Estimating the inpatient and outpatient costs of atrial fibrillation and associated adverse events

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INTRODUCTION

Atrial Fibrillation (AF) is the most common arrhythmia in the United States.[1] The disease affects both genders, with a lifetime risk of 1 in 4 for both men and women over the age of 40.[2] The risk of AF increases with age and as the elderly population increases, so will the prevalence of AF.[2] The prevalence of AF in the U.S. is projected to increase from 2.7 million in 2010 to 6 million by 2050.[3] AF alone is associated with a 4- to 5- fold increase risk of ischemic stroke, is attributable to 15% of strokes in persons <80, and 24% of ischemic strokes in person 80 to 89 years old.[4] In addition to ischemic stroke, patients with AF are at risk for other thrombotic events such as myocardial infarction (MI) and systemic embolism (SE).

The primary goal in treating AF is stroke prevention. The $CHADS_2$ score (Congestive heart failure, Hypertension, Age 75 or older, Diabetes, and history of Stroke) is a tool used to estimate risk of stroke and identify those patients who would most benefit from an anticoagulant. However, treatment with an anticoagulant is associated with increased risk of bleeding. Bleeding can be minor – a nosebleed or increased bruising – but there is risk of serious adverse events including gastrointestinal (GI) bleeds and intracranial hemorrhages (ICH), both of which necessitate hospitalization.

Healthcare utilization associated with AF is substantial and has been shown to be driven by hospitalizations.[5-9] Diagnosis with AF is associated with increased morbidity and mortality.[10-14] In the last several years three new anticoagulant options have come on to the market, altering the risk/benefit profile of stroke prevention therapy. In today's environment of limited resources, health technology assessment is an increasingly important aid to guiding resource use and is being used to compare treatment strategies in AF patients.[15-22]

The development of useful decision analytic models in atrial fibrillation (AF) is contingent on accurate estimates of costs. Estimated costs of AF include not only the cost of treating underlying AF, but also of treating the adverse clinical events occurring in the context of treatment. The safety and efficacy endpoints commonly used in AF clinical trials are ischemic stroke, MI, SE, ICH and GI bleed [23-26] impactful and costly events leading to hospitalization and associated with high morbidity and mortality. [2,27-28] AF cost-effectiveness (CEA) models typically focus on modeling the risk-benefit of these five events but, to date, have not incorporated AF specific event costs.[15-22] If costs of these events are different in the AF population than the general population from which the costs are derived, failure to incorporate AF specific costs may lead to over or under estimation of the cost-effectiveness of AF therapy options.

In AF, the traditional efficacy endpoint has been ischemic stroke and traditional safety endpoint bleeding events like ICH and GI bleed. To date, only two studies have quantified the incremental cost of ischemic stroke in patients with AF. These studies are of limited use in current research. One study used the Medicare 5% claims database, thereby limiting those included to patients over the 65 years of age and excluding out-of-pocket costs;[29] the other used health plan claims, but with cost data that is now more than a decade old.[30] Additionally, patients with previous stroke or bleed events were excluded from analysis possibly biasing results toward lower costs because prior history of stroke or bleed increases the risk of recurrent events and the subsequent cost of events.[29]

In terms of safety endpoints, four claims-based studies have characterized incremental costs of bleeding events in the AF population.[29-32] Two of these studies did not separate out ICH and GI bleed, reporting only composite major bleeds. [30,32] The combination of severe and less severe bleeding events reduces interpretability of presented cost estimates and does not allow for direct interpretation with clinical trial data or allow for direct use in CEAs.

Of the two studies that reported costs separately, one was in Medicare patients[29] and excluded out-of-pocket costs; the other used MarketScan Database.[31] The MarketScan analysis reported the annual percent increase in healthcare costs from baseline controls and annual total healthcare costs, but not the direct incremental cost of a bleed (GI or ICH) and did not report results for less than 12 months of follow-up.[31] Lack of incremental costs and reporting only 12 month totals, limits the translation of this research into CEA models. Furthermore, though SE and MI are widely used as clinical endpoints in AF clinical trials, their costs have not yet been estimated in the U.S. AF patient population.

This study builds on previous analyses by describing the incremental costs, over time, of key adverse events in a AF, a disease with increasing prevalence in the U.S.. The aim of this study was to describe the incremental 30, 90, 365 day costs of a stroke, MI, SE, ICH, or GI bleed hereafter termed '*event of interest',* in patients with AF. To determine the cost of each event of interest, separate from baseline AF costs, a matched (1:4) retrospective cohort study was conducted, comparing incremental costs in AF patients who had an event, to AF patients who did not have an event.

METHODS

Data Source

Data used for the analysis were derived from the Truvan Health MarketScan® 2007 to 2011 Commercial Claims and Medicare Supplemental and Coordination of Benefits Databases. The MarketScan Databases contain individual-level, de-identified, HIPAA compliant, enrollment history, inpatient, outpatient, and pharmacy claims information from more than 95 million employees, dependents, and retirees in the United States. The Commercial Claims Database includes private-sector health data from over 100 payers and represents more than 500 million claim records annually. The Medicare Supplemental and Coordination of Benefits Database contains claims information on Medicare recipients who subscribe to Medicare supplemental coverage through privately insured fee-for-service (FFS), point of service (POS), or capitated health plans. Data from individual patients are integrated from all providers of care, maintaining all healthcare utilization, claim payments, and out-of-pocket payment connections at the patient level. The database has been widely used to describe costs in different patient populations. The study was reviewed and approved under exempt status by the Institutional Review Board at the University of Washington.

Study Cohort Identification

The study cohort consisted of adults ≥18 years old with the first diagnosis of AF between January 1, 2007 and December 31, 2010. (Figure 1) First diagnosis of AF was identified by two outpatient claims within 365 days of each other or one inpatient claim with a *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) code 427.31 for AF. Subjects were eligible for inclusion if they had at least 12 months of continuous medical and pharmacy enrollment and no AF claims in the 12 months prior to index diagnosis (baseline period); the latter requirement to identify incident AF. Subjects were excluded if they had any diagnosis codes indicating valve replacement during baseline or follow-up or had more than one event of interest during the follow-up period. (Table 1)

Because duration of AF can affect medical costs, the study was limited to patients with incident AF.

Patient Characteristics

Demographic information including age, sex, type of insurer (employer versus health plan administrator), type of health plan and geographic region were assessed at index diagnosis. Total inpatient and outpatient healthcare costs (paid claims and out-of-pocket patient payments) were captured during the baseline period. Comorbidities and risk factors were assessed during the baseline period. The risk of stroke was quantified using the $CHADS_2$ score[33] while the Deyo adaptation of the Charlson Comorbidity Index (CCI)[34] quantified co-morbidity burden. (Table 1) The presence of comorbidities and risk factors was determined by at least one claim in the baseline period. Patients with previous ischemic or bleeding events were not excluded from the cohort instead, risk scores and total medical cost in the baseline period were adjusted for in the analysis.

Event Identification

Cases were identified as those AF patients who had an event of interest after the date of index diagnosis. All patients with incident AF were followed for first inpatient admission lasting greater than one day with a primary diagnosis of an event of interest using validated ICD-9 codes for administrative data. (Table 1)[35-38] Patients were excluded if the event was due to traumatic brain injury since those events were assumed to not be due to AF. For ease of analysis, if patients had a second hospitalization for an event of interest within 365 days of the first admission they were also excluded. After the date of the event of interest was identified, continuous pharmacy and medical enrollment was assured for the following 12 months. Patients who died during their admission or who did not have 12 months of follow up were excluded.

Matching

Cases were matched to controls in a 1:4 ratio using a greedy matching algorithm. Controls were subjects with AF but without an admission for an event of interest. Because disease duration can affect medical costs, it was important to match cases and controls on time between date of index diagnosis and date of event. To facilitate matching, a random date after AF diagnosis through 12/31/2010 was generated for the control group. The random date was used as a proxy for date of event of interest and used to match on months from AF diagnosis to month of event. Additionally, cases were matched to controls on gender, month of AF diagnosis, and geographic region. Age was intentionally not matched on to allow for analysis of the impact of age on medical costs. Unmatched cases and controls were excluded from final analysis.

Outcomes

The primary outcomes of interest were the incremental costs of each type of event of interest at 30, 90, and 365 days. Costs included all payer and out-of-pocket expenses for inpatient and outpatient claims; pharmacy claims were not included. Costs were inflated to 2012 US$. Control patients who did not have an event of interest were used to estimate the baseline cost of treating AF. The incremental cost of each event type was estimated as the difference in average costs between patients with events and their matched controls.

