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ORIGINAL ARTICLE

An economic model of adverse events and costs for oral anticoagulants used for atrial fibrillation

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Key words: **Anticoagulants – Cost-effectiveness – Economics – Warfarin**

ABSTRACT

Objective: To construct a semi-Markov model to compare health outcomes and medical costs associated with warfarin and a second anticoagulant over 1- and 5-year periods.

Design: We posited a hypothetical cohort of 10 000 identical 70-year-old patients with atrial fibrillation. We posited 20 scenarios for events that included four possibilities for ischemic strokes (mild, moderate, severe, death) and 16 possibilities for hemorrhages. The model allowed for four levels of International Normalized Ratio. Event rates were based on outcomes in clinical trials and observational studies. Costs were estimated from the perspective of the third-party payer.

Results: The greatest cost-generating events were virtually the same for the two drugs and included severe stroke ($1 758 548 for 1 year for both drugs), moderate stroke ($380 355 for 1 year for both drugs), and severe lower gastrointestinal (GI) hemorrhage ($193 804 for 1 year for warfarin and $193 474 for second drug). The least costly events for both drugs were mild intracranial or intracerebral hemorrhage ($7584 for warfarin and $4314 for second drug) and fatal upper GI hemorrhage ($16 781 and $16 752). Total costs for adverse events over 5 years were similar: $18 330 662 for warfarin and $17 102 847 for the second drug. Fatalities for 5 years were 123 for warfarin and 101 for the non-warfarin drug. Varying assumptions for nursing home care and numbers of ischemic strokes and hemorrhages generated the widest variation in costs.

Limitations: We did not account for out-of-pocket expenses, 'pain and suffering' costs, or variation across practice settings.

Conclusions: There was substantial variation in numbers and costs of adverse events across 20 scenarios, and for fatalities between the two drugs, but variation in costs between the two drugs was modest.

Introduction

More than two million Americans over the age of 60 have atrial fibrillation[1]. Roughly 2–15% develop acute ischemic stroke. Use of oral anticoagulants such as warfarin is recommended by current practice guidelines in patients with atrial fibrillation who have risk factors for ischemic stroke[1]. These factors (age over 65, hypertension, diabetes) are so common that the majority of patients with atrial fibrillation meet American College of Cardiology criteria for taking warfarin[1].

Although warfarin is effective, it must be monitored over time to optimize its benefit while simultaneously minimizing the risk of hemorrhages. Medical care providers must vigilantly monitor patients, asking them to provide repeated blood sampling to determine the

anticoagulant effect measured using the international normalized ratios (INR) of the prothrombin time. INR values above 3.0 are associated with an exponential increase in risk of bleeding, whereas INR values below 2.0 are associated with increased risk of ischemic stroke[2].

Studies have addressed the economics of warfarin and reviews are available[3,4]. Accurate determination of the costs associated with warfarin is important, particularly when performing cost–effectiveness analyses and making comparisons with other therapies, such as aspirin or one of the new oral anticoagulants now under development[5,6]. Essentially all of these newer drugs do not require chronic monitoring and, as a result, would reduce the costs to health systems and make life easier for patients. Recent studies have addressed varied issues: comparing costs of warfarin to another drug[7], estimating warfarin (only) costs in Finland[8], and developing an economic model of stroke in atrial fibrillation[9]. Our study contributes to the literature. First, compared to existing studies, we created a more comprehensive model that included: 20 adverse events, varying times in the therapeutic INR range, and detailed per-unit costs for two anticoagulants. Second, our model, formulas, and calculations are available for use in future studies by other researchers.

Methods

Our semi-Markov model assumed we followed a hypothetical cohort of 10 000 patients with chronic atrial fibrillation for 1 and 5 years (2003–2007). The cohort was comprised of 70-year-old patients who were identical at baseline except for their INR values. We assumed our cohort would be similar to the cohorts in Go *et al.*[10], Hylek *et al.*[11] and Douketis *et al.*[12], since figures from these three studies are heavily used in our model. Go *et al.*[10] and Hylek *et al.*[11] rely on the same observational study (not a clinical trial) in which the mean age was 72, percentage female was 43%, and risk factor percentages were: previous ischemic stroke 9.3%, hypertension 51.0%, and congestive heart failure 30.8%. Douketis *et al.*[14] was a clinical trial for which: ages were < 65 years (21–22%, depending on drug), 65–75 (40%), and > 75 (38–39%), percent female was 30–31%, and risk factor percentages were 21% for previous ischemic stroke, and 77% for hypertension. Our age 70 assumption was similar to highly regarded cost studies: ages 65 and 75 for Gage *et al.*[14] and exactly 70 years for O'Brien and Gage[7]. In addition, we followed Gage *et al.*[14] and O'Brien and Gage[7] by not distinguishing between men and women in our hypothetical cohort.

