Intracranial bleeding event	430.x, 431.x, 432.0, 432.1, 432.2, 432.9, or 851-854[b]

[a]Major GI bleeding event was defined as GI bleeding that required hospitalization, identified based on inpatient claims associated with an ICD-9-CM code for GI bleed. Minor GI bleeding event was identified by the presence of only an outpatient claim associated with a GI bleed ICD-9-CM code.

[b]ICD-9-CM codes 851-854 refer to intracranial injury. Specifically, 852 and 853 deal with hemorrhage after injury, while 851 mentions laceration and contusion and 854 includes all other nonspecified injuries.[35] Of 194 patients identified with an intracranial bleeding event, 19 were identified using codes 851-854, of whom 6 were identified using only codes 851 and 854.

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

FIGURE 1 Schematic Representation of Study Design



AF = atrial fibrillation.

Figure 1). To increase confidence in attributing bleeding events to warfarin therapy, only bleeding events within 30 days of a warfarin claim were considered. Subjects were categorized based on the type of first bleeding event observed during the follow-up period. A major GI bleeding event was defined as GI bleeding that required hospitalization, identified based on inpatient claims associated with an ICD-9-CM code for GI bleeding (Table 1). A minor GI bleeding event was identified by the presence of only an outpatient claim associated with a diagnosis code for GI bleeding. Because subjects may have a single episode with claims indicating both major and minor bleeding events, a 7-day time period was imposed to differentiate a minor GI outpatient claim and a major GI inpatient claim as related to 2 separate events if they were more than 7 days apart. In other words, a patient who had an index outpatient claim with a diagnosis of GI bleeding followed by an inpatient claim with a diagnosis of GI bleeding within 7 days of the outpatient claim was considered to have an index major GI bleeding event. IC bleeding events were identified by inpatient claims associated with an ICD-9-CM code for IC bleeding (Table 1).

Health care utilization data were assessed for 4 cohorts of subjects with the following: (a) first major GI bleeding and no subsequent IC bleeding (cohort 1), (b) first minor GI bleeding and no subsequent IC or major GI bleeding (cohort 2), (c) first IC bleeding and no subsequent GI bleeding (cohort 3), and (d) no bleeding events within 30 days of a warfarin claim during the follow-up period (cohort 4). Patients in the cohort for major GI bleeding might have subsequent minor GI bleeding events, but patients in the cohort for minor GI bleeding did not have any major GI bleeding by definition because a major GI bleeding event would have qualified them for the major GI bleeding cohort. All-cause hospitalizations, hospital days, ER visits, outpatient office visits, and their associated costs during the 12 months after the warfarin start date were assessed for subjects with at least 1 bleeding event (cohorts 1, 2, and 3) and subjects without a bleeding event (cohort 4).

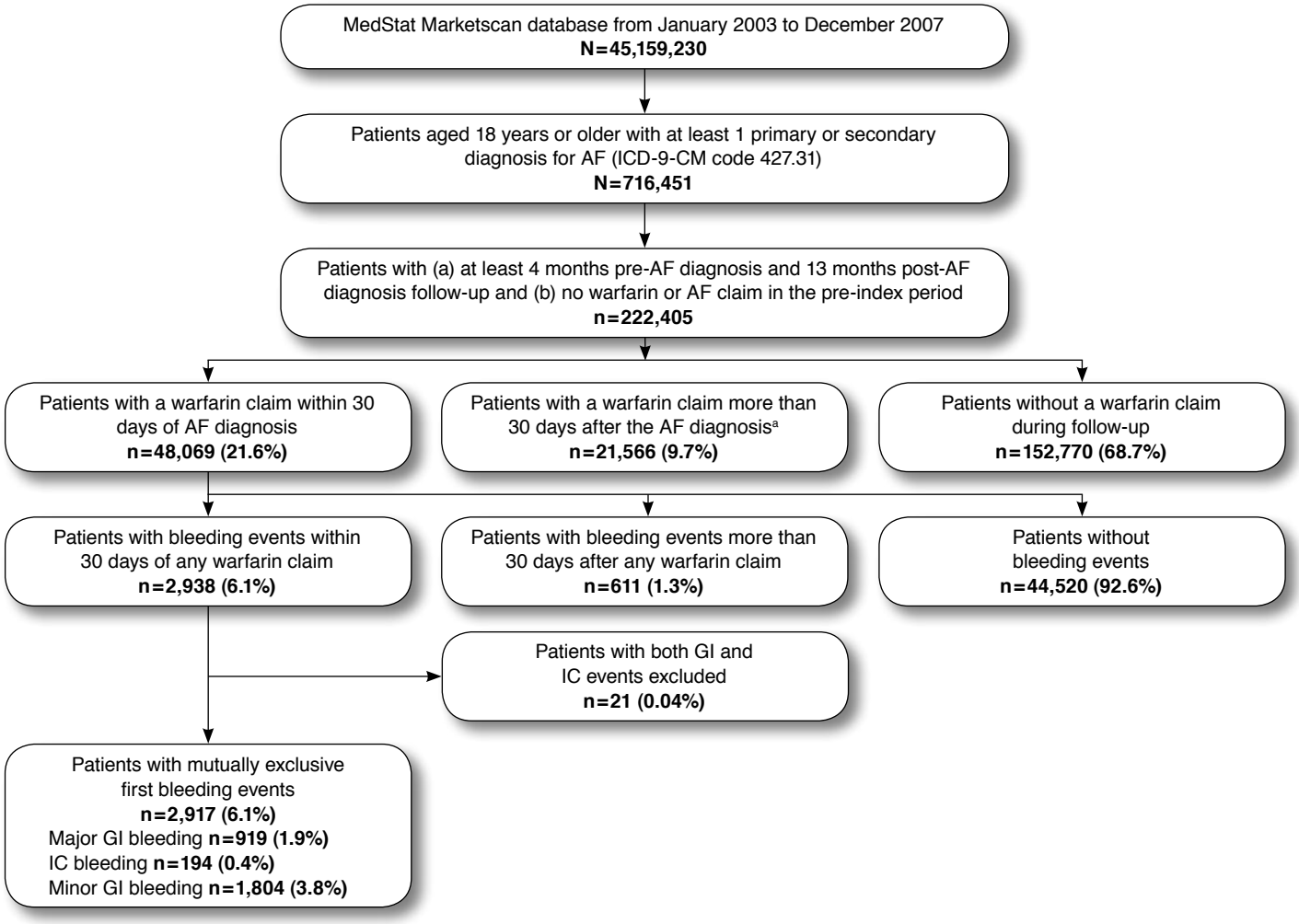
In cohorts with at least 1 bleeding event, health care utilization and cost associated specifically with a primary or secondary ICD-9-CM code for bleeding during the 12 months after the warfarin start date were reported separately. Because medical claims are not always coded properly, health care utilization and costs were assessed both for claims associated specifically with an ICD-9-CM code for bleeding and for all-cause health care claims during the 30 days following the first bleeding event to provide a more comprehensive view of health care resource utilization immediately after bleeding events. In addition, we assessed time from warfarin start date to first bleeding event and the number of days of warfarin supply before the first bleeding event.

