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Budget Impact Analysis: Warfarin and Newer Oral Anticoagulants for the Prevention of Stroke Among Veterans With Atrial Fibrillation

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PREFACE

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QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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POTENTIAL VA BUDGET IMPACT OF NEWER ANTICOAGULANTS FOR STROKE PREVENTION IN ATRIAL FIBRILLATION

A systematic literature review and meta-analysis by the Durham Veterans Affairs (VA) Evidence-based Synthesis Program (ESP), in addition to research by others, has shown that newer anticoagulants can potentially improve stroke prevention among patients with atrial fibrillation (AF). This systematic review[1,2] estimated lower all-cause mortality (risk ratio 0.88; risk difference 8 fewer deaths per 1000 treated patients) and fewer hemorrhagic strokes (risk ratio 0.48; 95% CI, 0.36 to 0.62) compared with adjusted-dose warfarin. Although the newer anticoagulants are expensive, economic analyses have shown that for certain subgroups of patients with AF, these newer anticoagulants are cost-effective under the traditional threshold of $50,000 per quality-adjusted life year saved. Inclusion of newer anticoagulants in the VA formulary may improve stroke prevention for Veterans with AF but may also lead to a dramatic increase in drug expenditure. However, some of the increased drug expenditure may be mitigated by reductions in other forms of healthcare expenditures inherent with warfarin use, such as reductions in long-term costs associated with stroke care. Thus, we conducted a budget impact analysis (BIA) from the perspective of the VA healthcare system, under different plausible drug access scenarios, in order to assess the potential overall annual budget impact of including newer anticoagulants in the VA formulary for stroke prevention in Veterans with AF.

METHODS

Study Design

In this BIA, we first undertook an additional literature review to augment the ESP report.[2] Because the newer anticoagulants either are new entrants into the market or are going through the regulatory approval process, their budgetary impact cannot be accurately estimated by observing their utilization in secondary administrative data. Also, the clinical administrative data do not include CHADS2 stroke risk score. Instead, to estimate the potential impact of newer anticoagulants on future VA budgets, we derived an algorithm that imputes the uptake of newer anticoagulants. The algorithm, discussed in detail below, takes into consideration an AF patient's CHADS2 stroke risk score, risk of bleeding, and quality of International Normalized Ratio (INR) control in predicting the proportions of AF patients likely to receive warfarin or a newer anticoagulant.

We envision three scenarios that establish lower and upper bounds of impact as well as an evidence-based middle ground. The lower bound is the "no access" budget impact scenario where the VA excludes newer anticoagulants from the formulary and maintains stroke prevention for AF patients via warfarin use only. In the upper bound "unrestricted access" budget impact scenario, all AF patients with a CHADS2 score of 0 but prescribed warfarin or CHADS2 score ≥1 receive the newer anticoagulant only. The middle ground is a "restricted-access" budget impact scenario where warfarin or a newer anticoagulant is prescribed based on stroke and major bleeding risk and ability to control international normalized ratio (INR). The middle ground scenario is the primary focus of this BIA.

Atrial Fibrillation Population

To estimate the size of the hypothetical cohort needed for the BIA, we identified patients with AF by searching for ICD-9 code 427.3 in the primary diagnosis code variable DXLSF in the VA's Outpatient Clinic dataset file for fiscal year 2011, the most current year for which a full year of clinical data was available at the time of analysis. We also queried all secondary diagnosis codes in the file and found no patients who had AF as a secondary diagnosis but not as a primary diagnosis. We then stratified this AF population by their risk of stroke using the CHADS2 score. We used the distribution of CHADS2 scores reported in the TREAT-AF study[3] for stratification because it was specific to the Veteran population. Next, we needed decision rules by which warfarin or a newer anticoagulant was prescribed to patients on a limited access. TREAT-AF investigators found that 55% of Veterans with AF received warfarin so therefore we assumed this would continue to be the case; the remaining 45% are assumed to receive aspirin treatment or no medication and are excluded from the analysis. For Veterans with CHADS2 scores ≥ 1, we adopted the algorithm prescribed by Shah, et al.,[4] to determine which anticoagulation treatment a patient received, as follows:

1. If CHADS2 score was either 1 or 2 they received warfarin, unless they had poor INR control or were at high risk of bleeding, in which case they received the newer anticoagulant;
2. If CHADS2 score was 3 to 6, they received the newer anticoagulant unless they had excellent INR control, in which case they received warfarin.