Our model also assumed varying amounts of time in the therapeutic INR range (INR 2.0–3.0), 20 adverse health events, nine categories for hospitalization (nine Diagnostic Related Groups – DRGs), seven physician procedures and encounters within the hospital (seven Current Procedural Terminology – CPTs), varying numbers of days spent in the hospital, varying types of post-hospital care including outpatient physical therapy visits and placement in a skilled nursing facility. Varying probabilities were assigned to the time within INR ranges and likelihood of adverse health events. Per-unit costs were assigned to the DRGs, CPTs, hospital visits, and post-hospital care.

An overview of the model appears in Table 1. The first category accounts for variation in steady-state INR values. We assumed varying amounts of time spent in each of these INRs based on values in the literature[10,11]. Within our base-case, the following percentages of time applied: 4.2% (INR = 1.0–1.4), 22.6% (INR = 1.5–1.9), 62.5% (INR = 2.0–3.0), and 10.70% (INR > 3.0). These percentages sum to 100%.

Our model contained 20 possible adverse health events, listed in column 2. The categories were broadly divided into the two groups of ischemic stroke and hemorrhage. Four severity categories of ischemic stroke were posited: mild, moderate, severe, and death. For each category and INR range we assumed a corresponding likelihood of occurance as estimated in Go *et al.*[10] and Hylek *et al.*[11]. Several diagnostic categories of hemorrhage were posited including intracranial subdural, intracranial intracerebral, upper gastrointestinal, lower gastrointestinal, retroperiotoneal, urine, epistaxis, and 'other.' Three to four severity categories were allowed for hemorrhage: mild, moderate, severe, and death. For each category of hemorrhage, severity, and INR range, we assumed a corresponding likelihood of occurance as estimated by Go *et al.*[10], Hylek *et al.*[11], and Douketis *et al.*[12]. We assumed no deaths or severe cases resulted from less serious bleeding involving retroperiotoneal, epistaxis, or urinary tract. Complete descriptions of 20 adverse health events are available in an unpublished appendix from the authors.

We assumed a third-party cost perspective that relied heavily on Medicare and Medicaid data. Column 3 lists nine possible Diagnostic Related Groups (DRGs) from Medicare that applied to the adverse events. These ranged from a craniotomy (DRG 1) to gastrointestinal (GI) hemorrhage with complications (DRG 174) to rehabilitation (DRG 426). For example: a craniotomy (DRG 1) applied to severe intracranial subdural hemorrhage; and DRG 14 applied to severe upper GI hemorrhage.

Seven Current Procedural Terminology (CPT) codes from Medicare were assumed to apply to the scenarios. The CPTs are listed in column 4. Most typical were 'history and physical' (CPT 99223) and 'follow-up visit in hospital' (CPT 99232). But some unique CPTs were

Table 1. *Model variables*

1. Ranges of INR	2. Health events	3. Diagnostic related groups (DRG)		4. Current procedural terminology codes (CPT)		5. Days in hospital	6. Post-hospital care
1.0–1.4	Ischemic stroke: mild	*Name*	*Number*	*Name*	*Number*	Range from 1.0 to 11.3 days in hospital depending on DRG and severity of health event	Outpatient visits by physical therapist
1.5–1.9	moderate severe	Craniotomy, age greater than 17, with complications	1	Embolization non-neuro	37 204		100 days in skilled nursing facility
2.0–3.0	death			Upper GI endoscopy	43 235		
> 3.0	Hemorrhage: Intracranial: Subdural: mild severe death Intracerebral: mild severe death Gastrointestinal: Upper: mild severe death Lower: mild moderate severe death Other: retroperiotoneal expistaxis and other urinary	Intracranial hemorrhage and stroke with infarction	14	Partial colectomy with anatomosis	44 140		2 years, 9 months in non-skilled nursing facility
		Epistaxis	66	Upper GI colonoscopy	45 378		
		Other circulatory system diagnosis without complication	145	Craniectomy with evacuation of hematome	61 312		
				History and physical	99 223		
		Major small and large bowel procedures with complications	148	Physician follow-up visit in hospital	99 232		
		Gastrointestinal hemorrhage with complications	174				
		Gastrointestinal hemorrhage without complications	175				
		Kidney and urinary tract signs and symptoms, age greater than 17, without complications	326				
		Rehabilitation	462				

applied such as partial colectomy (CPT 44140) for two lower GI hemorrhage scenarios.