Statistical Analysis

Univariate, descriptive analyses were conducted to estimate means with standard deviations for continuous variables and counts with percentages for categorical variables by case and control. For bivariate analyses, total average costs for cases and matched controls were compared using a 2-sided, 2-sample t-test assuming unequal variance; and compared to use of a simple ordinary least squares (OLS) regression with robust standard errors. Both

tests assumed a significance level of α=0.05. Stratified analyses were conducted to estimate costs at 30, 90, and 365 days.

To adjust for potential confounders that remained after matching, models estimating the incremental costs of events of interest were adjusted for the following covariates: age at AF diagnosis, $CHADS_2$ score, CCI score, baseline total inpatient and outpatient costs (including all claims and out-of-pocket payments), and type of health plan structure. Multivariate analyses were conducted using generalized linear modeling (GLM) and generalized estimating equations (GEE); multiple modeling techniques were used to allow model comparison for learning purposes. A flexible generalization of ordinary linear regression, GLM allows for dependent outcomes (in this case, cost variables) to have a non-normal distribution. GLM models require specification of a 'link' function to model the relationship between the dependent variable and the linear combination of independent variables and covariates, and an associated 'family' function to model the distribution of the dependent variable. Specifying GLM with the Gaussian distribution and identity link is the same as OLS. Specifying the gamma distribution and log (transformation) link allows for the regression to take into account the impact of right skewed (non-normal distribution) nature of cost data and is commonly used in conducting cost analyses. GEE is a specific type of GLM that allows correlations in the data to be taken into account; the same links and distributions are specified. The matching process induces correlation (thereby violating assumptions of independence) and GEE accounts for this in the regression. GEE using the Gaussian distribution, identity link, and independent correlation structure was evaluated, and is also the same as OLS; GEE using the Gaussian distribution, identity link, and the exchangeable correlation structure accounts for the induced correlation. GEE specifying the gamma distribution, log link, and exchangeable correlation structure accounts for the skewed nature of the cost data, while also taking into account the correlated nature of our data. All multivariate analyses included the use of robust standard errors and assumed a significance

level of α=0.05. All analyses were conducted using StataMP version 12.1 (StataCorp, College Station, TX).

RESULTS

Study Population

From 31,961,861 unique persons with an AF diagnosis between January 1, 2008 and December 31, 2010, 194,588 had 12 months of continuous enrollment preceding their diagnosis. (Table2) After applying additional exclusion criteria 1,788 patients who experienced one event of interest were identified along with 113,581 potential controls. (Figures 1 and 2) Table 2 compares the characteristics of potential cases and potential controls and is categorized by variables included in the matching and those included in the regressions (non-matched). Gender was well balanced between cases and potential controls. As an entire cohort, cases and controls were largely covered under a non-employer administered plan (>70%) and from the South and North Central regions of the U.S. (>53%). On average, the pre-matched cases were older (72:66 case:control), more often covered by comprehensive medical health plan, less often Fee-For-Service plan, and had a higher $CHADS_2$ Score and CCI Score. Matching was successfully completed on gender, health plan design and region, with only 4 cases not being matched. On average, cases had higher $CHADS_2$ and CCI scores compared to their controls.

Ischemic and Bleeding Events

All events were balanced by gender. (Table 2) When comparing age across types of events, those patients experiencing SE were youngest (68), while those experiencing ischemic strokes were the oldest (74). Ischemic events included stroke, MI, and SE and represented 72% of events of interest. MI occurred most frequently, with 512 cases out of 1,292 ischemic events and 1,788 total events of interest. Stroke occurred in 0.4%, MI in 0.6%, and SE in 0.3% of the AF population at risk while ICHs occurred in 0.06% and GI bleeds occurred in 0.4% of the AF population at risk (data not shown).

Costs

For all events of interest, overall healthcare costs at 30 days, 90 days and 365 days were significantly higher in cases than controls, but the magnitude of the difference diminished over time. (Table 3) The mean incremental cost of an ischemic stroke over baseline healthcare costs, 30 days after the event, was $20,710, an MI was $32,535, a SE $15,754, an ICH $45,242, and a GI bleed was $14,823 (2012 US$). At all time points, ICH was the most costly event and maintained the largest difference from controls and from 30 day costs. SE and GI Bleed were associated with the lowest costs, comparatively, followed by ischemic stroke. However after ICH, SE and MI maintained the largest cost difference between 30 and 365 days.

Model Selection

Table 4 provides a detailed comparison of the incremental costs associated with each event of interest when using a variety of regression techniques. Moving forward, appropriate model selection depends on the skewed (non-normal) distribution of the dependent variable, costs as a continuous outcome, and accounting for correlation in data that is introduced via the matching process. Due to the correlation and non-normal continuous outcome, the appropriate models are GEE with log link, gamma distribution, and exchangeable correlation structure.

DISCUSSION

This study characterized the incremental healthcare costs associated with key adverse events in newly diagnosed AF patients in the MarketScan Commercial Claims and Medicare Coordination of Benefits Databases. The findings suggest that occurrence of an adverse event is rare but costly. After 365 days costs had not returned to baseline, supporting previous studies suggesting that financial impact of events of ischemic and hemorrhagic events last beyond the initial admission. These findings build on previous cost per ischemic and hemorrhagic event by characterizing the incremental cost of an event of interest.

Ischemic Events

To date, this is the first study to look at the incremental cost of all five events: stroke, MI, SE, ICH, and GI Bleed using the large MarketScan database and to include patient out-of-pocket costs in the estimates. Despite long standing evidence that strokes in the AF population are more severe than those in the non-AF population, there is limited data on the incremental cost of ischemic stroke in this population.[14] Using the Medicare 5% sample, Mercaldi et al. estimated the one year incremental cost of an ischemic stroke in AF at $34,772 (2011 US$), which is slightly greater than the $29,128 (2012 US$) estimate found in this study; the difference may be due to the differences in the population studied, adjustments in the models, and sampling error.[29] Both estimates from Mercaldi et al. and our study are on the high end of stroke estimates for the general population reported in a systematic review by von Scheele et al. ($2,138 – $45,875) supporting observational studies that ischemic stroke in AF is more costly than in the general population.[39]

To date, no studies have characterized the incremental cost of SE and MI in the AF patient population. Therefore, this research presents an opportunity to add to the AF literature. MI has been characterized as costing about $18,000 for the initial hospitalization.[40] Our study suggests that an MI in patients with AF may be more costly, with an incremental cost of

$32,535 at 30 days and $38,651 at 365 days after the event (2012 US$). Though the occurrence of SE's has been widely reported in clinical trials of AF, the costs have not been described in the literature. This study indicates that SE's are costly events, similar in magnitude to stroke and GI bleed and are an important healthcare cost in the AF population.

Bleeding Events

Our study is the first to characterize the incremental cost of different types of bleeding events in the AF population. We estimate the annual incremental cost of an ICH to be $77,513 (2012 US$). This estimate is higher than other incremental estimates in AF. Mercaldi et al examined the annual incremental ICH costs in the Medicare 5% sample and obtained a lower estimate of $49,216 ($45,490-$53,431; 2011 USD).[29] Differences between Mercaldi and this study may be due to differences in patient populations and the ability of this analysis to capture out-of-pocket expenses associated with long term care of patients after an ICH.

Our study found the mean incremental cost of a GI bleed to be $24,078 365 days after the GI bleed, compared to AF patients without an event. This is similar to other studies that have found mean cost of a GI bleed over 12 months to be $16,457 - $25,442. [29,31] Overall, published data of events of interest in the AF patient population are limited.

Strengths and Limitations

There are a number of limitations associated with this database analysis. First, as a claims database, the analysis is inherently subject to a variety of limitations including non-differential misclassification bias due to missing or inaccurate coding and the lack of information on severity of disease that must then be inferred from the presence or absence of other ICD-9-CM codes. Additionally, change in severity of disease is not directly

ascertainable from ICD-9 codes. Second, as a claims database, the relationship between AF and bleeding and ischemic events must be inferred. Third, all observational studies are subject to a variety of types of bias, including healthy worker bias. Patients whose claims appear in a database such MarketScan, are those healthy enough to work and receive health insurance under a commercial plan, or have resources and health to be enrolled in a Medicare supplemental plan. Further, patients whose claims appear in the Marketscan database may reflect a socioeconomic status that is unique, in that they may be healthier and wealthier than the general population, due to their ability to purchase Medicare supplemental plans, and by definition, not uninsured or insured by Medicaid.