We also considered an alternative algorithm where if the CHADS2 score was 3 to 6, the patient received the newer anticoagulant regardless of how well controlled their INR was. We used the high risk of bleeding (4.4%) reported in a randomized controlled trial comparing clinic-based INR testing to self-testing among Veterans[5] to estimate the high risk of bleeding cohort. Shah defined poor INR control as time within therapeutic range (TTR) being less than 57.1 percent, and excellent INR control as TTR greater than 72.6 percent. The THINR authors reported a TTR of 62.4 ± 17.1 percent among the Veterans in their study. Assuming a normal distribution, we calculated the cumulative probability of poor and excellent INR control based on the THINR sample and applied them to our hypothetical cohort.

Atrial Fibrillation-related Events

The AF events we considered for this BIA were hemorrhagic and ischemic strokes, myocardial infarctions (MIs), and major bleeds (defined as gastrointestinal bleeds or intracranial hemorrhages). We relied on event rates reported in the respective clinical trials for each newer anticoagulant and warfarin control group to attribute AF-related events and their respective costs to the AF patients. To estimate the budget impact of Dabigatran, we relied on event rates reported in the RE-LY study.[6] We considered only the 150-mg twice daily treatment regimen because the 110-mg dosage is not approved for use in the U.S. For Rivaroxaban, we used event rates reported in the ROCKET AF study.[7] For Apixaban, we used the results of the ARISTOTLE study.[8] We did not include transient ischemic attacks in the analysis because the event rate was not reported in the clinical studies. Also, using the cost estimation procedure discussed below, we found that transient ischemic attacks were relatively inexpensive events (mean of $1,246) compared with the other two forms of stroke. We did not include minor bleeding or dyspepsia events because the

costs incurred for these events are minimal.[4,9,10] Pulmonary embolisms were not included because they rarely occurred and event rates were not significantly different among warfarin, Dabigatran, and Apixaban. Lastly, while death is an important outcome, it is difficult to attribute a cost to this outcome in a secondary data analysis such as this. Because of concern for additional MIs induced by newer anticoagulants, we also considered MI rates for warfarin and Dabigatran as estimated by meta-analysis.[11] Also, discontinuation of anticoagulant medications can occur due to side effects or drug or food interactions. Therefore, the drug discontinuation rates for both treatment arms reported in the respective clinical trials were used to reduce total cost estimates due to drug discontinuation in this BIA.

Costs

To derive costs for warfarin and Dabigatran, we relied on the VA PBM Prices.DBF file. The cost estimates used reflect drug acquisition cost as well as storage, dispensing, and indirect overhead costs. We used the average cost and ranges reported in a recent systematic review for INR testing costs.[12] Because Rivaroxaban and Apixaban are not currently available in the United States, the prices for these anticoagulants are not known. Rivaroxaban is available in Canada, where it is approximately twice the price of Dabigatran. Because Dabigatran was first to market in the United States, and because the effectiveness and side effect profile of Rivaroxaban and Apixaban are not significantly different from that of Dabigatran, we made the conservative assumption that Rivaroxaban and Apixaban will be priced the same as Dabigatran when they enter the U.S. market. If Rivaroxaban and Apixaban are priced higher than Dabigatran, then the difference in total costs between warfarin and these newer anticoagulants will be even greater than our estimates.