Baseline comorbidities were assessed using the D'Hoore adaptation of the Charlson Comorbidity Index (CCI),[23] which assigns a comorbidity score based on age and the ICD-9-CM codes associated with a subject's medical claims during the 4-month pre-index period (Appendix). The CCI score was used in this study because it controlled for pre-existing conditions that may affect the risk of thrombotic and hemorrhagic adverse events, such as prior stroke and peptic ulcer disease.

Analysis

Descriptive statistics were used to assess differences in baseline characteristics between subjects with bleeding and those without. Tests of proportions were used to compare

FIGURE 2 Flowchart of Patient Selection Criteria



[a]*Patients with a first warfarin claim more than 30 days after the AF diagnosis (n=21,566, 9.7%) were excluded from the study.*
AF=atrial fibrillation; GI=gastrointestinal; IC=intracranial; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification.

distributions of age, gender, plan type, region, and comorbid conditions between subjects with and without bleeding events. The Wilcoxon rank-sum test was used to compare the number of hospitalizations, hospital days, ER visits, and outpatient office visits between subjects with and without bleeding. Health care cost data are typically non-normally distributed with a skew towards the right. Therefore, we used a generalized linear model (GLM) with gamma distribution and log link controlling for age, gender, region, insurance plan type, and CCI score. All analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC) and Stata Version 10.0 (StataCorp LP, College Station, TX) and an *a priori* statistical significance level of 0.05.

Results

Based on the study criteria, 716,451 subjects aged 18 years or older with at least 1 diagnosis of AF were identified in the Medstat Marketscan database between January 1, 2003, and December 31, 2007 (Figure 2). Of these, 222,405 subjects provided data for a 4-month pre-index period, did not have a claim for warfarin during the 4-month pre-index period, and provided at least 13 months post-index follow-up data. Of these subjects, 48,069 (21.6%) had at least 1 claim for warfarin within 30 days of AF diagnosis; 21,566 (9.7%) had a warfarin claim more than 30 days after AF diagnosis; and 152,770 (68.7%) did not have a warfarin claim during the 12-month follow-up period.

Of the 48,069 subjects who had a warfarin claim within 30

TABLE 2 Demographics and Characteristics of Subject Cohorts

	Subjects with Bleeding[a]						Subjects with No Bleeding (n = 44,520)	
	Major GI[a] (n = 919)		IC[a] (n = 194)		Minor GI[a] (n = 1,804)			
Mean [SD] age in years	73.9	[9.8][b]	74.5	[9.9][b]	72.7	[10.3][b]	70.4	[11.5]
Age group (years) % (n)								
< 50	1.4[b]	(13)	1.0[b]	(2)	2.1[b]	(37)	4.8	(2,145)
50-64	17.4[b]	(160)	18.6[b]	(36)	19.5[b]	(351)	25.2	(11,216)
65-79	49.0	(450)	42.3	(82)	51.8[b]	(935)	46.5	(20,711)
≥ 80	32.2[b]	(296)	38.1[b]	(74)	26.7[b]	(481)	23.5	(10,448)
Gender % (n)								
Male	55.8	(513)	57.2	(111)	55.5[c]	(1,001)	57.9	(25,789)
Female	44.2	(406)	42.8	(83)	44.5[c]	(803)	42.1	(18,731)
Plan type % (n)								
FFS	56.0[b]	(515)	54.1	(105)	56.0[b]	(1,010)	48.3	(21,509)
MCO	43.2[b]	(397)	44.3	(86)	41.5[b]	(748)	47.8	(21,295)
Unknown	0.8[b]	(7)	1.5	(3)	2.5[b]	(46)	3.9	(1,716)
Region % (n)								
Northeast	9.4	(86)	9.3	(18)	8.5	(154)	9.7	(4,335)
North-central	41.6	(382)	44.8[c]	(87)	40.7	(735)	37.0	(16,472)
South	28.6	(263)	23.7	(46)	30.7	(554)	30.2	(13,460)
West	19.8	(182)	21.6	(42)	18.7	(338)	19.8	(8,823)
Unknown	0.5	(5)	0.5	(1)	0.3	(5)	0.4	(196)
Not reported	0.1	(1)	0	(0)	1.0	(18)	2.8	(1,234)
Charlson Comorbidity Index % (n)								
0	4.1[b]	(38)	4.6[b]	(9)	6.5[b]	(117)	11.4	(5,086)
1	9.9[b]	(91)	13.4[c]	(26)	12.5[b]	(225)	16.6	(7,404)
2	19.6[b]	(180)	23.7	(46)	22.5[c]	(406)	25.2	(11,203)
3	29.7[b]	(273)	32.0[b]	(62)	26.8[b]	(484)	23.8	(10,589)
4 or more	36.7[b]	(337)	26.3	(51)	31.7[b]	(572)	23.0	(10,238)
Mean [SD] time from warfarin start date to first bleeding event in days	153.01	[105.22]	173.13	[100.72]	140.66	[109.87]	NA	
Mean [SD] number of days of warfarin supply prior to first bleeding event	168.23	[115.5]	184.51	[107.96]	152.8	[118.26]	NA	