In addition to limitations due to the use of a database, there are a number of limitations due to study design. Foremost, this analysis lacked information on pharmacy claims. MarketScan has Medicare supplemental claims but not Medicare Part D claims, under which is the prescription drug plan for the majority of individuals 65 and older. Lack of pharmacy claims data was systematically missing from our analysis, making all cost estimates presented, underestimates by an unknown degree. The lack of pharmacy claim data also prevented our analysis from taking into account warfarin exposure. Warfarin is a commonly used anti-coagulant in AF, and is indicated to prevent stroke at the risk of increased bleeding. Though >60% of cases had a $CHADS_2$ of 2 or greater, indicating warfarin to be appropriate, ascertaining drug exposure was outside the scope of this analysis. Another limitation, inherent to our study design, was the exclusion criteria of multiple events of interest and requiring 365 days of follow-up after an event of interest. This criteria biases the sample towards healthier patients, in that, to live a year after an event of interest you must be healthy enough to survive. People who are able to survive for one year may have different costs than those who do not. Additionally, people who have multiple events may be sicker than those described in this sample and have higher costs, therefore the costs in this study likely underestimate the costs in patients with multiple events of interest.[29] Finally, inflation

was not accounted for in this analysis meaning that costs presented may be underestimates of costs in today's dollars.

Strengths of this study include the costing of key AF associated adverse event in the AF patient population. Secondly, this study was able to capture out-of-pocket costs, an important component missing from many previously published studies and thus provide perspective of the patients as well as the payers. MarketScan contains data on persons <65, so despite the mean age of cases being 72, the sample did include non-Medicare subjects, increasing the generalizability of our results. Due to the large sample size and patient-level data we were also able to analyze costs at the level of the day and present costs at 30, 90, and 365 day intervals. The level of detail in the dataset and the sample size allowed for matching on month of diagnosis and month of event helping to compare patients at similar level of AF disease progression. An additional strength of our study is matching design, which allowed for analysis of the incremental cost of an event in a scientifically rigorous manner. Though we did not match on risk scores ($CHADS_2$ and CCI) they were adjusted for in regression analysis, thus helping ensure that health status at diagnosis was similar between cases and controls.

CONCLUSION

The results of this study provide unique quantifications of the incremental 30, 90, and 365 day costs of ischemic stroke, MI, ICH, SE, and GI bleed in patients with AF. This analysis is the first to describe the incremental costs of all events of interest in AF, using a single dataset, as well as include out-of-pocket costs in the incremental estimations. This analysis also provides the first AF specific estimates of the cost of MI and SE in the AF patient population. A cost effectiveness model that takes into account the incremental costs of these key ischemic and hemorrhagic events is now possible, and can be used to more accurately inform the risk and benefit profile of AF.

ACKNOWLEDGEMENTS

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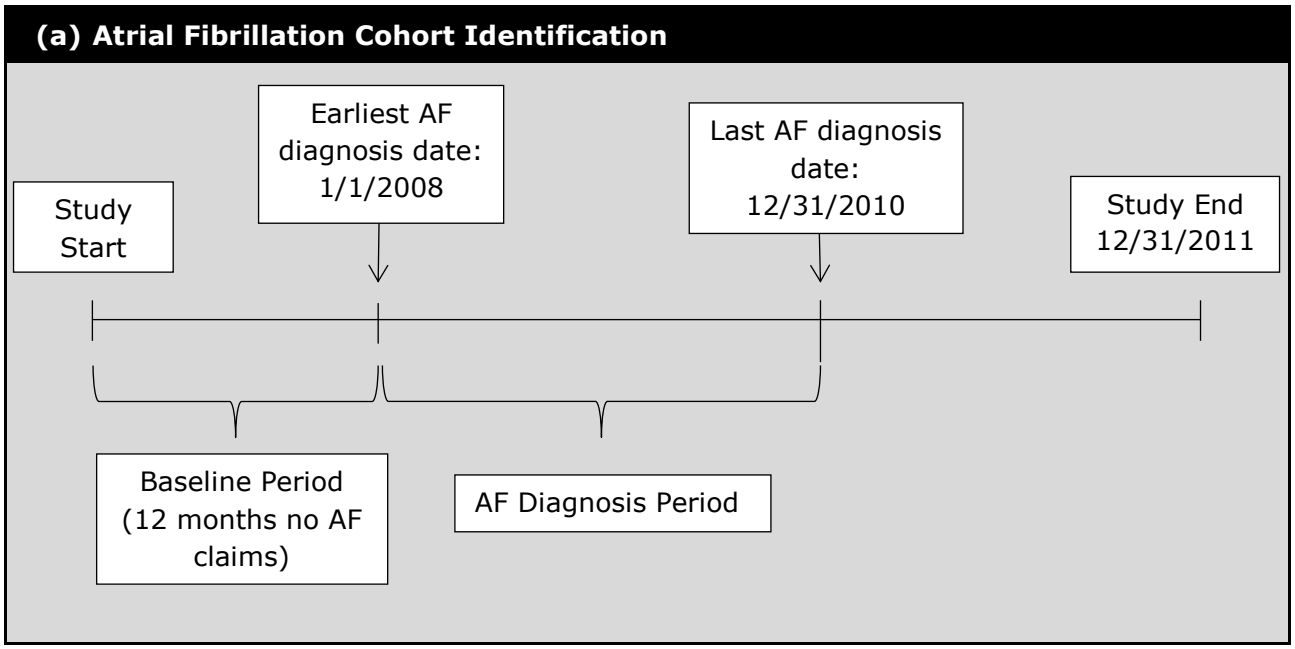
FUNDING

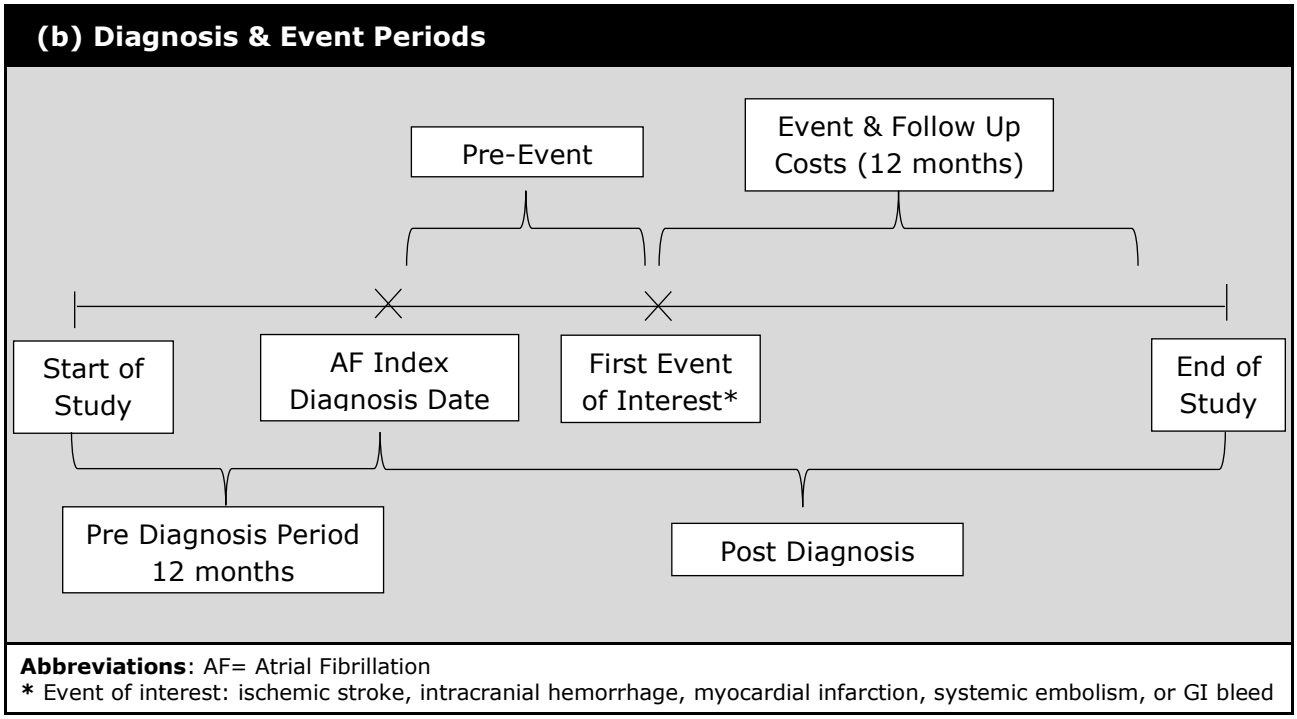
None.