For costs of hemorrhagic and ischemic strokes and MI events, we relied on updated cost models based on previous research.[13] Costs for patients who used VA for healthcare between 2000 and 2008 were obtained from VA administrative records. These costs were estimated by the VA Health Economics Resource Center using hypothetical Medicare payments for outpatient and inpatient services and VA costs for medications. Healthcare services obtained outside of VA that were reimbursed by VA were also included in the calculations. Costs were inflated to 2012 dollars using the general consumer price index. The marginal cost per patient attributable to a given health condition in each year was estimated using a regression model. Model fitting indicated that, in this case, ordinary least squares performed better than other cost modeling approaches such as semi-log or generalized linear model log link with a gamma distribution. The dependent variable in the regression model was total cost, and the independent variables included covariates for approximately 40 different chronic conditions, demographic characteristics, a means test indicator, a service connection level, insurance status, a dummy variable for the year cost was incurred, and an interaction term for year with each chronic condition. For major bleed cost, we used the average of the costs in the Shah[4] and Freeman[9] studies inflated to 2012 dollars.

Budget Impact Analysis

For the lower bound scenario with closed access to newer anticoagulants, we multiplied the proportion of Veterans with CHADS2 score 0 receiving warfarin according to the TREAT-AF study[3] and all AF patients with CHAD2 score ≥1 by the annual cost of warfarin and INR testing to derive total warfarin cost. We added INR testing cost in the following manner: (1) for patients with poor INR control, we assumed they received INR testing an average of every 2 weeks; (2) for patients with good INR control, we assumed they received INR testing once per month; (3) for patients with excellent INR control, we assumed they received INR testing every 3 months.[14] The number of INR tests was multiplied by cost per INR test to derive total INR testing cost. We averaged the hemorrhagic and ischemic strokes and major bleeding rates observed in the three clinical trials along with the MI rates reported in the Uchino meta-analysis[11] and then multiplied these rates by their respective event costs to derive total cost of AF-related events for warfarin.

For the upper bound scenario with open access to the newer anticoagulants, we multiplied all Veterans with an AF diagnosis by the annual cost of the newer anticoagulant to calculate total newer anticoagulant cost. We used the same approach as for the lower bound to derive AF-related event costs, except that we averaged the newer anticoagulant event rates from the three main clinical trials. For both bounds, we multiplied the total cost results by 1 - the average percentage of patients observed to discontinue use of warfarin and the newer anticoagulants, respectively, in the three major clinical trials to factor in reduced total cost due to drug discontinuation.

For the middle ground scenario with restricted access to newer anticoagulants, we derived cohorts of patients receiving warfarin or newer anticoagulants using the algorithm described above. To estimate the budget impact of each cohort, we multiplied the cohort size by its respective medication cost (and in the case of warfarin, also INR testing cost), the probabilities of hemorrhagic and ischemic strokes, major bleeds, and MIs and multiplied each by their respective estimated annual costs of these events. These costs for medications and AF-related events were aggregated to derive the subtotal. The subtotal was reduced due to drug discontinuation to derive total cost.

To assess the potential range of budget impact, we considered these other scenarios and factors:

1. Patients with CHADS2 scores of 3 to 6 received Dabigatran whether or not they had excellent INR control.
2. There is concern in the literature that newer anticoagulants increase the risk of an MI occurring in patients with AF; therefore, we assessed the budget impact based on a meta-analysis of MI rates conducted by Uchino.[11]
3. To calculate the best-case scenario for newer anticoagulants, stroke, major bleeding, and MI event rates were assigned their respective minimum hazard ratios relative to the warfarin risk probabilities, and costs were assigned the lowest values. To calculate the worst-case scenario for newer anticoagulants, the AF-related events were assigned the maximum hazard ratio relative to the warfarin risk probabilities and costs were assigned their highest values.
4. To calculate the budget impact of the newer anticoagulants Rivaroxaban and Apixaban, we used the respective AF-related event rate probabilities and their hazard ratios.