Days in hospital appear in column 5. Days in hospital ranged from 1.0 for a mild ischemic stroke and for intracranial, intracerebral mild hemorrhage, to 11.3 for a severe lower GI hemorrhage ending in death.

Clinical judgment informed our decisions when selecting the DRGs, CPTs, and some of the expected length of stays in the hospital. Most estimates for days in hospital were drawn from estimates of mean number of days for specific DRGs[15]. Cost data on DRGs and CPTs were derived from national estimates (2003 US dollars)[15,16].

Post-hospital care was posited based on clinical judgment and on Medicare allowances and requirements. We assumed, for example, eight outpatient visits by a physical therapist followed a mild stroke. We assumed Medicare paid $98.54 per visit in 2003. As another example, following a severe stroke, we assumed Medicare paid for 100 days of care at a skilled nursing facility for $276.60 per day in 2003. Estimates for cost of physical therapy were drawn from Medicare and Bureau of Labor Statistics (BLS) studies (Centers for Medicare and Medicaid Services and BLS websites: www.cms.hhs.gov/home/rsds.asp, accessed 12/1/2006 and www.bls.gov/cpi/, accessed 10/9/2006). Data on skilled nursing facilities were drawn from Medicare studies (same website) and Bodenheimer and Grumbach[17]. We assumed family members or friends cared for the patient after these 100 days so that third-party payer costs were zero.

Our method is outlined in Figure 1. Chances of adverse events were multiplied by percent of time in INR ranges to yield patient years for each event which, in turn, were then multiplied by unit costs for medical care to yield total costs for each adverse event. Our method can be most easily understood following a sample scenario, 1a: mild ischemic stroke in Table 2, which applies to only 1 year (years 2, 3, 4 and 5 were adjusted to reflect attrition due to death and severe hemorrhage). The assumption regarding time in INR range 1.0–1.4 (4.2%) was drawn from Go *et al.*[10] (page 2688). The assumption regarding chance of any ischemic stroke in INR range 1.0–1.4 (7.7%) was drawn from Hylek *et al.*[11] (their Table 5). We assumed that if there was an ischemic stroke in patients whose INR was in the range 1.0–1.4, the chance that the ischemic stroke was mild was 3%[11]. The value 0.97 in line 5 in the top panel is the number of patients in this category who sustained an ischemic stroke. This 0.97 value is obtained by multiplying the number of cases, times the risk of having a low INR, times the risk of having an ischemic stroke in this INR range, times the chance that the ischemic stroke was mild: $10\,000 \times 0.042 \times 0.077 \times 0.03$.

Continuing further down Table 2, the next two panels apply to the number of ischemic strokes associated with an INR in the range 1.5–1.9, and INR between 2.0 and 3.0. 'Sum of sub-totals' adds the number of patients with stroke: 0.97 + 1.29 + 0.69 or 2.95 patients. This number for patients, 2.95, is then multiplied by costs-per-patient with the DRG categories, CPT categories, and other categories and these products are added to post-hospital care. Costs for hemorrhages were similarly calculated.

Numerical assumptions behind our base-case appear in Table 3 which lists the eight most expensive scenarios and the unique variables within each of these eight scenarios. (A long table listing all 20 scenarios is available from the authors.). In Table 3, to conserve space, we did not list variables in subsequent scenarios if those variables were listed in previous scenarios or in Table 2. For example 'time in INR range 1.0–1.4' was included in Table 2 so we did not list it in Table 3.

We also calculated costs associated with a second anticoagulant based upon ischemic stroke and bleed risks reported for ximelagatran[10–12]. Because the literature suggests strong similarities for ischemic stroke risks between warfarin and ximelagatran, we assumed ximelagatran would result in the same number and kinds of strokes associated with warfarin. We also assumed the second anticoagulant generated the same per-unit costs for each type of ischemic stroke event as warfarin. Full descriptions for both drugs, each scenario, with sources, are in an unpublished appendix and spreadsheets for all calculations and are available from the authors.