DISCLOSURES

MarketScan is a registered trademark of Truvan Health Analytics

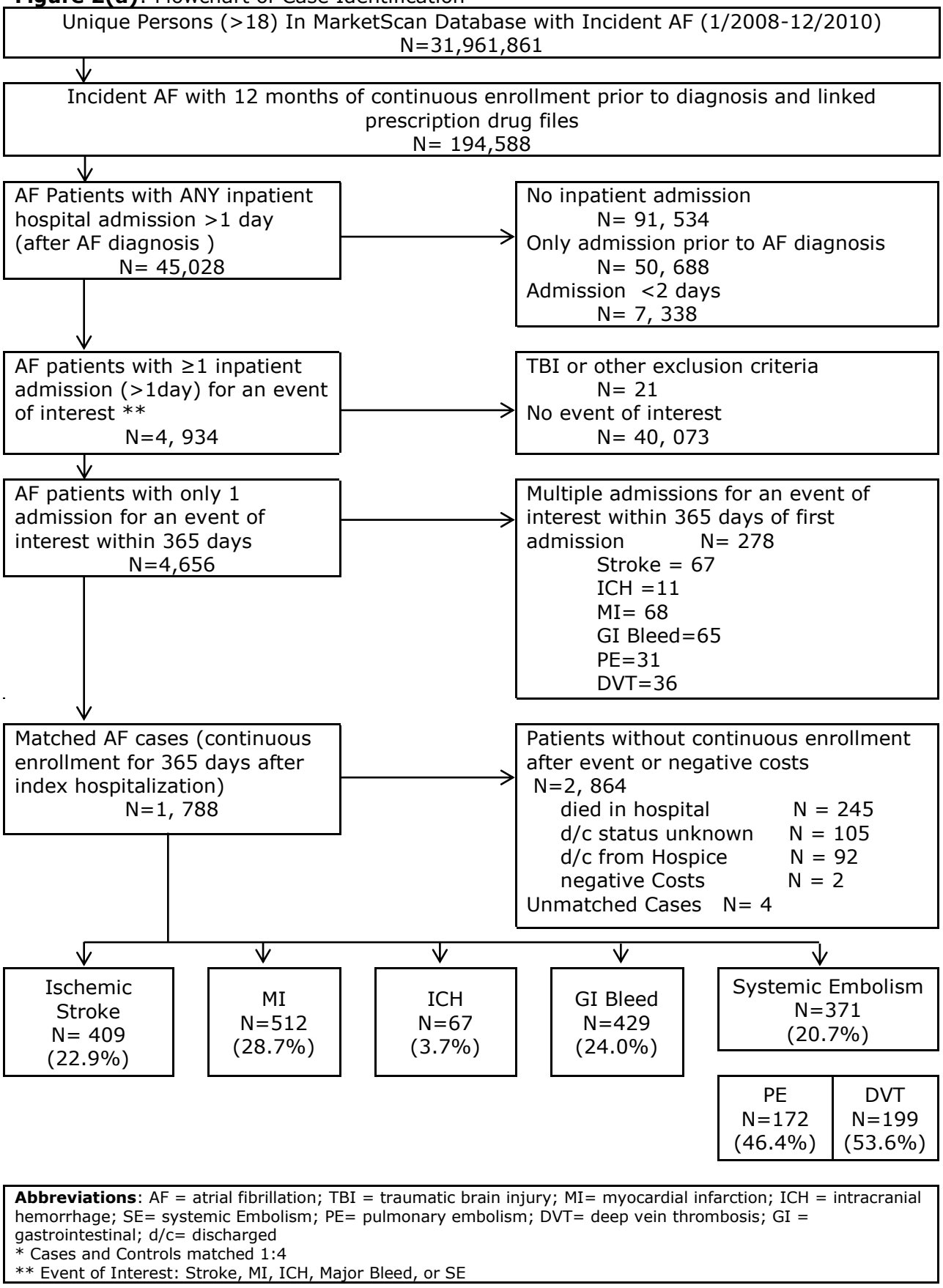
Figure 1: Schematic Representation of Study Design





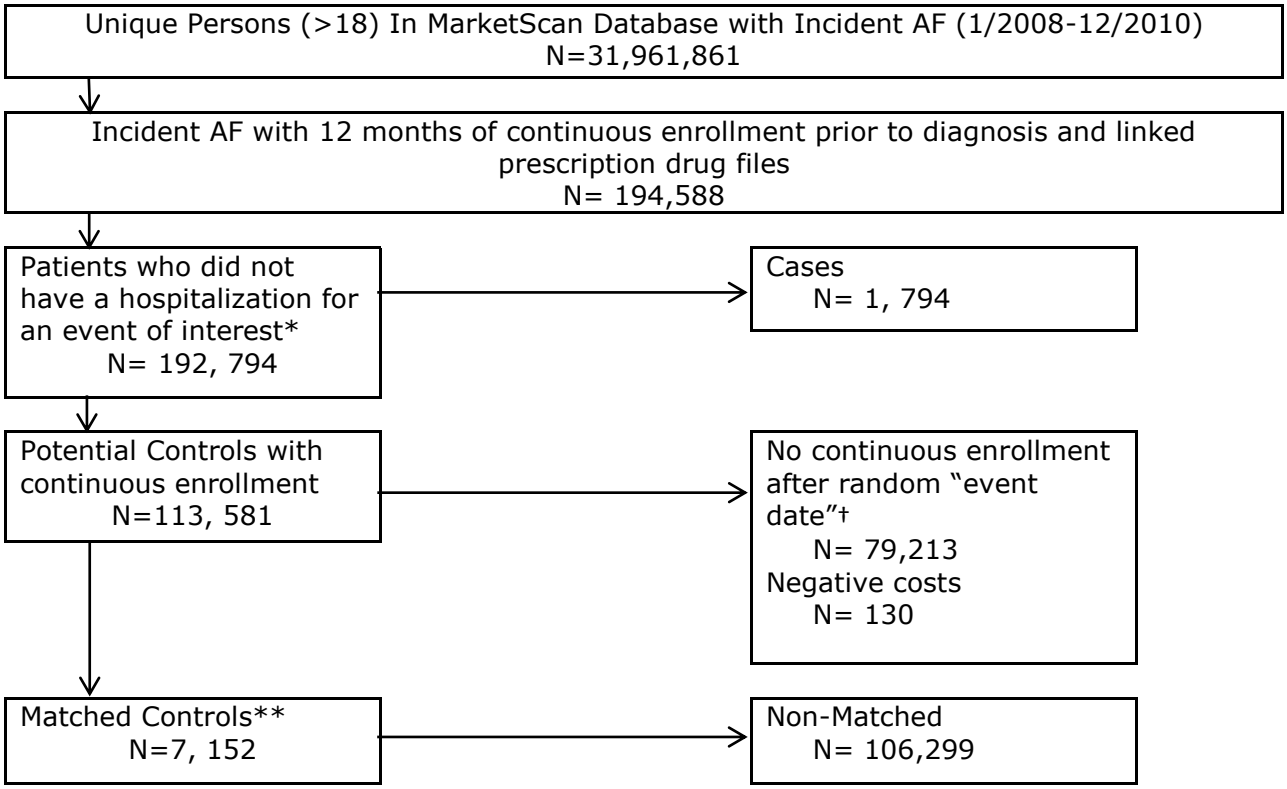
Abbreviations: AF= Atrial Fibrillation
***** Event of interest: ischemic stroke, intracranial hemorrhage, myocardial infarction, systemic embolism, or GI bleed

Figure 2(a): Flowchart of Case Identification



Abbreviations: AF = atrial fibrillation; TBI = traumatic brain injury; MI= myocardial infarction; ICH = intracranial hemorrhage; SE= systemic Embolism; PE= pulmonary embolism; DVT= deep vein thrombosis; GI = gastrointestinal; d/c= discharged
* Cases and Controls matched 1:4
** Event of Interest: Stroke, MI, ICH, Major Bleed, or SE

Figure 2(b): Flowchart of Control Identification



Abbreviations: AF = atrial fibrillation; TBI = traumatic brain injury; MI= myocardial infarction; ICH = intracranial hemorrhage; SE= systemic embolism; PE= pulmonary embolism; DVT= deep vein thrombosis; GI = gastrointestinal; d/c= discharged
* event of interest: ischemic stroke; MI; SE; ICH; GI Bleed
** Cases and Controls matched 1:4
†All controls were assigned an 'event date' using a random date generator to allow for date to be matched on and costs assessed

Table 1: ICD-9 Codes

Condition	ICD-9 Code
Atrial Fibrillation	427.31
$CHADS_2$	
Congestive Heart Failure*	398.91, 402.x1, 404.x1, 404.x3, 428
Hypertension	401, 402, 403, 404, 405, 437.2x
Diabetes	250, 357.2x, 362.0, 366.41
Prior Stroke or TIA*	433.x1, 434.x1, 435, 436, 438
Charlson Comorbidity Index[1] **	
Myocardial Infarction*	410, 412
Congestive Heart Failure*	428
Peripheral Vascular Disease	441, 443.9, 785.4, V424
Cardiovascular Disease	430, 431, 432, 433, 434, 435, 436, 437, 438
Chronic Obstructive Pulmonary Disease	490, 491, 493, 494, 495, 496, 500, 510, 502, 503, 504, 505, 506.4
Dementia	290
Rheumatic Disease	725, 710.0, 710.1, 710.4, 714.0, 714.1, 714.2
Peptic Ulcer Disease	531,532,533,534
Liver Disease	571.2, 571.4, 571.5, 571.6
Liver Disease, complicated	572.2, 456.0, 456.1, 456.20, 456.21
Diabetes, no complications	250.00, 250.01, 250.02, 250.03, 250.07
Diabetes, complications	250.04, 250.05, 250.06
Paralysis	342, 244.1
Renal Disease	582, 583, 585, 586, 588
Cancer	148-195, 200-208
Metastatic Cancer	196, 197, 198
AIDS	042, 043, 044
Events of Interest	
Ischemic Stroke[2] *	434, 436, 433.x1
Myocardial Infarction[3,4]*	410
Systemic Embolism[5]	415.1, 451, 452, 453
Intracranial Hemorrhage[2]	431, 432
GI Bleed[4]	578, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6,
Exclusion Codes	
Cardiac Valve Replacement	V42.2, V43.3
Traumatic Brain Injury[2]	800 - 804, 850-854

Abbreviations: TIA= transient ischemic attack; GI= gastrointestinal; AIDS = acquired immunodeficiency syndrome

***** Differences in ICD-9-CM codes used are due to different sensitivity and specificity levels for identifying events of interest versus identifying comorbid conditions versus quantifying stroke risk ($CHADS_2$ Score)

** Charlson Comorbidity Score is calculated using the Deyo adaptation[1]

1. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–619.