[a]Based on first bleeding event occurring within 30 days following a warfarin claim during 12-month follow-up. Bleeding events were defined using primary or secondary diagnoses (Table 1). Major GI means that the first bleeding event was GI bleeding associated with an inpatient hospital stay, with no subsequent IC bleeding (n = 919); minor GI means that the first bleeding event was GI bleeding not associated with an inpatient hospital stay, with no subsequent major GI or IC bleeding (n = 1,804); and IC means that the first bleeding event was IC bleeding, with no subsequent GI bleeding (n = 194).

[b]P < 0.01 compared with the no-bleeding cohort using Stata (StataCorp LP, College Station, TX) test for proportions.

[c]P < 0.05 compared with the no-bleeding cohort using Stata test for proportions.

FFS = fee-for-service; GI = gastrointestinal; IC = intracranial; MCO = managed care organization; NA = not applicable; SD = standard deviation.

days of AF diagnosis, 44,520 (92.6%) had no bleeding events within 30 days of a warfarin claim; 2,938 (6.1%) had a bleeding event within 30 days of a warfarin claim; and 611 subjects (1.3%) had a bleeding event more than 30 days after a warfarin claim during the 12-month follow-up period after the warfarin start date (Figure 2). The latter group was excluded from data analysis.

Subjects with a bleeding event within 30 days of a warfarin claim were categorized based on the nature of the first (index) bleeding event they had during the follow-up period. The numbers of subjects who had first major GI bleeding, minor GI bleeding, and IC bleeding events were 926, 1,811, and 201, respectively. To maintain mutual exclusivity between the cohorts with GI bleeding and IC bleeding, a total of 21 subjects who had both GI and IC bleeding events after the warfarin start date were excluded from analysis, leaving a final total sample size of 47,437 (Figure 2). The final numbers of subjects in each cohort with bleeding were as follows: first major GI bleeding and no subsequent IC bleeding (n = 919, 1.9%), first minor GI bleeding and no subsequent GI or IC bleeding (n = 1,804, 3.8%), and first IC bleeding and no subsequent GI bleeding (n = 194, 0.4%). The majority of major GI, minor GI, and IC bleeding events occurred after the first 30 days of warfarin initiation. Among patients with bleeding (n = 2,917), the numbers (percentages) of patients with major GI, minor GI, and IC bleeding events within the first 30 days of the warfarin start date were 130 (14.1% of 919 with major GI bleeding), 282 (15.6% of 1,804), and 11 (5.7% of 194), respectively (data not shown in figure).

Table 2 provides the demographics and characteristics of

TABLE 3 Number of Hospitalizations, Length of Stay, ER Visits, and Office Visits in the 12 Months After First Warfarin Claim and 30 Days After First Bleeding Event[a]

	Subjects with Bleeding[a]						Subjects with No Bleeding n = 44,520	
	Major GI[a] n=919		IC[a] n=194		Minor GI[a] n=1,804			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Number of hospitalizations								
All-cause hospitalizations in 12 months after first warfarin claim	2.09[b]	1.36	1.94[b]	1.22	0.91[b]	0.98	0.98	0.98
Hospitalizations associated with ICD-9-CM codes for bleeding in the 12 months after first warfarin claim	1.11	0.40	1.09	0.37	NA	NA	NA	NA
All-cause hospitalizations within 30 days after first bleeding event	1.07	0.28	1.12[c]	0.38	0.05[c]	0.24	NA	NA
Hospitalizations associated with ICD-9-CM codes for bleeding within 30 days after first bleeding event	1.03	0.17	1.07[d]	0.30	NA	NA	NA	NA
Length of stay (hospital days)								
All-cause hospitalizations in 12 months after first warfarin claim	12.88[b]	19.10	13.10[b]	15.20	4.68	9.65	4.73	8.78
Hospitalizations associated with ICD-9-CM codes for bleeding in the 12 months after first warfarin claim	6.96	11.80	8.55[c]	11.20	NA	NA	NA	NA
All-cause hospitalizations within 30 days after first bleeding event	6.59	10.10	8.87	9.31	0.34[c]	2.81	NA	NA
Hospitalizations associated with ICD-9-CM codes for bleeding within 30 days after first bleeding event	6.21	9.23	7.88[c]	7.06	NA	NA	NA	NA
Number of ER visits								
All-cause visits in 12 months after first warfarin claim	2.72[b]	3.62	3.02[b]	3.46	1.93[b]	2.91	1.02	1.59
Visits associated with ICD-9-CM codes for bleeding in the 12 months after first warfarin claim	0.53	0.93	0.49	0.76	0.22[c]	0.57	NA	NA
All-cause visits within 30 days after first bleeding event	0.76	0.98	0.90	1.04	0.27[c]	0.77	NA	NA
Visits associated with ICD-9-CM codes for bleeding within 30 days after first bleeding event	0.36	0.61	0.38	0.65	0.09[c]	0.36	NA	NA
Number of outpatient office visits								
All-cause visits in 12 months after first warfarin claim	17.73[b]	12.49	14.52	8.91	17.49[b]	11.23	13.63	9.33
Visits associated with ICD-9-CM codes for bleeding in the 12 months after first warfarin claim	0.37	0.81	0.46	0.88	0.54	0.79	NA	NA
All-cause visits within 30 days after first bleeding event	1.73	1.64	1.13[c]	1.28	1.98[c]	1.74	NA	NA
Visits associated with ICD-9-CM codes for bleeding within 30 days after first bleeding event	0.19	0.49	0.18	0.46	0.35[c]	0.54	NA	NA