We constructed a 5-year semi-Markov model. Attrition was allowed for fatalities and severe bleeds. We reasoned that patients with severe bleeds would be taken off any anticoagulant. We retained patients with severe ischemic strokes within the model. We assumed that persons with severe ischemic strokes and severe bleeds would generate greater costs than the average for other patients retained over 5 years. Specifically, we assumed that subsequent annual costs for patients after their severe ischemic strokes and bleeds would equal 20% of the medical costs (excluding nursing facilities) generated by their severe events. These 20% cost amounts were roughly three times the average costs for all hypothetical patients.

We conducted sensitivity analyses based upon reasonable alternative values for the most consequential variables.

Results

Table 3 presents the costs of the eight most expensive adverse health events associated with chronic anti-

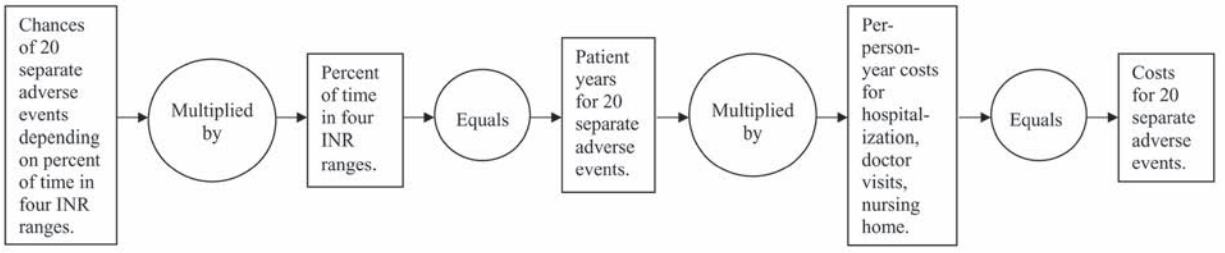

Figure 1. *Arithmetic scheme for model*

Table 2. *Example of a scenario*

Variable	Value	Source
	Scenario 1a – Mild stroke	
Patient years	10 000	Our assumptions: year 1 only
Time in INR range 1.0–1.4	4.20%	Go, Hylek, page 2688[10]
Chance any stroke in INR range 1–1.4	7.70%	Hylek, Go, Table 5[11]
Chance stroke is mild in INR range 1–1.4	3.00%	Hylek, Go, Table 2[11]
Sub-total in INR range 1–1.4	0.97	Product of 4 previous numbers
Patient years	10 000	Our assumptions: year 1 only
Time in INR range 1.5–1.9	22.60%	Go, Hylek, page 2688[10]
Chance any stroke in INR range 1.5–1.9	1.90%	Hylek, Go, Table 5[11]
Chance stroke is mild in INR range 1.5–1.9	3.00%	Hylek, Go, Table 5[11]
Sub-total in INR range 1.5–1.9	1.29	Product of 4 previous numbers
Patient years	10 000	Our assumptions: year 1 only
Time in INR range 2–3	62.50%	Go, Hylek, page 2688[10]
Chance any stroke in INR range 2–3	0.55%	Hylek, Go, Table 5[11], weighted average
Chance stroke is mild in INR range 2–3	2.00%	Hylek, Go, Table 5[11]
Sub-total in INR range 2–3	0.69	Product of 4 previous numbers
Sum of sub-totals, patient years	2.95	
DRG: Intracranial hemorrhage and stroke with infarction	Number 14	RHW clinical judgment
Cost, national average, DRG14	$5567.40	Hart and Schmitt (2003)[15]
CPT: History and physical	99 223	Clinical judgment
Cost, national average, CPT99223	$154.95	Wasserman (2004)[16]
CPT: Physical follow-up visit in hospital	99 232	Clinical judgment
Cost, national average, CPT99232	$54.89	Wasserman (2004)[16]
Days in hosptial minus one	1	Hart and Schmitt (2003)[15]
Post-hospital care	$2333.44	See footnote
Sum of costs for Scenario 1a	$19 352.61	Sum and product of (sum of subtotals), cost for DRGs and CPTs, hospital days, and post-hospital care

Assumed eight outpatient visits by physical therapist (assumption attributed to clinical judgment of David Kilmer, MD, Physical Medicine and Rehabilitation, UC Davis). We assumed paid by Medicare (our judgment) and no deductible or co-payment on home healthcare (Bodenheimer and Grumbach, 3rd edn, 2002, p. 10)[17]