2. Andrade SE, Harrold LR, Tjia J, Cutrona SL, Saczynski JS, Dodd KS, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. Pharmacoepidemiol Drug Saf 2012;21 Suppl 1:100-28.

3. Metcalfe A, Neudam A, Forde S, Liu M, Drosler S, Quan H, et al. Case definitions for acute myocardial infarction in administrative databases and their impact on in-hospital mortality rates. Health Serv Res 2013;48:290-318

4. Wahl PM, Rodgers K, Schneeweiss S, Gage BF, Butler J, Wilmer C, et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. Pharmacoepidemiol Drug Saf 2010;19:596-603

5. Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. Pharmacoepidemiol Drug Saf 2012;21 Suppl 1:154-62.

Table 2: Characteristics of Cases and Controls with AF

	Cohort (Prior to Matching)			Ischemic Stroke		Myocardial Infarction		Systemic Embolism	
	Cohort** (n=194,588)	**Potential Cases** (n=1,792)	**Potential Controls** (n=113,451)	**Cases*** (n=409)	**Controls*** (n=1,636)	**Cases*** (n=512)	**Controls*** (n=2,048)	**Cases*** (n=371)	**Controls*** (n=1,484)
MATCHING CHARACTERISTICS[†]									
Male, % (n)	57 (110,556)	53 (956)	57 (65,009)	51 (207)	51 (828)	58 (296)	58(1,184)	53 (195)	53 (780)
Health Plan Type, %(n)									
Health Plan	68 (133,055)	80(1,426)	72 (81,585)	83 (341)	83(1,364)	79 (404)	79(1,616)	74 (276)	74(1,104)
Employer	32 (61,533)	20 (366)	28 (31,866)	17 (68)	16 (272)	21 (108)	21 (432)	26 (95)	26 (380)
Region, % (n)									
North East	17 (31,124)	15 (277)	18 (20,559)	13 (55)	13 (22)	16 (81)	16 (324)	16 (59)	16 (236)
North Central	32 (61,927)	39 (701)	20 (32,913)	42 (173)	42 (692)	37 (187)	37 (748)	39 (146)	39 (584)
South	33 (65,083)	30 (548)	33 (37,254)	29 (117)	29 (458)	33 (170)	33 (680)	30 (113)	30 (452)
West	17 (33,951)	15 (261)	19 (21,941)	16 (64)	16 (256)	14 (74)	14 (296)	14 (52)	14 (208)
Unknown	1 (1,503)	0 (5)	0 (784)	0 (0)	0 (0)	0 (0)	0 (0)	0 (1)	0 (4)
NON-MATCHED CHARACTERISTICS									
Age, years (sd)	67 (15)	72 (13)	66 (14)	74 (12)	66 (13)	72 (12)	65 (14)	68 (14)	64 (14)
Days to Event, (sd)	n/a	265 (238)	235 (220)	306 (249)	266(229)	243 (233)	263(234)	234(223)	249 (222)
Plan Type [‡,§] %(n)									
Unknown	2 (4,215)	2 (37)	2 (2,310)	3 (11)	2 (34)	2 (12)	3 (65)	2 (7)	4 (53)
Comprehensive	28 (54,049)	40 (708)	29 (33,050)	45 (184)	31 (503)	39 (202)	27 (553)	33 (122)	27 (397)
HMO	15 (29,763)	16 (281)	17 (18,825)	13 (54)	10 (172)	17 (85)	10 (211)	17 (62)	11 (156)
FFS	52 (102, 128)	41 (731)	50 (56,385)	38 (155)	54 (877)	40 (204)	56(1144)	45 (167)	56 (827)
CDHP & HDHP	2 (4,433)	2 (35)	3 (2,881)	1 (5)	3 (50)	2 (9)	4 (75)	4 (13)	3 (51)
CHADS$_2$ Score, %(n)									
0	26 (50, 394)	13 (231)	28 (31,615)	11 (47)	28 (459)	13 (68)	31 (625)	17 (63)	29 (435)
1	31 (59,424)	27 (481)	32 (35,988)	24 (98)	34 (563)	26 (132)	33 (680)	34 (127)	33 (494)
2	25 (49,083)	30 (541)	25 (28,423)	28 (116)	25 (405)	32 (162)	23 (471)	29 (107)	24 (356)
3	11 (22,267)	17 (298)	10 (11,337)	18 (72)	9 (142)	18 (92)	9 (185)	12 (44)	9 (133)
4+	7 (13,420)	13 (241)	5 (6,088)	19 (76)	4 (67)	11 (58)	4 (87)	8 (30)	4 (66)
Charlson Comorbidity Index,[d] % (n)									
0	39 (76, 831)	25 (443)	43 (49,141)	26 (108)	45 (735)	24 (123)	46 (939)	30 (110)	43 (645)
1	21 (40,774)	21 (372)	22 (24,616)	22 (89)	22 (354)	21 (106)	22 (454)	22 (80)	24 (349)
2	15 (29, 431)	19 (336)	15 (17,124)	20 (83)	14 (237)	19 (96)	15 (303)	17 (62)	13 (196)
3+	24 (47,552)	36 (641)	20 (22,570)	32 (129)	19 (310)	37 (187)	17 (352)	32 (119)	20 (294)

Abbreviations: HMO =health maintenance organization; FFS= fee for service; CDHP= consumer driven health plan; HDHP= high deductible health plan; ; SD = standard deviation
* After matching ** Characteristics of the all cohort members with AF and 12 months of continuous enrollment prior to index diagnosis
[†] Matching criteria also included: month of diagnosis and event month (month was randomly generated for controls)
[‡] HMO includes Exclusive Provider Organization, HMO, and Fee-For-Service with Capitation; FFS includes Point of Service and Preferred Provider Organization Benefit Design

Table 2: Characteristics of Cases and Controls with AF, continued

	ICH		GI Bleed	
	Cases* (n=67)	**Controls*** (n=268)	**Cases*** (n=429)	**Controls***(n=1,716)
MATCHING CHARACTERISTICS*				
Male, %(n)	49 (33)	49 (132)	51 (222)	52 (888)
Health Plan Type, %(n)				
Health Plan	72 (48)	72 (192)	83 (355)	83 (1,420)
Employer	28 (19)	28 (76)	17 (74)	17 (296)
Region, %(n)				
North East	21 (14)	21 (56)	16 (68)	16 (272)
North Central	33 (22)	33 (88)	40 (173)	40 (692)
South	30 (20)	30 (80)	30 (128)	30 (512)
West	16 (11)	16 (44)	14 (60)	14 (240)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)
NON-MATCHED CHARACTERISTICS				
Age, yrs (sd)	72 (13)	65 (14)	74 (12)	66 (13)
Days to Event, (sd)	241 (235)	243 (217)	281 (241)	275 (240)
Plan Type,** † %(n)				
Unknown	2 (1)	3 (9)	1 (6)	3 (45)
Comprehensive	37 (25)	25 (68)	40 (173)	31 (531)
HMO	24 (16)	26 (42)	15 (64)	10 (166)
FFS	36 (24)	53 (142)	42 (179)	53 (917)
CDHP & HDHP	2 (1)	3 (7)	2 (7)	3 (57)
$CHADS_2$ Score, %(n)				
0	11 (7)	33 (90)	11 (46)	29 (500)
1	22 (15)	31 (82)	25 (108)	35 (604)
2	31 (21)	26 (70)	31 (133)	23 (396)
3	15 (10)	6 (15)	18 (79)	7 (128)
4+	21 (14)	4 (11)	15 (63)	5 (88)
Charlson Comorbidity Index,§ %(n)				
0	16 (11)	44 (117)	21 (91)	46 (782)
1	30 (20)	23 (62)	17 (74)	22 (372)
2	21 (14)	13 (35)	19 (81)	14 (247)
3+	33 (22)	20 (54)	43 (183)	18 (315)

§ The Deyo method was used to ascertain scores

1. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–619.