RESULTS

Table 1 presents the event rates and hazard ratios for hemorrhagic and ischemic strokes, MIs, major bleeds, and drug discontinuation rates used for the BIA. Table 2 presents the cost estimates used in the BIA. A literature review yielded a mean cost of $36 (95% CI, $6 to $62) per INR test[11] and $5,250 ($1,500 to $8,000) per major bleed.[4,8] Cost modeling yielded mean costs of $27,702 (95% CI, $22,443 to $32,962) attributable to hemorrhagic strokes; $4,847 (95% CI, $4,021 to $5,675) for ischemic strokes; and $43,988 (95% CI, $40,020 to $47,957) for MIs. Table 3 presents the numbers of Veterans with each CHADS2 stroke risk score, the number likely to have poor or excellent INR control, and the number at risk of a major bleed.

Lower Bound

In FY2011, there were 135,782 Veterans with a diagnosis of AF. Of the 23,490 patients with the lowest CHADS2 stroke risk score, 12,849 were assumed to receive warfarin therapy and included in the budget impact analysis; the remaining 10,641 patients were assumed to receive either an aspirin regimen or no medications and were excluded from this analysis. The remaining 112,292 Veterans, with a CHADS2 stroke risk score greater than or equal to 1, were expected to receive warfarin therapy. We calculated that 38 percent of patients receiving warfarin will have poor INR control and will require INR testing every two weeks; 35 percent will have good INR control and require INR testing 12 times per year. The remaining 27 percent will have excellent INR control and will require only four INR tests per year. At a monthly warfarin cost of $5.38 plus a cost of $36 per INR test, this cohort is estimated to incur a total warfarin treatment cost of $74,702,966 per year. In terms of major AF-related events, patients incurred $14,896,904 in hemorrhagic stroke; $7,415,395 in ischemic stroke; $21,557,119 in major bleeding; and $43,458,803 in MI costs. If the entire Veteran population with AF that was indicated to receive warfarin therapy received it, the annual cost incurred would be $162,031,187. However, because a substantial portion of the population will not be able to tolerate warfarin, the final total cost is expected to be $136,106,197 (Table 4).

Middle Ground

Treatment population

Based on the algorithm, 31,114 patients with a CHADS2 stroke risk score of 1 or 2 were predicted to have poor INR control and 2,234 patients were at high risk of a major bleed and thus received a newer anticoagulant. Conversely, 8,341 patients with a CHADS2 score ≥3 had excellent INR control and low risk of bleeding and thus received warfarin (Table 3). In total, we estimated that 56% of Veterans with AF (n=69,721) would receive warfarin and 46% (n=55,339) would receive a newer anticoagulant. In the alternative scenario where all patients with a CHADS2 score ≥3 received a newer anticoagulant, the respective cohorts nearly equal with 61,450 patients receiving warfarin and 63,680 receiving a newer anticoagulant.

Dabigatran cost

Table 4 also provides the budget impact results for the middle ground scenarios. In the base-case restricted access to Dabigatran scenario, the VA would incur $44,660,368 in intervention costs among warfarin patients and $203,203,381 among the Dabigatran patients. Once AF-related

comorbidities and drug discontinuation are considered, warfarin patients are expected to incur $80,142,130 while Dabigatran patients are expected to incur $201,740,261. Therefore, the total annual cost for anticoagulation among AF patients is estimated to be $281,882,391. If the more cautious decision rule is adopted, where all AF patients with CHADS2 scores ≥3 receive the newer anticoagulant regardless of their ability to control their INR, the relatively fewer patients receiving warfarin and more patients receiving Dabigatran leads total cost to increase to $302,785,186. With prices and event rates most favorable toward Dabigatran (i.e., best-case scenario), total costs incurred by Dabigatran patients could decrease by $11,311,997; under the worst-case conditions, costs incurred by Dabigatran patients could be an additional $25,803,734.