Table 3. *Eight most expensive scenarios, variables, base-case values, first year only (abbreviated list, no variables repeated across scenarios. Complete list in Appendix available from authors)*

Variable	Warfarin value	Non-warfarin, if different
1. Scenario 1b – Moderate stroke		
Chance stroke is moderate in INR range 1–1.4	38.00%	
Chance stroke is moderate in INR range 1.5–1.9	38.00%	
Chance stroke is moderate in INR range 2–3	55.00%	
Days in hospital minus one 1b	5.1	
Post-hospital care 1b	$95 170	
Sum of costs for Scenario 1b	$380 355	
2. Scenario 1c – Severe stroke		
Chance stroke is severe in INR range 1–1.4	50.00%	
Chance stroke is severe in INR range 1.5–1.9	50.00%	
Chance stroke is severe in INR range 2–3	42.00%	
Days in hospital minus one 1c	7	
Post-hospital care 1c		
100 days	$1 440 533	
3 years	$5 537 927	
Sum of costs for Scenario 1c (100 days)	$1 758 548	
3. Scenario 2b – Intracranial subdural bleed, severe		
Time in INR range 2–3	62.50%	
Chance of any bleed INR range 2–3	2.83%	2.12%
Chance bleed is intracranial	10.66%	8.14%
Chance intracranial is subdural	54.00%	
Chance subdural bleed is mild	40.00%	
Time in INR range greater than 3	10.70%	
Chance of any bleed in INR range greater than 3	8.49%	6.37%
Sum of costs for Scenario 2a	$35 613	$20 382
Chance subdural bleed is severe	40%	
DRG: Craniotomy, age greater than 17 with complications	Number 1	
Cost, national average, DRG1	$15 885.65	
Days in hospital minus one 2b	9.9	
CPT: craniac with evacuation of hemotome	61 312	
Cost, national average, CPT61312	$1633.97	
Sum of costs for Scenario 2b	$112 302	$64 274
4. Scenario 3a – GI, upper, mild		
Chance of any GI bleed	40.16%	53.49%
Chance GI is upper, nonfatal	63.00%	
Chance upper GI bleed is mild	50.00%	
DRG: GI hemorrhage without complications	Number 175	
Costs, national average, DRG175	$2452.69	
CPT: upper GI endoscopy	43 235	
Costs, national average, CPT43235	$283.39	
Days in hospital minus one 3a	1.9	
Sum of costs for Scenario 3a	$101 444	$101 271
5. Scenario 3b – GI, upper, severe		
Chance upper GI bleed is severe	50.00%	
DRG: GI hemorrhage with complications	Number 174	
CPT: colonoscopy	45 378	
Costs, national average, CPT45378	$372.25	
Days in hospital minus one 3b	5	
Sum of costs for Scenario 3b	$176 200	$175 900
6. Scenario 3f – GI, lower, severe		
Chance lower GI bleed is severe	33.30%	
CPT: partial colectomy with anatomosis	44 140	
Cost, national average, CPT44140	$1203.76	
Days in hospital minus one 3f	11.3	
Sum of costs for Scenario 3f	$193 804	$193 474

Table 3. (Continued.)

Variable	Warfarin value	Non-warfarin, if different
7. Scenario 3g – GI, lower, death		
Chance lower GI bleed is fatal	4.00%	
Days in hospital minus one 3g	11.3	
Sum of costs for Scenario 3g	$72 749	$72 625
8. Scenario 4b – Epistaxis and other		
Chance bleed is expitaxis	20.49%	13.95%
DRG: epistaxis	Number 66	
Cost, national average, DRG66	$2551.03	
Days in hospital minus one 4b	2.1	
Sum of costs for Scenario 4b	$154 761	$78 972
Grand total for all 20 (12 not shown), first year assuming severe stroke patients spend 100 days in nursing facility	$3 386 072	$3 158 049

coagulation therapy for 10 000 hypothetical patients followed for 1 year. The greatest cost-generating events were the same for warfarin and a second anticoagulant. These highest-cost events for 1 year were: severe stroke ($1 758 540), moderate stroke ($380 355), and severe lower gastrointestinal (GI) hemorrhage ($193 804 for warfarin, and $193 474 for second drug). The least costly events for both drugs were mild intracranial or intracerebral hemorrhage ($7584 for warfarin and $4314 for second drug), and fatal upper GI hemorrhage ($16 781 for warfarin and $16 752 for second drug).