[a]Based on first bleeding event occurring within 30 days following a warfarin claim during 12-month follow-up. Bleeding events were defined using primary or secondary diagnoses (Table 1). Major GI means that the first bleeding event was GI bleeding associated with an inpatient hospital stay, with no subsequent IC bleeding (n = 919); minor GI means that the first bleeding event was GI bleeding not associated with an inpatient hospital stay, with no subsequent major GI or IC bleeding (n = 1,804); and IC means that the first bleeding event was IC bleeding, with no subsequent GI bleeding (n = 194). All statistical comparisons were made using the Wilcoxon rank-sum test.

[b]P < 0.01 in a comparison of cohorts with bleeding with the no-bleeding cohort.

[c]P < 0.01 in a comparison of IC with major GI and minor GI with major GI.

[d]P < 0.05 in a comparison of IC with major GI and minor GI with major GI.

ER = emergency room; GI = gastrointestinal; IC = intracranial; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; NA = not applicable; SD = standard deviation.

subjects in each cohort. Subjects with bleeding events were significantly older than subjects with no bleeding events ($P < 0.01$). Age distributions among the 3 bleeding cohorts were generally similar. The proportions of females in the cohorts with bleeding were statistically similar to that of the no-bleeding cohort, except that the proportion of females was significantly higher ($P < 0.05$) in the cohort with minor GI bleeding than in the no-bleeding cohort. The cohorts with major and minor GI bleeding (56.0% each) had a significantly higher proportion of subjects with fee-for-service (FFS) insurance compared with the no-bleeding cohort (48.3%), but there was no significant difference in insurance types between the cohort with IC bleeding (54.1% FFS) and the no-bleeding cohort. Subjects in all 3 cohorts with bleeding had significantly more comorbidities compared with the no-bleeding cohort ($P < 0.05$), except that the proportions of patients with CCI scores of 2 and 4 or more in the cohort with IC bleeding were similar to those of the no-bleeding cohort. The medication possession ratio for warfarin possession (calculated as the proportion of days covered by days supply of warfarin prior to first bleeding event) was more than 100% for each cohort with bleeding (data not shown). Therefore, it is likely that subjects were on

TABLE 4 *Unadjusted Mean Inpatient, Outpatient, and Pharmacy Costs by Study Cohort*

	Subjects with Bleeding[a]						Subjects with No Bleeding n = 44,520	
	Major GI[a] n = 919		IC[a] n = 194		Minor GI[a] n = 1,804			
	Mean ($)	SD ($)	Mean ($)	SD ($)	Mean ($)	SD ($)	Mean ($)	SD ($)
Inpatient costs								
All-cause inpatient claims in the 12 months after first warfarin claim	22,325[b]	47,507	25,124[b]	46,194	7,799[b]	44,992	12,382	28,689
Inpatient claims associated with ICD-9-CM codes for bleeding in the 12 months after first warfarin claim	11,830	23,596	19,273	36,852	—	—	—	—
All-cause inpatient claims within 30 days after first bleeding event	11,836	24,613	18,461[c]	28,752	720[c]	11,783	—	—
Inpatient claims associated with ICD-9-CM codes for bleeding within 30 days after first bleeding event	10,654	19,285	17,744[c]	27,982	—	—	—	—
Outpatient medical costs								
All-cause outpatient claims in 12 months after first warfarin claim	13,701[b]	28,870	12,969[b]	16,430	12,333[b]	23,183	8,388	15,929
Outpatient claims associated with ICD-9-CM codes for bleeding in the 12 months after first warfarin claim	432	1,686	1,526[c]	3,238	636	1,511	—	—
All-cause outpatient claims within 30 days after first bleeding event	1,747	4,995	2,866[c]	3,681	1,907[c]	3,520	—	—
Outpatient claims associated with ICD-9-CM codes for bleeding within 30 days after first bleeding event	230	677	839[c]	1,927	400	786	—	—
Outpatient pharmacy costs								
All-cause pharmacy costs in the 12 months after first warfarin claim	4,560[b]	4,152	3,811	3,682	4,217[b]	3,824	3,359	3,530
Totals								
Total all-cause costs in the 12 months after first warfarin claim	40,586[b]	65,164	41,903[b]	56,654	24,347	56,488	24,129	36,425
Total costs associated with ICD-9-CM codes for bleeding in the 12 months after first warfarin claim	12,262	23,692	20,799[c]	37,104	636[c]	1,511	NA	NA
Total all-cause costs within 30 days after first bleeding event	13,584	25,628	21,328[c]	29,056	2,627[c]	12,476	NA	NA
Total costs associated with ICD-9-CM codes for bleeding within 30 days after first bleeding event	10,893	19,304	18,583[c]	28,217	400[c]	786	NA	NA

[a]Based on first bleeding event occurring within 30 days following a warfarin claim during 12-month follow-up. Bleeding events were defined using primary or secondary diagnoses (Table 1). Major GI means that the first bleeding event was GI bleeding associated with an inpatient hospital stay, with no subsequent IC bleeding (n = 919); minor GI means that the first bleeding event was GI bleeding not associated with an inpatient hospital stay, with no subsequent major GI or IC bleeding (n = 1,804); and IC means that the first bleeding event was IC bleeding, with no subsequent GI bleeding (n = 194).