Table 3: Results: Incremental Cost of Events, 2012 US$

	Stroke $ (95% CI)	Myocardial Infarction $ (95% CI)	Systemic Embolism $ (95% CI)	Intracranial Hemorrhage $ (95% CI)	GI Bleed $ (95% CI)
T-TEST					
30 days	20,988 (18,613 – 23,363)	31,462 (28,222 – 34,701)	16,386 (14748 – 18,025)	42,041 (30,111 – 53,971)	15,785 (13,600 – 17,970)
90 days	26,129 (21,988 – 30,269)	37,627 (32,845 – 42,408)	18,990 (16,531 – 21,449)	55,105 (37,979 – 72,232)	18,540 (15,288 – 21,792)
365 days	29,410 (25,732 – 37,851)	47,542 (40,343 – 54,741)	32,237 (25,672 – 38,802)	75,306 (43,848 – 106,764)	29,545 (23,468 – 35,623)
ADJUSTED 30 DAY COSTS					
GEE[§,¶]	20,710 (18404 – 23,016)	32,535 (29,187 – 35,884)	15,754 (14,317 – 17,192)	45,242 (32,426 – 58,059)	14,823 (12,591 – 17,054)
GEE[||, ¶]	34,206 (n/a)	38,279 (n/a)	19,374 (n/a)	79,497 (n/a)	31,248 (n/a)
ADJUSTED 90 DAY COSTS					
GEE[§, ¶]	25,499 (21,308 – 29,690)	38,294 (33,415 – 43,173)	17,659 (15,348 – 19,970)	59,495 (41,700 – 77,290)	16,132 (12,129 – 20,136)
GEE[||, ¶]	34,541 (n/a)	44,833 (n/a)	28,244 (n/a)	59,681 (n/a)	51,643 (n/a)
ADJUSTED 365 DAY COSTS					
GEE[§, ¶]	29,128 (22,903 – 35,353)	38,651 (38,281 – 52,632)	27,938 (21,572 – 34,306)	77,513 (46,935 – 108,091)	24,078 (16,763 – 31,393)
GEE[||, ¶]	42,207 (n/a)	52,763 (n/a)	36,714 (n/a)	79,908 (n/a)	57,612 (n/a)

Abbreviations: OLS = Ordinary Least Squares Regression ; GEE= Generalized Estimating Equation; CI= Confidence Interval
[§] Gaussian Family, Identity Link, exchangeable correlation structure, and robust standard errors
[||] Gamma Family, Log Link, robust standard errors
[¶] Adjusted for: age at diagnosis of Atrial Fibrillation, CHADS2 category, charlson comorbidity category, medical costs during baseline, & healthplan type

Table 4: Model Selection, by Event Type, 2012 US$
(a) Ischemic Stroke

Type of Analysis	Incremental Event Cost ($)	Standard Errors ($)	Confidence Intervals ($)*
30 DAY COSTS9			
T-Test	20,988	1,208	(18,613 – 23,363)
Unadjusted OLS	20,988	657	(19,699 – 22,277)
robust		1,208	(18,620 – 23,356)
cluster		1,212	(18,606 – 23,370)
Adjusted¶ OLS	20,713	681	(19,378 – 22,047)
robust		1,157	(18,443 – 22,982)
cluster		1,181	(18,392 -23,034)
GLM†, ¶	20,713	681	(19,379 – 22,047)
robust		1,153	(18,452 – 22,973)
GEE‡,¶	20,712	1,177	(18406 – 23,019)
GEE§,¶	20,710	1,177	(18404 – 23,016)
GLMǁ, ¶	43,725	n/a	n/a
GEE ǁ, ¶	34,206	n/a	n/a
90 DAY COSTS			
T-Test	26,129	2,107	(21,988 – 30,269)
Unadjusted OLS	26,129	1,310	(23,559 – 28,698)
robust		2,105	(22,000 – 30,257)
cluster		2,115	(21,971 – 30,286)
Adjusted¶ OLS	25,515	1,352	(22,862 – 28,167)
robust		2,119	(21,358 – 29,671)
cluster		2,151	(21,286 – 29,743)
GLM†, ¶	25,515	1,352	(22,864 – 28,165)
robust		2,112	(21,375 – 29,654)
GEE‡,¶	25,515	2,144	(21,313 – 29,716)
GEE§,¶	25,499	2,138	(21,308 – 29,690)
GLMǁ, ¶	30,813	8,966	(13,240 – 48,387)
GEE ǁ, ¶	34,541	n/a	n/a
365 DAY COSTS			
T-Test	31,792	3,084	(25,732 – 37,851)
Unadjusted OLS	31,791	2,565	(26,761 – 36,823)
robust		3,082	(25,747 – 37,837)
cluster		3,129	(25,641 – 37,943)
Adjusted¶ OLS	29,218	2,552	(24,214 – 34,222)
robust		3,113	(23,112 – 35,323)
cluster		3,194	(22,940 – 35,496)
GLM†, ¶	29,218	2,552	(24,217 – 34,219)
robust		3,103	(23,137 – 35,299)
GEE‡,¶	29,218	3,183	(22,980 – 35,456)
GEE§,¶	29,128	3,176	(22,903 – 35,353)
GLMǁ, ¶	38,217	9,522	(19,554 – 56,879)
GEE ǁ, ¶	42,207	n/a	n/a

Abbreviations: OLS = Ordinary Least Squares Regression ; GLM = Generalized Linear Model; GEE= Generalized Estimating Equation
*P-values are <0.001 unless otherwise listed
† Uses Gaussian Family and Identity Link
‡ Gaussian Family, Identity Link, independent correlation structure, and robust standard errors
§ Gaussian Family, Identity Link, exchangable correlation structure, and robust standard errors
ǁ Gamma Family, Log Link, robust standard errors, presented
¶ Adjusted for: age at diagnosis of Atrial Fibrillation, CHADS2 category, charlson comorbidity category, medical costs during baseline, & healthplan type

(b) Myocardial Infarction

Type of Analysis	Incremental Event Cost ($)	Standard Errors ($)	Confidence Intervals ($)*
30 DAY COSTS			
T-Test	31,462	1,649	(28,222 – 34,701)
Unadjusted OLS	31,461	880	(29737 – 33,187)
robust SE's		1,648	(28,230 – 34,693)
cluster		1,645	(28,230 – 34,693)
Adjusted[¶] OLS	32,533	905	(30,759 – 34,308)
robust SE's		1,701	(29,198 – 35,868)
cluster		1,713	(29,168 – 35,899)
GLM[†, ¶]	32,533	905	(30,760 – 34,307)
robust SE's		1,696	(29,209 – 35,858)
GEE[‡,¶]	32,533	1,709	(29,185 – 35,882)
GEE[§,¶]	32,535	1,708	(29,187 – 35,884)
GLM[||, ¶]	30,879	3,018	(24,964 – 36,794)
GEE [||, ¶]	38,279	n/a	n/a
90 DAY COSTS			
T-Test	37,627	2,434	(32,845 – 42,408)
Unadjusted OLS	37,627	1,453	(34,778 – 40,476)
robust SE's		2,432	(32,857 – 42,397)
cluster		2,444	(32,824 – 42,429)
Adjusted[¶] OLS	38,281	1,487	(35,364 – 41,197)
robust SE's		2,454	(33,469 – 43,092)
cluster		2,491	(33,386 – 43,175)
GLM[†, ¶]	38,281	1,487	(35,366 – 41,196)
robust SE's		2,447	(33,484 – 43,077)
GEE[‡,¶]	38,281	2,484	(33,411 – 43,150)
GEE[§,¶]	38,294	2,489	(33,415 – 43,173)
GLM[||, ¶]	32,701	3,178	(26,473 – 38,930)
GEE [||, ¶]	44,833	n/a	n/a
365 DAY COSTS			
T-Test	47,542	3,665	(40,343 – 54,741)
Unadjusted OLS	47,542	2,436	(42,765 – 52,320)
robust SE's		3,663	(40,359 – 54,725)
cluster		3,696	(40,281 – 54,803)
Adjusted[¶] OLS	45,452	2,438	(40,671 – 50,232)
robust SE's		3,593	(38,406 – 52,497)
cluster		3,665	(38,251 – 52,653)
GLM[†, ¶]	45,452	2,438	(40,674 – 50,230)
robust SE's		3,583	(38,429 – 52,475)
GEE[‡,¶]	45,452	3,655	(38,288 – 52,616)
GEE[§,¶]	45,456	3,651	(38,281 – 52,632)
GLM[||, ¶]	39,206	3,510	(32,326 – 45,085)
GEE [||, ¶]	52,763	n/a	n/a