Table 4 presents similar data, including number of events and costs over 5 years. Data on ischemic strokes for patients appear in the top of the table. The greatest number and cost of events within our separate 20 scenarios occurred for moderate and severe strokes for warfarin and summed to 489.94 events and $11 154 508 costs. For hemorrhage, the greatest number and costs occurred for the severe upper and lower gastrointestinal scenarios combined: 222.97 events and $2 546 167 costs for warfarin, 223.00 events and $2 545 807 costs for the second coagulant.

For both drugs, the number of deaths and the costs of these fatalities were greater for hemorrhages than for the ischemic strokes. For warfarin, for example, the number and costs were 87.71 and $929 905 for all hemorrhages and 35.02 and $213 868 for all ischemic strokes. Again, for both oral anticoagulants, although the number of severe ischemic strokes was similar to the number of severe hemorrhages, the costs were considerably higher for ischemic strokes. For warfarin, for example, there were 256.20 severe ischemic strokes that cost, in total, $9 283 306, whereas there were 275.9 combined severe bleeds that cost, in total, $3 645 711.

Differences between the costs associated with the two drugs appear in the final column (warfarin minus second drug). Differences range from –$15 755 to +$372 144. For ischemic strokes, differences were small. Apart from the ischemic stroke results, the greatest similarities between the two drugs occurred for both upper and lower gastrointestinal events. The greatest differences between the two drugs occurred for both subdural and intracerebral hemorrhage as well as retroperiotoneal and especially 'epistaxis and other' bleeds. Using the data reported by Douketis *et al.*[12], we assumed there were a little more than twice the number of warfarin cases that experienced more minor or 'other bleeding' when compared to the second drug. This 'other' category included intraocular, subcutaneous hematoma, muscle hematoma, hemoptysis, tongue hematoma, rectal and vaginal bleeding, among others.

Over 5 years, the model calculated 123 fatalities for warfarin and 101 fatalities for the second anticoagulant.

We conducted sensitivity analyses (Figure 2) for significant model assumptions including: time in nursing home, time (or probability) outside therapeutic range, chance of stroke, and chance of hemorrhage. These sensitivity analyses applied only to patients with warfarin. We found the sensitivity analyses applied to patients with the second anticoagulant were strikingly similar.

Our base-case assumed patients with a severe ischemic stroke would spend 100 days in a skilled nursing facility paid by Medicare. For sensitivity analyses, in our first new assumption, we allowed there to be 2 additional years and 9 months spent in a nursing home paid by Medicaid for an increase in cost. The second assumption allowed for the elimination of 100 days in a skilled nursing facility paid by Medicare and led to a decrease in costs. The Medicaid spending added an additional $78 675

Table 4. *Number, costs and pharmaceuticals across adverse events for 5 years*

	Warfarin		Second drug		Difference
	Number of events	Costs ($)	Number of events	Costs ($)	Warfarin costs minus second drug costs ($)
Stroke					
Mild	14.49	95 208	14.52	95 381	–173
Moderate	233.74	1 871 202	234.17	1 874 609	–3407
Severe	256.20	9 283 306	256.67	9 299 061	–15 755
Death	35.02	213 868	35.09	214 257	–389
Hemorrhage					
Intracranial subdural					
Mild	30.33	175 203	17.39	100 457	+74 746
Severe	30.33	774 623	17.39	444 237	+330 386
Death	15.16	276 243	8.69	158 390	+117 853
Intracranial intracerebral					
Mild	6.46	37 312	3.70	21 394	+15 918
Severe	22.60	324 921	12.96	186 709	+138 212
Death	35.52	213 208	20.37	122 248	+90 960
Gastrointestinal, upper					
Mild	166.61	499 065	166.63	499 123	–58
Severe	166.61	1 213 559	166.63	1 213 428	+131
Death	15.87	82 556	15.87	82 565	–9
Gastrointestinal, lower					
Mild	56.36	173 835	56.37	173 855	–20
Moderate	56.36	321 450	56.37	321 487	–37
Severe	56.36	1 332 608	56.37	1 332 379	+229
Death	21.16	357 898	21.16	357 939	–41
Retroperitoneal	75.60	210 415	34.51	96 064	+114 351
Epistaxis and 'other'	269.87	761 365	137.96	389 221	+372 144
Urinary tract	54.00	112 817	57.46	120 043	+7 226
Total	1618.67	18 330 662	1390.29	17 102 847	+1 261 991

per patient or $20 156 535 in total spending over 5 years. The ratio of this additional cost to our base-case is roughly 1.10/1.0 indicating a 110% increase over the base-case. This first new assumption by far exceeded the costs of any of the other new assumptions entertained in our sensitivity analyses. The next greatest variation derived from increasing the numbers of ischemic strokes or hemorrhages by 50%. The dollar and percentage changes for the 50% increase and decrease for strokes and hemorrhages were equal because the model was linear, i.e. the model did not include, for example, polynomials or log transformations.