AF-related comorbidity costs

In the base case, the total cost *of hemorrhagic strokes* is expected to be $8,872,234, with $7,339,343 incurred by warfarin patients and $1,532,990 incurred by Dabigatran patients. Under the best circumstances, Dabigatran patients incur $660,725, and under the worst, $3,396,421 in hemorrhagic stroke costs. AF patients incur $6,522,923 in total *ischemic stroke* cost in the base case, with $4,055,242 incurred by warfarin patients and $2,467,681 by Dabigatran patients. In the best circumstances, Dabigatran patients incur $2,029,351 for ischemic stroke cost and $3,693,188 in the worst case. In the base case, patients are expected to incur $21,334,164 in *major bleeds* cost with warfarin patients incurring $12,298,753 and Dabigatran patients incurring $9,035,412. There is a large difference between best-case and worst-case scenarios for major bleeds cost for Dabigatran. In the best case, major bleeds cost is $2,259,143; however, in the worst case, major bleeds cost may be as high as $15,916,270. In the base case, AF patients are expected to incur $34,267,799 in *MI* cost, with $16,254,461 incurred among warfarin patients and $18,013,338 incurred among Dabigatran patients. In the best case, MIs cost $14,788,204 whereas in the worst case they result in $33,847,277. Alternatively, if MI rates from the Uchino meta-analysis are used, total MI-related cost is much higher at $53,195,742 with warfarin patients expected to incur $24,228,347 and Dabigatran patients expected to incur $28,967,395.

Rivaroxaban and Apixaban

Because these two drugs are not available in the U.S. yet we assumed that they would be priced the same as the first-to-market Dabigatran. Using event rates for warfarin and Rivaroxaban from the ROCKET AF trial, total cost of the restricted use scenario was estimated to be $312,700,880. Rivaroxaban had higher stroke, major bleed, and MI and therefore total costs compared to Dabigatran. Based on event rates from the ARISTOTLE trial, Apixaban use had a total cost of $261,199,134, which was less than what was incurred by Dabigatran use. Rivaroxaban use led to higher hemorrhagic cost but resulted in lower ischemic, MI, and especially major bleed costs.

Upper Bound

With an annual cost of $3,672 per patient for newer anticoagulants, if all AF patients eligible for anticoagulation were to be prescribed a newer anticoagulant, the intervention cost alone could be as high as $459,218,232. Patients would incur an additional $6,928,793 in hemorrhagic strokes, $6,526,356 in ischemic strokes, $19,346,694 in major bleeding events, and $65,463,260 in MI costs. The total cost incurred would be $557,483,334— or $460,852,889 if drug discontinuation is taken into consideration.

DISCUSSION

A total of 135,782 Veterans had an AF diagnosis in FY2011. Of these, 125,059 were estimated to be eligible for anticoagulation and were included in the BIA. If access to newer anticoagulants is closed and only warfarin is used to treat these patients, the VA is estimated to incur approximately $162 million annually. If discontinuation of warfarin use is factored in, total cost is reduced to $136 million. More than half of the total cost was due to warfarin and INR testing; the remaining half was due to AF-related comorbidities costs. We note that the TREAT-AF[5] study showed that only 52-63% of AF patients in the VA were being anticoagulated with warfarin, even among the higher risk CHADS2 patients. We chose to utilize an intention-to-treat approach to estimate budget impact because a) the goal is to anticoagulate all eligible patients; and b) it is difficult to determine what treatments the 37-48% of patients not receiving warfarin are getting and therefore what AF-related comorbidity costs they are incurring. Conversely, an unrestricted policy toward newer anticoagulants yielded a budget impact between $461 million and $557 million, with more than 80 percent of the cost attributed to the newer anticoagulants. However, it should be noted that this total cost is overestimated because some patients may have contraindications (e.g., severe renal function) or advanced age that precludes them from using newer anticoagulants.

If the VA were to adopt a restricted-access policy where only AF patients with moderate to high risk of stroke or major bleeding or poor INR control were allowed to receive newer anticoagulants, the budgetary impact would be substantial. We estimated the annual budget impact to increase to between $261 million to $313 million annually depending on the newer anticoagulant being used. There are two main reasons for this dramatic increase. The most obvious factor is that the newer anticoagulants cost nearly six times as much as warfarin, even after including the cost of frequent INR testing ($3,672 vs. $641). Second, in the case of Dabigatran, while we did estimate that some cost savings are likely to be gained from averting strokes and major bleeds, these savings are more than offset by the potential increase in MI cost. This result is exacerbated by the fact that MI is by far the most expensive AF-related event, being an order of magnitude higher than ischemic stroke and major bleeding costs and 37 percent higher than hemorrhagic stroke cost, while also occurring with greater frequency than hemorrhagic strokes. However, Apixaban did not exhibit higher MI cost, which would favor its consideration when it becomes available. However, the favorable MI cost would be mitigated if the prices of factor Xa inhibitors are higher than Dabigatran, as is the case in Canada.