Abbreviations: OLS = Ordinary Least Squares Regression ; GLM = Generalized Linear Model; GEE= Generalized Estimating Equation

*P-values are <0.001 unless otherwise listed

[†] Uses Gaussian Family and Identity Link

[‡] Gaussian Family, Identity Link, independent correlation structure, and robust standard errors

[§] Gaussian Family, Identity Link, exchangeable correlation structure, and robust standard errors

[||] Gamma Family, Log Link, robust standard errors

[¶] Adjusted for: age at diagnosis of Atrial Fibrillation, CHADS2 score, charlson comorbidity category, baseline medical costs , & healthplan type

(c) Systemic Embolism

Type of Analysis	Incremental Event Cost ($)	Standard Errors ($)	Confidence Intervals ($)*
30 DAY COSTS			
T-Test	16,386	833	(14,748 – 18,025)
Unadjusted OLS	16,386	512	(15,382 – 17,391)
robust SE's		833	(14,753 – 18,020)
cluster		799	(14,814 – 17,958)
Adjusted[¶] OLS	15,749	508	(14,753 – 16,744)
robust SE's		784	(14,201 – 17,286)
cluster		737	(14,299 – 17,198)
GLM[†, ¶]	15,749	508	(14,754 – 16,743)
robust SE's		781	(14,218 – 17,280)
GEE[‡,¶]	15,749	734	(14,309 – 17,188)
GEE[§,¶]	15,754	734	(14,317 – 17,192)
GLM[ǁ, ¶]	19,984	10,166	(58 – 39,909)
GEE [ǁ, ¶]	19,374	n/a	n/a
90 DAY COSTS			
T-Test	18,990	1,251	(16,531 – 21,449)
Unadjusted OLS	18,990	1,020	(16,989 – 20,990)
robust SE's		1,250	(16,538 – 21,442)
cluster		1,230	(16,571 – 21,409)
Adjusted[¶] OLS	17,662	1,008	(15,685 – 19,639)
robust SE's		1,211	(15,286 – 20,038)
cluster		1,184	(15,334 – 19,989)
GLM[†, ¶]	17,662	1,008	(15,686 – 19,637)
robust SE's		1,207	(15,296 – 20,027)
GEE[‡,¶]	17,662	1,180	(15,351 – 19,973)
GEE[§,¶]	17,659	1,180	(15,348 – 19,970)
GLM[ǁ, ¶]	29,426	n/a	n/a
GEE [ǁ, ¶]	28,244	n/a	n/a
365 DAY COSTS			
T-Test	32,237	3,341	(25,672 – 38,802)
Unadjusted OLS	32,237	2,633	(27,072 – 37,402)
robust SE's		3,338	(25,690 – 38,784)
cluster		3,390	(25,571 – 38,903)
Adjusted[¶] OLS	27,938	2,571	(22,895 – 32,980)
robust SE's		3,199	(21,665 – 34,211)
cluster		3,265	(21,518 – 34,358)
GLM[†, ¶]	27,938	2,571	(28,899 – 32,977)
robust SE's		3,186	(21,692 – 34,183)
GEE[‡,¶]	27,938	3,253	(21,563 – 34,313)
GEE[§,¶]	27,938	3,249	(21,572 – 34,306)
GLM[ǁ, ¶]	34,488	13,883	(7,277 – 61,698)
GEE [ǁ, ¶]	36,714	n/a	n/a

Abbreviations: OLS = Ordinary Least Squares Regression ; GLM = Generalized Linear Model; GEE= Generalized Estimating Equation

*P-values are <0.001 unless otherwise listed

[†] Uses Gaussian Family and Identity Link

[‡] Gaussian Family, Identity Link, independent correlation structure, and robust standard errors

[§] Gaussian Family, Identity Link, exchangeable correlation structure, and robust standard errors

[ǁ] Gamma Family, Log Link, robust standard errors

[¶] Adjusted for: age at diagnosis of Atrial Fibrillation, CHADS2 score, charlson comorbidity category, baseline medical costs , & healthplan type

(d) Intracranial Hemorrhage

Type of Analysis	Incremental Event Cost ($)	Standard Errors ($)	Confidence Intervals ($)*
30 DAY COSTS			
T-Test	42,041	5,975	(30,111 – 53,971)
Unadjusted OLS	42,041	2,987	(36,166 – 47,917)
robust SE's		5,948	(30,340 – 53,742)
cluster		6,007	(30,049 – 54,034)
Adjusted[¶] OLS	45,241	3,220	(38,906 – 51,575)
robust SE's		6,627	(33,202 – 58,279)
cluster		6,672	(31,921 – 58,561)
GLM[†, ¶]	45,241	3,220	(38,931 – 51,551)
robust SE's		6,487	(32,527 – 57,954)
GEE[‡,¶]	45,241	6,530	(32,442 – 58,040)
GEE[§,¶]	45,242	6,539	(32,426 – 58,059)
GLM[ǁ, ¶]	42,794	8,521	(26,094 – 59,494)
GEE [ǁ, ¶]	79,497	n/a	n/a
90 DAY COSTS			
T-Test	55,105	8,578	(37,979 – 72,232)
Unadjusted OLS	55,106	4,300	(46,648 – 63,562)
robust SE's		8,540	(38,307 – 71,904)
cluster		8,639	(37,856 – 72,354)
Adjusted[¶] OLS	59,497	4,638	(50,372 – 68,622)
robust SE's		9,236	(41,327 – 77,667)
cluster		9,267	(40,997 – 77,998)
GLM[†, ¶]	59,497	4,638	(50,407 – 68,587)
robust SE's		9,040	(41,779 – 77,215)
GEE[‡,¶]	59,497	9,070	(41,720 – 77,274)
GEE[§,¶]	59,495	9,080	(41,700 – 77,290)
GLM[ǁ, ¶]	55,776	14,074	(28,193 – 83,360)
GEE [ǁ, ¶]	59,681	n/a	n/a
365 DAY COSTS			
T-Test	75,306	15,760	(43,848 – 106,764)
Unadjusted OLS	75,306	8,523	(59,071 – 91,540)
robust SE's		15,690	(44,442 – 106,169)
cluster		15,890	(43,581 – 107,030)
Adjusted[¶] OLS	77,520	8,857	(60,094 – 94,945)
robust SE's		15,828	(46,379 – 108,660)
cluster		15,931	(45,712 – 109,328)
GLM[†, ¶]	77,520	8,857	(60,160 – 94,879)
robust SE's		15,493	(47,154 – 107,885)
GEE[‡,¶]	77,520	15,594	(46,956 – 108,084)
GEE[§,¶]	77,513	15,601	(46,935 – 108,091)
GLM[ǁ, ¶]	77,411	28,612	(21,332 – 133,490)
GEE [ǁ, ¶]	79,908	n/a	n/a

Abbreviations: OLS = Ordinary Least Squares Regression ; GLM = Generalized Linear Model; GEE= Generalized Estimating Equation

*P-values are <0.001 unless otherwise listed

[†] Uses Gaussian Family and Identity Link

[‡] Gaussian Family, Identity Link, independent correlation structure, and robust standard errors

[§] Gaussian Family, Identity Link, exchangeable correlation structure, and robust standard errors

[ǁ] Gamma Family, Log Link, robust standard errors

[¶] Adjusted for: age at diagnosis of Atrial Fibrillation, CHADS2 score, charlson comorbidity category, baseline medical costs , & healthplan type