Discussion

Our study estimated the cost of oral anticoagulants in a hypothetical cohort of 10 000 senior patients with atrial fibrillation. We posited 20 scenarios corresponding to adverse events involving ischemic strokes and hemorrhages. The model allowed for varying time within four INR ranges: 1.0–1.4, 1.5–1.9, 2.0–3.0, and >3.0. We estimated costs over 1 year ($3 386 072 for warfarin and $3 158 079 for the second drug) and 5 years ($18 330 662 and $17 049 391). In the first year, per-person estimated costs of adverse events for warfarin were $338.61 and for the non-warfarin drug were $315.80. For both the 1-year and 5-year results and for both drugs, the numbers and costs of fatalities were greater in association with hemorrhagic complications compared to strokes. However, severe ischemic strokes were considerably more costly than severe hemorrhages for both drugs. The difference was attributed largely to our assumption that severe strokes resulted in rehabilitation and skilled nursing home stays but that severe bleeds did not. Differences in 5-year costs for strokes were negative for two reasons:

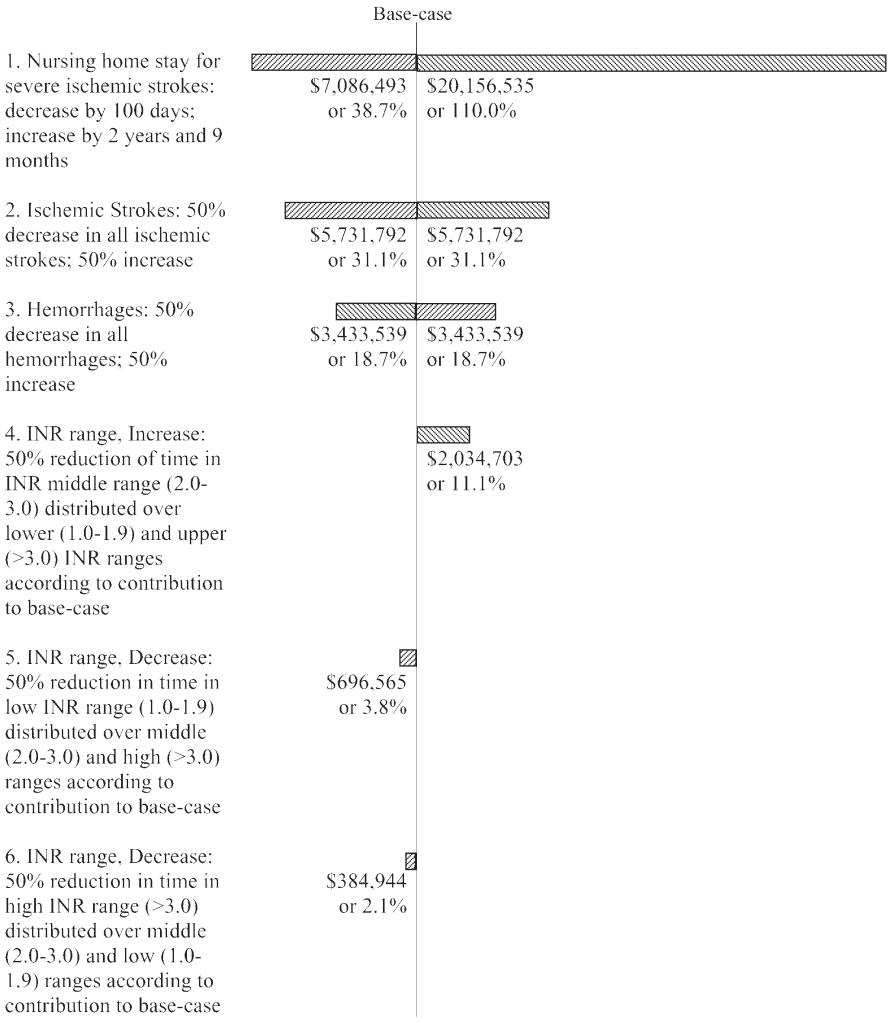

Figure 2. *One-way sensitivity analysis on influential variables for warfarin, 5 years*