[b]P < 0.01 using a Wilcoxon rank-sum test to compare bleeding cohorts with the no-bleeding cohort.

[c]P < 0.01 using a Wilcoxon rank-sum test to compare IC with major GI and minor GI with major GI.

GI = gastrointestinal; IC = intracranial; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; NA = not applicable; SD = standard deviation.

uninterrupted warfarin therapy from warfarin start date to the date of first bleeding event.

Health Care Resource Use

During the 12 months after the first warfarin claim, several all-cause utilization measures were significantly higher for subjects with a major GI or IC bleeding event than for those without a bleeding event (Table 3). These included hospitalizations (2.09 and 1.94 vs. 0.98, respectively, $P < 0.001$), hospital days (12.88 and 13.10 vs. 4.73, $P < 0.001$), and ER visits (2.72 and 3.02 vs. 1.02, $P < 0.001$). All-cause outpatient office visits were significantly higher for subjects with major GI bleeding events (17.73 vs. 13.63, $P < 0.001$) compared with those without bleeding events. Subjects with minor GI bleeding had significantly fewer all-cause hospitalizations but significantly more ER visits and outpatient office visits ($P < 0.001$) than subjects with no bleeding events. Among the cohorts with bleeding, the length of stay for hospitalizations that were associated with a primary or secondary ICD-9-CM code for bleeding was significantly longer ($P < 0.001$) in subjects with IC bleeding than subjects with major GI bleeding during the 12 months after the first warfarin claim.

In the 30 days immediately after the first bleeding event, subjects with IC bleeding had significantly more all-cause hospitalizations ($P < 0.001$) but significantly fewer outpatient office visits ($P < 0.001$) than subjects with major GI bleeding (Table 3). Subjects with minor GI bleeding had fewer all-cause hospitalizations, hospital days, and ER visits ($P < 0.001$) but significantly more outpatient office visits ($P < 0.001$) during the 30 days after the first bleeding event compared with subjects with major GI bleeding. Subjects with IC bleeding had significantly more hospitalizations and hospital days associated with a diagnosis of bleeding ($P < 0.001$) than subjects with major GI bleeding during the 30 days after the index bleeding event.

TABLE 5 Gamma Regression Model of All-Cause 12-Month Costs (N = 47,437)

	Adjusted Coefficients	95% Confidence Interval		*P* Value
Intercept	10.7064	10.3419	11.0708	<0.001
Age (years)	-0.0041	-0.0151	0.0070	0.471
Age (squared)	-0.0002	-0.0003	-0.0001	<0.001
Gender				
Male	Reference			
Female	-0.0217	-0.0471	0.0036	0.093
Insurance type				
FFS	Reference			
MCO[a]	0.2463	0.2192	0.2734	<0.001
Unknown	-0.3045	-0.3706	-0.2383	<0.001
Baseline CCI				
0	Reference			
1	0.3321	0.2803	0.3839	<0.001
2	0.5726	0.5165	0.6288	<0.001
3	0.8203	0.7589	0.8817	<0.001
4 or more	1.1130	1.0512	1.1749	<0.001
Bleeding events[b]				
No bleed	Reference			
Minor GI[b]	0.0087	-0.0557	0.0730	0.792
Major GI[b]	0.4896	0.4003	0.5789	<0.001
IC[b]	0.6435	0.4510	0.8360	<0.001

[a]MCO health plans include exclusive provider organizations, health maintenance organizations, point-of-service plans, PPOs, PPOs with capitation, and consumer-driven health plans.

[b]Based on first bleeding event occurring within 30 days following a warfarin claim during 12-month follow-up. Bleeding events were defined using primary or secondary diagnoses (Table 1). Major GI means that the first bleeding event was GI bleeding associated with an inpatient hospital stay, with no subsequent IC bleeding (n = 919); minor GI means that the first bleeding event was GI bleeding not associated with an inpatient hospital stay, with no subsequent major GI or IC bleeding (n = 1,804); and IC means that the first bleeding event was IC bleeding, with no subsequent GI bleeding (n = 194).

CCI = Charlson Comorbidity Index; FFS = fee-for-service; GI = gastrointestinal; IC = intracranial; MCO = managed care organization; PPO = preferred provider organization.

Inpatient, Outpatient, Pharmacy, and Total Costs

Inpatient Costs. In the 12 months after the warfarin start date, subjects with a major GI bleeding or IC bleeding event had significantly higher unadjusted all-cause mean inpatient costs than subjects with no bleeding events ($P < 0.001$), but subjects with minor GI bleeding had significantly lower unadjusted mean all-cause inpatient costs than subjects with no bleeding events ($P < 0.001$; Table 4). In the 12 months after the warfarin start date, 53.0% and 76.7% of unadjusted mean inpatient costs in subjects with major GI and IC bleeding, respectively, were from claims with ICD-9-CM codes for bleeding (percentages not shown in table).