There are several limitations to this BIA. First, we had to rely on intention-to-treat approaches for the no access (lower bound) and unrestricted access (upper bound) scenarios and an imputed uptake approach for the restricted access (middle-ground) scenario instead of direct observation in estimating warfarin and newer anticoagulation use and costs. Because Dabigatran is new to the market and Rivaroxaban and Apixaban are not yet available, querying the VA utilization and cost databases would not provide an accurate picture of the budget impact. Our analysis assumes perfect adherence to clinical guidelines on the part of physicians and treatment regimen on the part of all patients, which we know does not happen in the real world. For example, because newer anticoagulants are easier to use, it is possible that more AF patients will elect anticoagulation. The imputed uptake approach precludes assessment of the impact of this phenomenon. Also, there are a large number of patients who insist upon staying on aspirin because of their perception of bleeding risks with warfarin and because of the inconveniences of INR monitoring. What portion of these patients will want to stay on

aspirin or will want to transition to a newer anticoagulant is unknown. We attempted to address the various less than perfect adherence, medication tolerance, and patient perceptions by incorporating discontinuation rates reported in the clinical trials. After discontinuation of a newer anticoagulant, the patient may be prescribed warfarin (or less commonly, aspirin), but this was not factored into our BIA because the degree to which this switchover occurs is unknown. In the middle ground case, we do not account for the time cost for physicians to complete a restricted drug approval consultation (the presumed mechanism for implementing this approach) and the time required by a pharmacist to review and approve. These costs will increase the overall cost incurred by VA.

Second, we considered only two possible decision rules for allocating patients to receive warfarin or a newer anticoagulant for the middle ground scenario. Obviously, many other decision rules are possible. For example, it is possible that patients with a CHADS2 score of 1 are also prescribed aspirin. We plan to assess other decision rules and assess inclusion of aspirin in the BIA in future research.

Third, we do not know what the price of Rivaroxaban or Apixaban will be after they enter the U.S. market. Rivaroxaban has been recently introduced in the Canadian market, where it is approximately twice as expensive as Dabigatran. For this BIA, we conservatively assumed that Rivaroxaban and Apixaban will be priced the same as Dabigatran because it was first-to-market. However, if they are priced higher than Dabigatran, then the budget impact will be even higher than we have estimated.

Fourth, a BIA by its very nature is limited in scope. It assesses only the costs associated with anticoagulation use—it cannot take into consideration the effectiveness of the medications or other outcomes, such as life expectancy, quality of life, patient satisfaction, etc., that are also important in decision-making.

Fifth, we only incorporated the first year costs of strokes, major bleeds, and MIs into the budget impact analysis. The budget impact results may change if lifetime costs of these diseases are considered.[15] However, assessing the lifetime costs of these diseases is complex and beyond the scope of this sub-study.

We believe our study also has strengths. Our approach allowed us to assess the budget impacts of Rivaroxaban and Apixaban even though they are not currently available options but will be in the near future. Our analysis included only the incremental cost attributable to AF-related events in our cost calculations, which we estimated from cost modeling. If total costs were used instead, there would have been conflating of costs unrelated to AF.

IMPLICATIONS

Stroke prevention in patients with AF is an important healthcare issue in VA. Use of warfarin or newer anticoagulants has implications not only for stroke prevention but also for major bleeding and MI events. This BIA shows that even restricted access to newer anticoagulants will have a dramatic impact on the VA's medication budget. Cost savings from fewer strokes and major bleeding events may be more than offset by more frequent, costly MI events associated with Dabigatran or Rivaroxaban use. However, Apixaban may hold promise as it was shown to have lower MI cost. Judicious consideration of clinical factors such as stroke, major bleeding, MI risks and costs, and ability to keep INR under control in utilizing anticoagulants in a manner that maximizes health outcomes while balancing the impact that the newer anticoagulants may have on budgets.