we assumed the same *annual* risk of strokes for the two drugs, but the second drug was returning more patients than warfarin to the model in each year. That is, over the 5 years, warfarin was responsible for more deaths and severe bleeds than the second anticoagulant. The cost of adverse gastrointestinal events for warfarin were quite similar to those for the non-warfarin drug. A sensitivity analysis demonstrated that variation in assumptions regarding nursing home stays generated great variation in costs, but that plausible variation in other assumptions generated only modest variation in costs.

We compared our model to two representative studies[7,14]. Gage *et al.*[14] and O'Brien and Gage[7] develop cost–effectiveness models to compare warfarin with aspirin and with ximelagatran, respectively. Like us, both Gage *et al.*[14] and O'Brien and Gage[7] posit hypothetical populations (>65 years old for Gage *et al.*[14] and exactly 70 years old for O'Brien and Gage[7]) involved in therapy for many years. Also, like us, they rely on Medicare costs.

There are three broad advantages of our model over Gage *et al.*[14] and O'Brien and Gage[7], as well as over other published studies[20–25]: the comprehensive modeling of the entire spectrum of adverse events that are included in our model, the corresponding variety of unit prices for DRGs and CPTs, and the inclusion of varying levels of INR. Gage *et al.*[14] consider only four scenarios: major GI hemorrhages, hemorrhagic stroke, minor hemorrhages, and ischemic stroke. Whereas O'Brien and Gage[7] do allow for the four categories for ischemic stroke we included, they allow for only four hemorrhages.

Our study has some limitations. First, whereas we considered only values and ranges for the number of adverse events that were consistent with the literature, the depth of this literature is not great. Some values and ranges for the incidence rates we used might be higher or lower than the values that will be reported in future research. Second, we took the perspective of the third-party payers – Medicare and Medicaid. We ignored out-of-pocket expenses, any additional provider costs not covered by Medicare and Medicaid payments, and any costs associated with 'pain and suffering' that might be accounted for in a societal perspective of costs[26]. Third, we omitted costs for 101 to 123 fatalities over 5 years. From the strict point of view of Medicare and Medicaid,

a death reduces future costs. But from the societal point of view, a death is a great loss. Fourth, we restricted attention to only those patients with atrial fibrillation. Fifth, we used only DRGs and CPTs which we judged most appropriate for each adverse event. Additional DRGs and CPTs that others might view as appropriate are in Appendix C, available from authors. Sixth, we relied on the clinical judgment of only one physician to estimate number of outpatient visits.

Variables for age, gender, and risk factors such as previous ischemic stroke or hypertension were not explicitly included in the model. These were implicitly captured, however, in the values on variables reflecting time in various INR ranges, chances of different severities of ischemic stroke and hemorrhages since these values correspond to cohorts from Go *et al.*[13] and Douketis *et al.*[14]. Our age 70 assumption appears to be closer to clinical trial studies (age 69) than patients seen in clinical practice (age 75)[1].

A final limitation is that we did not account for any variation across practice settings. Lafata *et al.*[20,21] estimate a monitoring cost differential of $157 (1997 dollars) for 'usual' care with a primary care physician and $233 (1997 dollars) for care in an anticoagulation clinic. But when Lafata *et al.*[20,21] combine the costs of monitoring with adverse events, the overall costs are very similar – $420 for usual care and $406 clinic care – suggesting that any account of usual and clinic care would not have appreciatively altered our findings. On the other hand, the Lafata *et al.*[20,21] studies were conducted prior to the 2006 Guidelines[1] so that this similarity of costs between usual and clinic care may not hold today.

Conclusions

We found considerable variation in costs associated with 20 adverse events. For example, the numbers and costs of fatalities were greater for hemorrhages than ischemic strokes; but the number and costs for severe disabling non-fatal events were greater for ischemic strokes than for hemorrhages. Variation in assumptions for nursing home stays generated the greatest variation in costs. We also found that warfarin generated about 7% more costs and 22% more fatalities than the non-warfarin drug. Despite limitations, we believe the detail associated with our 20-scenario model will prove useful to future researchers attempting to compare the costs of warfarin with other potential pharmaceutical agents.

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