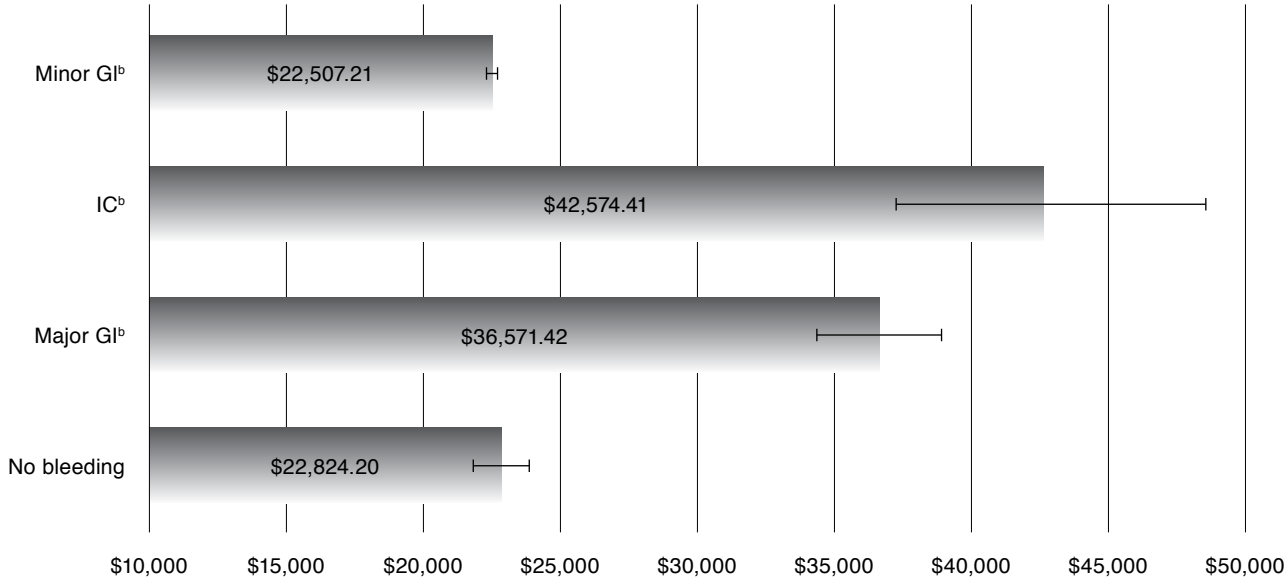
About 53.0% and 73.5% of unadjusted mean all-cause inpatient costs in the 12 months after the first warfarin claim occurred within the 30 days after the first bleeding event among subjects with major GI bleeding and IC bleeding, respectively (Table 4; percentages not shown in table). In contrast, only 9.2% of unadjusted mean all-cause inpatient costs in the 12 months after the warfarin start date occurred during the 30 days after the first bleeding event in the cohort with minor GI bleeding. As expected, unadjusted mean all-cause inpatient cost in the 30 days after the first bleeding event was significantly higher in the cohort with major GI bleeding than in the cohort with minor GI bleeding ($P < 0.01$) but significantly lower ($P < 0.01$) than in the cohort with IC bleeding. During the 30 days after the first bleeding event, the unadjusted mean inpatient cost associated with a diagnosis of bleeding was also higher for subjects with IC bleeding than for subjects with major GI bleeding ($P < 0.01$).

Outpatient Costs. Unadjusted mean all-cause outpatient medical costs (including ER visits and outpatient office visits) in the 12 months after the warfarin start date were also significantly higher for all cohorts with bleeding than for the no-bleeding cohort ($P < 0.001$; Table 4). During the 12 months after the first warfarin claim, ER and outpatient office visit claims with diagnosis codes for bleeding accounted for only 3.2%, 11.8%, and 5.2% of unadjusted mean all-cause outpatient medical costs in the cohorts with major GI bleeding, IC bleeding, and minor GI bleeding, respectively (percentages not shown in table).

About 12.8%, 22.1%, and 15.5% of unadjusted mean all-cause outpatient medical costs in the 12 months after the warfarin start date were incurred in the 30 days after the first bleeding event in the cohorts with major GI bleeding, IC bleeding, and minor GI bleeding, respectively (Table 4; percentages not shown in table). Unadjusted mean all-cause outpatient costs in the 30 days after the first bleeding event were significantly lower in the cohort with major GI bleeding than in the cohorts with IC bleeding and minor GI bleeding ($P < 0.01$). In the 30 days after the first bleeding event, the unadjusted mean outpatient costs for claims with an ICD-9-CM code for bleeding were significantly lower in the cohort with major GI bleeding than in the cohort with IC bleeding ($P < 0.01$). Unadjusted mean outpatient pharmacy costs were significantly higher in subjects with major GI and minor GI bleeding than in subjects without bleeding (both $P < 0.001$) during the 12 months after the warfarin start date, but the difference between subjects with IC bleeding and subjects with no bleeding was not significant.

Total Unadjusted Costs. Unadjusted overall mean total all-cause costs in the 12 months after the warfarin start date were significantly higher for subjects with major GI or IC bleeding than for the no-bleeding cohort, but there was no significant difference between the cohorts with minor GI bleeding and no bleeding (Table 4). Claims with a diagnosis of bleeding accounted for 49.6%, 30.2%, and 2.6% of unadjusted mean

FIGURE 3 Mean Adjusted All-Cause 12-Month Health Care Costs[a]



[a]Measured during the 12 months following the warfarin start date. Mean adjusted costs (bars) and 95% confidence intervals (lines) were obtained as least-squares means (LSmeans) in a generalized linear regression model. Mean costs were adjusted for age, gender, region, insurance type, and comorbidities.