Table 1. Atrial Fibrillation-Related Events

Annual Event	RE-LY Study rates		Hazard	ROCKET AF Study		Hazard	ARISTOTLE Study		Hazard
	Warfarin	Dabigatran	Ratio (95% CI)	Warfarin	Rivaroxaban	Ratio (95% CI)	Warfarin	Apixaban	Ratio (95% CI)
Stroke, %									
Hemorrhagic	0.38	0.10	0.26 (0.14,0.49)	0.44	0.26	0.59 (0.37,0.93)	0.47	0.27	0.51 (0.35,0.75)
Ischemic	1.20	0.92	0.76 (0.60,0.98)	1.42	1.34	0.94 (0.75,1.17)	1.05	0.97	0.92 (0.74,1.13)
Myocardial infarction, %	0.53	0.74	1.38 (1.00,1.91)	1.12	0.91	0.81 (0.63,1.06)	0.61	0.53	0.88 (0.66,1.17)
Major bleed, %	3.36	3.11	0.93 (0.81,1.07)	3.40	3.60	1.04 (0.90,1.20)	3.09	2.13	0.69 (0.60,0.80)
Drug discontinuation, %	10	16		14.3[a]	14.3[a]		23.7	21.7	

[a]14.3% of randomized treatment; not reported separately by treatment.

Table 2. Cost Variables

Parameter	Mean	95% CI	Source
Per INR test	$ 36	$ 6 - $ 62	Chambers, 2010
Dabigatran[a]	$ 3,672		VA PBM Prices.DBF file
Stroke			Based on Yoon, 2011
Hemorrhagic	$ 27,702	$ 22,443 - $ 32,962	
Ischemic	$ 4,847	$ 4,021 - $ 5,675	
Myocardial infarction	$ 43,988	$ 40,020 - $ 47,957	Based on Yoon, 2011
Major bleed	$ 5,250	$ 1,500 - $ 8,000	Shah, 2011; Freeman, 2011

[a]Rivaroxaban and Apixaban are not available yet in the United States; since Dabigatran is first to market, it is assumed for analysis purposes that Rivaroxaban and Apixaban will be priced the same as Dabigatran.

Table 3. Treatment Population

CHADS2 Score	VA Population Distribution	Veterans with CHADS2 score N	Poor INR Control N	Excellent INR Control N	High Risk of Bleeding N
0	17.30%	23,490			
1	30.40%	41,278	15,686	11,351	1,126
2	29.90%	40,599	15,428	11,165	1,108
3	15.30%	20,775	7,894	5,713	567
4	5.10%	6,925	2,631	1,904	189
5	1.61%	2,173	826	597	59
6	0.34%	175	175	127	13