(e) GI Bleed

Type of Analysis	Incremental Event Cost ($)	Standard Errors ($)	Confidence Intervals ($)*
30 DAY COSTS			
T-Test	15,785	1,112	(13,600 – 17,970)
Unadjusted OLS	15,785	623	(14,564 – 17,007)
robust SE's		1,111	(13,607 – 17,964)
cluster		1,116	(13,591 – 17,980)
Adjusted[¶] OLS	14,819	646	(13,552 – 16,086)
robust SE's		1,141	(12,582 – 17,057)
cluster		1,141	(12,577 – 17,062)
GLM[†, ¶]	14,819	646	(13,553 – 16,086)
robust SE's		1,137	(12,591 – 17,048)
GEE[‡,¶]	14,819	1,137	(12,591 – 17,048)
GEE[§,¶]	14,823	1,139	(12,591 – 17,054)
GLM[ǁ, ¶]	52,741	n/a	n/a
GEE [ǁ, ¶]	31,248	n/a	n/a
90 DAY COSTS			
T-Test	18,540	1,656	(15,288 – 21,792)
Unadjusted OLS	18,540	1,556	(15,490 – 21,590)
robust SE's		1,655	(15,294 – 21,785)
cluster		1,591	(15,414 – 21,666)
Adjusted[¶] OLS	16,140	1,615	(12,973 – 19,307)
robust SE's		2,257	(11,714 – 20,567)
cluster		2,051	(12,108 – 20,172)
GLM[†, ¶]	16,140	1,615	(12,975 – 19,305)
robust SE's		2,250	(11,731 – 20,550)
GEE[‡,¶]	16,140	2,045	(12,133 – 20,148)
GEE[§,¶]	16,132	2,042	(12,129 – 20,136)
GLM[ǁ, ¶]	75,206	n/a	n/a
GEE [ǁ, ¶]	51,643	n/a	n/a
365 DAY COSTS			
T-Test	29,545	3,094	(23,468 – 35,623)
Unadjusted OLS	29,545	2,559	(24,526 – 34,564)
robust SE's		3,092	(23,481 – 35,609)
cluster		3,108	(23,436 – 35,655)
Adjusted[¶] OLS	24,080	2,590	(19,001 – 29,159)
robust SE's		3,827	(16,574 – 31,586)
cluster		3,745	(15,720 – 31,440)
GLM[†, ¶]	24,080	2,590	(19,004 – 29,156)
robust SE's		3,815	(16,603 – 31,557)
GEE[‡,¶]	24,080	3,732	(16,765 – 31,395)
GEE[§,¶]	24,078	3,732	(16,763 – 31,393)
GLM[ǁ, ¶]	69,053	n/a	n/a
GEE [ǁ, ¶]	57,612	n/a	n/a

Abbreviations: OLS = Ordinary Least Squares Regression ; GLM = Generalized Linear Model; GEE= Generalized Estimating Equation

*P-values are <0.001 unless otherwise listed

[†] Uses Gaussian Family and Identity Link

[‡] Gaussian Family, Identity Link, independent correlation structure, and robust standard errors

[§] Gaussian Family, Identity Link, exchangeable correlation structure, and robust standard errors

[ǁ] Gamma Family, Log Link, robust standard errors

[¶] Adjusted for: age at diagnosis of Atrial Fibrillation, CHADS2 score, charlson comorbidity category, baseline medical costs , & healthplan type

REFERENCES

1. Go AS, Mozaffarian D, Roger VL; et al. Heart Disease and Stroke Statistics—2013 Update: A report from the American Heart Association. Circulation 2013;127:e6-245

2. Miyasaka Y, Barnes ME, Gersh BJ; et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980-2000, and implications on the projections for future prevalence [published correction appears in *Circulation*. 2006;114:e498]. Circulation 2006;114:119-25.

3. Go AS, Hylek EM, Phillips KA; et al. Prevalence of diagnosed atrial fibrillation in adults: the AnTicoagulation and Risk Factor (ATRIA) Study JAMA 2001;285:2370-5.

4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study; Stroke 1991;22:983-8.

5. Luengo_fernandez R, Gram AM, Rothwell PM. Costs of stroke using patient-level data: a critical review of the literature Stroke 2009;40:e18-e23.

6. Coyne KS, Paramore C, Grand S; et al. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. Alue Health 2006;9:348-56

7. Cappato R, Calkins H, Chen SA; et al. Prevalence and cause of fatal outcome in catheter ablation of atrial fibrillation J Am Coll Cardiol 2009;53:1798-1803.

8. Kim M, Lin J, Hussein M; et al. Cost of atrial fibrillation in United States managed care organizations. Adv Terh 2009;26:847-57.

9. Wodchis WP, Bhatia RS, Leblanc K; et al. A review of the Cost of Atrial Fibrillation. Value Health 2012:15;240-8.

10. Miyasaka Y, Barnes ME, Bailey KR; et al. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. J Am Coll Cardiol 2007;49:986-92

11. Wang TJ, Larson MG, Levy D; et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003; 107:2920-5

12. Mamas MA, Cladwell JC, Chacko St; et al. A Meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. Eur J Heart Fail 2009;11:676-83

13. Jabre P, Roger VL, Murad MH; et al. Mortality associated with atrial fibrillation in patients with myocardial infarction: a systematic review and meta-analysis. Circulation 2011;123:1587-93.

14. Lin HJ, Wolf PA, Kelly-Hayes M. Stroke severity in atrial fibrillation: the Framingham Study. Stroke 1996;27:1760-4.

15. Kamel H, Easton JD, Johnston SC, and Kim AS. Cost-effectiveness of apixaban vs warfarin for secondary stroke prevention in atrial fibrillation. Neurology 2012;79(14):1428-34

16. Kansal AR, Sorensen SV, Gani R, Robinson P, Pan F, Plumb JM, Cowie MR. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation. Heart. 2012 Apr;98(7):573-8.

17. O'Brien CL, Gage BF. Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. JAMA. 2005 Feb 9;293(6):699-706

18. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. Circulation. 2011 Jun 7;123(22):2562-70

19. Coleman CI, Straznitskas AD, Sobieraj DM; et al. Cost-effectiveness of clopidogrel plus aspirin for stroke prevention in patients with atrial fibrillation in whom warfarin is unsuitable. Am J Cardiol 2012;109(7):1020-5.

20. Mercaldi CJ, Ciarametaro M, Hahn B; et al. Cost efficiency of anticoagulation with warfarin to prevent stroke in Medicare beneficiaries with nonvalvular atrial fibrillation. Stroke. 2011 Jan;42(1):112-8.

21. Leey JA, McCabe S, Koch JA, Miles TP. Cost-effectiveness of genotype-guided warfarin therapy for anticoagulation in elderly patients with atrial fibrillation. Am J Geriatr Pharmacother. 2009;7(4):197-203

22. Freeman JV, Zhu RP; et AL. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Ann Intern Med 2011;154(1):1-11.

23. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al: RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51. Erratum in: N Engl J Med 2010;363:1877. (PubMed ID: 19717844)

24. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006;367:1903-12. (PubMed PMID: 16765759)

25. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91. (PubMed PMID: 21830957)

26. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92. (PubMed PMID: 21870978)

27. Khairallah F, Ezzedine R, Ganz LI; et al. Epidemiology and determinants of outcome of admissions for atrial fibrillation in the United States from 1996 to 2001. Am J Cariol 2004;94:500-4.

28. Miyasaka Y, Barnes ME, Gersh BJ; et al. Changing trends of hospital utilization in patients after their first episode of atrial fibrillation. Am J Cardiol 2008;102:568-72.

29. Mercaldi CJ, Siu K, Sander SD; et al. Long-Term Costs of Ischemic Stroke and Major Bleeding Events among Medicare Patients with Nonvalvular Atrial Fibrillation. Cardiol Res Pract 2012;2012:645469

30. Boccuzzi SJ, Martin J, Stephenson J; et al. Retrospective study of total healthcare costs associated with chronic nonvalvular atrial fibrillation and the occurrence of a first transient ischemic attack, stroke or major bleed. Curr Med Res Opin 2009;25(12):2853-64.

31. Ghate SR, Biskupiak J, Ye X, Kwong WJ, Brixner DI. All-cause and bleeding-related health care costs in warfarin-treated patients with atrial fibrillation. J Manag Care Pharm. 2011 Nov;17(9):672-84.

32. Kim MM, Metlay J, Cohen A; et al. Hospitalization costs associated with warfarin-related bleeding events among older community-dwelling adults. Pharmacoepidemiol Drug Saf 2010;19:731-6.

33. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864-70.

34. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–619.

35. Andrade SE, Harrold LR, Tjia J, Cutrona SL, Saczynski JS, Dodd KS, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. Pharmacoepidemiol Drug Saf 2012;21 Suppl 1:100-28. (PubMed PMID: 22262598)

36. Metcalfe A, Neudam A, Forde S, Liu M, Drosler S, Quan H, et al. Case definitions for acute myocardial infarction in administrative databases and their impact on in-hospital mortality rates. Health Serv Res 2013;48:290-318. (PubMed PMID: 22742621.)

37. Wahl PM, Rodgers K, Schneeweiss S, Gage BF, Butler J, Wilmer C, et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. Pharmacoepidemiol Drug Saf 2010;19:596-603. (PubMed PMID: 20140892.)

38. Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. Pharmacoepidemiol Drug Saf 2012;21 Suppl 1:154-62. (PubMed PMID: 22262602.)

39. Von Scheele B, Fernandez M, Hogu SL, Kwong WJ. Review of economics and cost-effectiveness analyses of amticoagulant therapy for stroke prevention in atrial fibrillation in the US. Ann Pharmacother 2013;46:671-85

40. Kauf TL, Velazquez EJ, Crosslin DR, Weaver WD, Diaz R, Granger CB, et al. The cost of acute myocardial infarction in the new millennium: evidence from a multinational registry. Am J Heart 2006;151: 206-12