[b]Based on first bleeding event occurring within 30 days following a warfarin claim during 12-month follow-up. Bleeding events were defined using primary or secondary diagnoses (Table 1). Major GI means that the first bleeding event was GI bleeding associated with an inpatient hospital stay, with no subsequent IC bleeding (n = 919); minor GI means that the first bleeding event was GI bleeding not associated with an inpatient hospital stay, with no subsequent major GI or IC bleeding (n = 1,804); and IC means that the first bleeding event was IC bleeding, with no subsequent GI bleeding (n = 194).

GI = gastrointestinal; IC = intracranial.

total costs in the 12 months after the warfarin start date in patients with IC bleeding, major GI bleeding, and minor GI bleeding, respectively (percentages not shown in table). About 50.9%, 33.5%, and 10.8% of unadjusted mean total all-cause costs in the 12 months after the warfarin start date were incurred within 30 days of the first IC, major GI, and minor GI bleeding events, respectively.

Generalized Linear Model Results. Table 5 presents results of the GLM regression of overall total all-cause costs during the 12 months after the warfarin start date controlling for demographics and comorbidities. Subjects with major GI and IC bleeding had overall adjusted mean total costs that were 49% and 64% higher, respectively, compared with subjects with no bleeding events. The adjusted difference in overall mean total costs between subjects with minor GI bleeding and subjects with no bleeding was not significant. As expected, overall adjusted mean total all-cause costs were highly influenced by baseline health status as assessed by the CCI. Compared with subjects with no comorbidities, subjects with a CCI score of 1 had 33% higher overall adjusted mean total costs, but overall adjusted mean total cost was 111% higher for subjects with a CCI score of 4 or more. Subjects in managed care plans had 25% higher overall adjusted mean total costs compared with subjects with FFS insurance. After controlling for demographics, insurance type, and comorbidities, the mean adjusted all-cause annual costs obtained from the regression model were $42,574, $36,571, $22,824, and $22,507 for subjects with IC bleeding, major GI bleeding, minor GI bleeding, and no bleeding, respectively (Figure 3).

Discussion

This study found that all-cause health care utilization and costs among warfarin-treated patients with AF are significantly higher for patients with major GI or IC bleeding events than for patients with no bleeding events. While the higher cost observed in subjects with major GI and IC bleeding events was driven primarily by inpatient service utilization, subjects with minor GI bleeding used significantly more outpatient health care resources. Findings of the current study may be used in cost-effectiveness models comparing different treatment options, including newer anticoagulants.

Previous studies using administrative claims have identified costs and resource utilization of bleeding events measured by claims with ICD-9-CM codes for bleeding.[17,18] However, medical coding is not always accurate. Patients may have

complications related to the first bleeding event that require medical attention but may not be recorded as related to the bleeding event. The current study tried to address this limitation by assessing health care and resource utilization within 30 days after the first bleeding event. Although the choice of a 30-day period was arbitrary, the 30-day cost data can complement cost estimates limited to claims with diagnosis codes for bleeding to offer a more comprehensive picture of the health care resources required to manage warfarin patients during the period immediately following a bleeding event.

The rate of anticoagulation observed in the present study (21.6%) was considerably lower than the rate of 65% previously reported by the Fibrillation Registry Assessing Costs, Therapies, Adverse events, and Lifestyle (FRACTAL) study.[12] The FRACTAL study is an AF registry with patients enrolled from 17 academic medical centers in the United States and Canada. The Medstat MarketScan database used in the current study includes patients from a variety of practice settings. Regional differences in practice patterns may make a difference in warfarin utilization. Also, academic medical centers tend to have better infrastructure to facilitate international normalized ratio (INR) monitoring than other community practice settings. The availability of this infrastructure in the FRACTAL study may have increased physicians' comfort in prescribing warfarin compared with other settings.[24] Finally, the inclusion criteria imposed in the current study were stringent and may have resulted in conservative estimates of anticoagulation.

The prevalence of minor GI bleeding observed in our study (3.8%) is within the range reported in published clinical trials (1.5% to 14.0%).[25,26] However, the prevalence rates of major GI or IC bleeding events in the present study sample were slightly higher than those observed in previously published clinical trials. In a recent meta-analysis of the efficacy and safety of antithrombotic therapy in AF, the incidence rates for IC and major extracranial hemorrhage for patients receiving adjusted-dose warfarin therapy were 0.2% and 1.0%,[27] compared with 0.4% and 1.9% in the present study.

While IC bleeding is a life-threatening medical condition and always results in a hospitalization and inpatient claim, it is important to note that the definition of major GI bleeding used in this study is somewhat different from definitions commonly used in clinical trials. Due to data availability, we defined major GI bleeding as a bleeding event associated with a hospitalization without consideration of the source of bleeding, hemoglobin level, or blood transfusion requirement.[28] The less stringent definition of major bleeding used in this study might have resulted in a slightly higher rate of major GI bleeding than in published clinical trials. It has also been noted that clinical trials tended to include patients who had received warfarin therapy for varying lengths of time without major bleeding events prior to study entry or patients who were at lower risk of bleeding.[27] The inclusion of "warfarin-experienced" or lower bleeding risk subjects in previous clinical trials could probably bias toward a lower bleeding rate than inclusion of warfarin-naïve subjects, for whom the current study was targeted. Nevertheless, it is important to note that more recent clinical trials of dabigatran and rivaroxaban versus warfarin therapy observed higher rates of bleeding associated with warfarin than reported in previous warfarin trials and in the current study.[29-31] These differences highlight the challenges in comparing bleeding rates across studies of different patient populations, study designs, and bleeding definitions.