Table 4. Budget Impact Analysis Cost Results

	Intervention Cost	Hemorrhagic	Ischemic	Major Bleed	Myocardial Infarction	Subtotal	Reduction for Drug Discontin.	Total
Lower Bound—								
Warfarin only	$ 74,702,966	$14,896,904	$ 7,415,395	$21,557,119	$43,458,803	$162,031,187	$25,924,990	$136,106,197
Upper Bound—								
Newer anticoag. only	$459,218,232	$ 6,928,793	$ 6,526,356	$19,346,694	$65,463,260	$557,483,334	$96,630,444	$460,852,889
Dabigatran								
Base-Case								
Warfarin + INR tests (a)	$ 44,660,368	$ 7,339,343	$ 4,055,242	$12,298,753	$16,254,461	$ 84,608,167	$ 4,466,037	$ 80,142,130
Dabigatran (b)	$203,203,381	$ 1,532,990	$ 2,467,681	$ 9,035,412	$18,013,338	$234,252,802	$32,512,541	$201,740,261
Subtotal	$247,863,749	$ 8,872,334	$ 6,522,923	$21,334,164	$34,267,799	$318,860,969	$36,978,578	$281,882,391
All CHADS2 Score 3-6 Patients Receive Dabigatran								
Warfarin + INR tests	$ 39,362,107	$ 6,468,644	$ 3,574,150	$10,839,696	$14,326,121	$ 74,570,718	$ 3,936,211	$ 70,634,507
Dabigatran	$233,834,350	$ 1,764,074	$ 2,839,661	$10,397,414	$20,728,676	$269,564,175	$37,413,496	$232,150,679
Subtotal	$273,196,457	$ 8,232,718	$ 6,413,811	$21,237,110	$35,054,797	$344,134,892	$41,349,707	$302,785,186
Uchino meta-analysis of MI rate								
Warfarin + INR tests	$ 44,660,368	$ 7,339,343	$ 4,055,242	$12,298,753	$24,228,347	$ 92,582,054	$ 4,466,037	$ 88,116,017
Dabigatran	$203,203,381	$ 1,532,990	$ 2,467,681	$ 9,035,412	$28,967,395	$245,206,859	$32,512,541	$212,694,318
Subtotal	$247,863,749	$ 8,872,334	$ 6,522,923	$21,334,164	$53,195,742	$337,788,912	$36,978,578	$300,810,335
Best case for Dabigatran	$203,203,381	$ 660,725	$ 2,029,351	$ 2,259,143	$14,788,204	$222,940,804	$32,512,541	$190,428,264
Worst case for Dabigatran	$203,203,381	$ 3,396,421	$ 3,693,188	$15,916,270	$33,847,277	$260,056,536	$32,512,541	$227,543,995

	Intervention Cost	Hemorrhagic	Ischemic	Major Bleed	Myocardial Infarction	Subtotal	Reduction for Drug Discontin.	Total
Rivaroxaban[a]								
Base-Case								
Warfarin + INR tests	$ 44,660,368	$ 8,498,187	$ 4,798,703	$12,445,166	$34,349,050	$104,751,474	$ 6,386,433	$ 98,365,042
Rivaroxaban	$203,203,381	$ 3,985,775	$ 3,594,232	$10,458,998	$22,151,537	$243,393,921	$29,058,083	$214,335,838
Subtotal	$247,863,749	$12,483,962	$ 8,392,934	$22,904,164	$56,500,587	$348,145,396	$35,444,515	$312,700,880
Best case for Rivaroxaban	$203,203,381	$ 2,021,918	$ 2,369,801	$2,369,801	$15,626,579	$225,761,721	$29,058,083	$196,703,638
Worst case for Rivaroxaban	$203,203,381	$ 7,464,100	$ 5,039,192	$5,039,192	$31,506,790	$265,275,985	$29,058,083	$236,217,901
Apixaban[a]								
Base-Case								
Warfarin + INR tests	$ 44,660,368	$ 9,077,609	$ 3,548,337	$3,548,337	$18,707,965	$87,304,738	$10,584,507	$ 76,720,231
Apixaban	$203,203,381	$ 3,679,177	$ 2,601,795	$2,601,795	$12,901,445	$228,574,037	$44,095,134	$184,478,903
Subtotal	$247,863,749	$12,756,785	$ 6,150,131	$6,150,131	$31,609,409	$315,878,775	$54,679,641	$261,199,134
Best case for Apixaban	$203,203,381	$ 2,574,004	$ 2,178,299	$2,178,299	$11,233,455	$221,418,916	$44,095,134	$177,323,782
Worst case for Apixaban	$203,203,381	$ 8,100,935	$ 4,694,573	$4,694,573	$23,863,283	$253,650,161	$44,095,134	$209,555,028

[a]Rivaroxaban and Apixaban are assumed to be priced the same as Dabigatran, given that it was first to market; also, effectiveness and side-effect profiles are not appreciably better for Rivaroxaban and Apixaban.

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