The current study adds to the available data on the costs of warfarin-associated bleeding by providing cost data specific to different types of bleeding events in a nationally representative sample of AF patients covered by commercial insurance. A recently published study by Kim et al. (2010) assessed hospitalization cost associated with warfarin-related bleeding events in older community-dwelling adults who were beneficiaries of the Pennsylvania Pharmaceutical Assistance Contract for the Elderly.[17] The authors reported that the mean (standard deviation) hospitalization cost associated with a warfarin-related hospitalization was $10,819 ($11,536). Results for major GI and IC bleeding were not reported separately by Kim et al. Additionally, the study by Kim et al. was conducted with low-income elderly residents who received prescription assistance from the state of Pennsylvania and thus may have limited generalizability to a commercial insurance plan. The current study was not limited to elderly patients receiving warfarin in a specific geographical region, and the results may be generalizable to commercially insured patients. Also, the current study provides estimates of all-cause and bleeding-related costs associated with individual bleeding events.

Our study also represents one of the first attempts to estimate the cost associated with minor bleeding in warfarin patients. Minor bleeding events are generally considered nonthreatening in nature, since they do not result in an inpatient hospitalization or blood transfusion. The minor bleeding events identified in this study, however, were clinically relevant as they required medical management resulting in outpatient claims associated with bleeding diagnoses. In this study, we found the outpatient and pharmacy cost and resource requirement cost in managing patients with minor GI bleeding to be similar and in a few comparisons higher than patients with major GI bleeding events. Although the health care costs associated with treating minor GI bleeding are substantially lower compared with major bleeding events, these costs are still relevant for health care organizations focused on the delivery of outpatient care.

Limitations

The findings of this study should be viewed in light of several limitations. First, the study may have been subject to selection

bias. The study required subjects to provide at least 13 months of follow-up data after the first AF diagnosis date. Therefore, subjects who discontinued health plan coverage or died during the follow-up period were not included in the study. These patients may have incurred higher or lower costs, which are not reflected in the current study findings. This methodological limitation would certainly affect the cost estimate for IC bleeding more than GI bleeding because the former is associated with a much higher mortality rate. Unfortunately, the Medstat MarketScan database does not contain information for death; therefore, patients who die during the study period cannot be identified.

Second, as with other retrospective claims data analysis, in the absence of additional clinical information, the causal relationship between bleeding events and warfarin therapy cannot be confirmed. We also do not have laboratory data to confirm the differentiation of major and minor bleeding events using hemoglobin levels.[32] Third, patients were categorized based on the first occurrence of a bleeding event. Patients who had both GI and IC bleeding events (n = 21) were excluded from the analysis to keep the cohorts mutually exclusive. In addition, patients in the minor GI bleeding cohort were required to have no inpatient claim associated with diagnosis of GI bleeding or any claim associated with a diagnosis of IC bleeding. These methods of exclusion and classification may have led to an under-representation of the economic impact of minor GI bleeding, especially in situations in which minor GI bleeding was followed by major GI bleeding. Therefore, the cost estimates reported in the current study should be interpreted within the context of the bleeding definitions and methodology used in the study.

Fourth, matching was not conducted in this study, and the significant difference observed in the unadjusted resource utilization and health care costs among the bleeding and no bleeding cohorts may be due to the observed differences in age and comorbidities. It is also possible that patients with more comorbidities are more frail, are at higher risk of drug interaction, and are more likely to experience bleeding when put on warfarin therapy. Previous studies have reported higher costs among older patients.[33,34] The mean adjusted costs obtained from the GLM analysis adjusted for measurable confounders. However, unmeasured confounders may still have influenced the results of this study.

Conclusion

Major GI and IC bleeding events in warfarin-treated patients with AF occurred rarely but were associated with higher inpatient, outpatient, and prescription drug utilization and costs. The cost of bleeding should be considered when evaluating the cost-effectiveness of anticoagulant therapy.

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DISCLOSURES

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APPENDIX Charlson Comorbidity Index[a]

Comorbidity	D'Hoore ICD-9-CM Codes	Charlson Weight
Myocardial infarction	410, 411	1
Congestive heart failure	398, 402, 428	1
Peripheral vascular disease	440-447	1
Cerebrovascular disease	430-433, 435	1
Dementia	290, 291, 294	1
Chronic obstructive pulmonary disease	491-493	1
Rheumatologic disease	710, 714, 725	1
Peptic ulcer disease	531-534	1
Mild liver disease	571, 573	1
Diabetes	250 (excluding 250.4-250.6)	1
Hemiplegia or paraplegia	342, 434, 436, 437	2
Moderate or severe renal disease	403, 404, 580-586	2
Diabetes with complications	250.4-250.6	2
Malignancy	200, 202, 203	2
Moderate or severe liver disease	070, 570, 572	3
Metastatic solid tumor	196-199	6
AIDS	042-044	6

[a]The CCI encompasses 19 medical conditions weighted on a scale of 16. From the weighted conditions, a summed score can be tallied to yield the total comorbidity score. To account for increasing age, 1 point is added to the CCI score for each decade of life over the age of 50 years (1 point for 60-69 years, 2 points for 70-79 years, 3 points for 80 or older.) Thus, possible CCI scores range from 0 to 36.
AIDS = acquired immune deficiency syndrome; CCI = Charlson Comorbidity Index; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.