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Cost-Effectiveness of Dabigatran (150 mg Twice Daily) and Warfarin in Patients ≥65 Years With Nonvalvular Atrial Fibrillation

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Abstract

Dabigatran has been shown to be superior to warfarin for stroke prevention in nonvalvular atrial fibrillation (NVAF) but with higher out-of-pocket costs for patients. Although dabigatran has been shown to be cost effective from a societal perspective, cost implications for individual patients and insurers are not well described. We aimed to assess cost perspectives of each payer (Medicare and patient) in relation to administration, monitoring, and adverse outcomes for dabigatran and warfarin in patients with and without prescription drug coverage. Using a Markov model, we performed a decision analysis comparing 2 treatment strategies (dose-adjusted warfarin and dabigatran 150 mg twice daily) in patients 65 years old with NVAF, $CHADS_2$ scores ≥1, and Medicare insurance. Patients have a quality-adjusted life expectancy of 8.998 quality-adjusted life years with warfarin and 9.39 quality-adjusted life years with dabigatran 150 mg twice daily. From Medicare's perspective, the incremental cost-effectiveness ratio comparing dabigatran with warfarin was $35,311 for patients with Part D coverage and cost saving for patients without coverage. From the patient's perspective, the incremental cost-effectiveness ratio comparing

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Supplementary Data

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Disclosures

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dabigatran with warfarin was cost saving for patients with Part D coverage and $63,884 for those without coverage. In patients ≥65 years with NVAF and prescription insurance coverage, dabigatran 150 mg twice daily is both cost effective (Medicare's perspective) and cost saving (patient perspective) compared with warfarin, at a willingness-to-pay threshold of $100,000. However, patients without prescription drug coverage have a high out-of-pocket cost burden with dabigatran therapy, leading to a reduction in its cost-effectiveness compared with warfarin therapy. In conclusion, this Markov model suggests that Medicare Part D coverage influences the cost-effectiveness of dabigatran 150 mg daily compared with dose-adjusted warfarin from multiple payer perspectives.

For decades, standard therapy for nonvalvular atrial fibrillation (NVAF) has been dose-adjusted warfarin. However, because of a narrow therapeutic window, interindividual variability, drug-drug interactions, and drug-food interactions, alternative oral agents were developed with the potential to minimize those limitations. One alternative, dabigatran 150 mg twice daily, was shown to be superior to warfarin for the prevention of stroke and systemic embolism in the RE-LY trial.[1] However, at a cost of $295.71 per month, dabigatran is significantly more expensive than warfarin ($3.04 per month).[2] Previous research demonstrated dabigatran's cost-effectiveness compared with standard warfarin therapy from a societal perspective. These studies estimated dabigatran's incremental cost-effectiveness ratio (ICER) at $12,000, $45,372, and $25,000 per quality-adjusted life-year (QALY) over warfarin from a societal viewpoint.[3–5] Freeman et al used a higher market price estimate for dabigatran than its eventual market price, which may account for the larger ICER estimation ($45,372). Because of the complexity of payment for the components of each therapy (e.g., drug monitoring vs medication cost) in the US health care system, individual payers (Medicare and patients) may have financially divergent preferred therapies not captured in a societal perspective analysis. A better understanding of the cost-effectiveness of therapies from societal, Medicare, and patient perspectives can have significant impacts in patient decision making and health care policy between the newer direct oral anticoagulants and warfarin therapy. Our study aimed to assess the unique perspectives of society, Medicare, and the patient in the cost-effectiveness of dabigatran 150 mg twice daily versus dose-adjusted warfarin and the influence of varying risk for ischemic stroke (IS) and Medicare Part D coverage.

Methods

Our analysis used a state-transition model of anticoagulation therapy for IS prophylaxis in subjects ≥65 years with NVAF at increased risk of stroke ($CHADS_2$ score ≥1 or equivalent), creatinine clearance ≥50 ml/min, and no contraindications to anticoagulation therapy. Results were expressed in QALYs, 2013 US dollars, and ICERs. Model analyses used TreeAge Pro Suite 2014 (TreeAge Software, Williamstown, Massachusetts) and Microsoft Excel 2007 (Microsoft, Redmond, Washington). This analysis was based on the results from previous studies and did not use human subjects, so IRB approval was not necessary.

Using a Markov model, we compared 2 strategies for the prevention of IS in patients with NVAF: dose-adjusted warfarin with goal international normalized ratio (INR) 2.0 to 3.0 and

dabigatran 150 mg twice daily. The base case scenario was a hypothetical cohort of patients ≥65 years with NVAF at increased risk of stroke ($CHADS_2$ score ≥1 or equivalent), renal clearance ≥50 ml/min, Medicare Parts A, B, and D coverage, and no contraindication to anticoagulation therapy. Quality-adjusted life expectancy, net costs, and adverse event risks were calculated for 35 years (to age 100) or until death. Patient movement between health states occurred in 1-month cycles. During each cycle, patients could be affected by adverse events, with changes in utility and costs for each health state transition. The following health states were included in our model: healthy with NVAF; IS: transient ischemic attack, minor, major, or fatal; intracranial hemorrhage (ICH): minor, major, or fatal; extracranial hemorrhage (ECH): minor, major, or fatal; myocardial infarction (MI): nonfatal or fatal; and death (see Appendix Figures 1 and 2 for primary and secondary model branches). Adverse events incurred direct costs and reduced quality of life. Warfarin and dabigatran anticoagulation therapy also incurred indirect costs, including the economic cost of patient time for warfarin anticoagulation management.[6] The estimated cost of clinic visits alone was used for patients receiving dabigatran.

Patients were of age 65 to represent the age of Medicare coverage initiation. Adverse event risks were obtained from the RE-LY trial and related trials of warfarin therapy for IS prevention as listed in Appendix Table 1.[1] Mortality, IS, ICH, and MI rates were adjusted for age beginning at 65 years.[7–9] Adjustments for IS and MI rates based on $CHADS_2$ scores (categorized ≤1, 2, or ≥3) were performed for comparative analyses.[10,11] Relative risks of death for each health state, including NVAF, post-MI, post-ICH, post-ECH, and post-IS, were included.[12,13] We assumed patients with ICH and major ECH discontinued anticoagulation therapy and initiated lifelong aspirin therapy. Patients with minor ECH discontinued anticoagulation therapy for 2 days before reinitiating anticoagulation. Patients in a minor adverse event state who accrued a second minor adverse event were assumed to move into the major adverse event state associated with the initial adverse event.

Age-related baseline mortality rates for patients with NVAF were obtained through the United States Life Tables 2004, as listed in Appendix Table 1.[14] We assumed increased relative risk of mortality with history of MI, IS, and ICH (1.3, 1.4, and 1.97, respectively).[7–9] Baseline utilities were adjusted for age, anticoagulation treatment, and NVAF diagnosis. Utilities associated with other health states based on previously published research (see Appendix Table 1). Because of the inconvenience of warfarin therapy, being healthy on dabigatran was given a higher utility than being healthy on warfarin, consistent with previous analyses of warfarin and dabigatran.[3–5] Future costs and benefits were discounted at a rate of 3% annually.

Our model adopted societal, Medicare, and patient perspectives of inpatient, outpatient, and prescription medical care. Indirect costs of the economic value of patient time were included using the human capital method and the national average wage, $19.29 per hour, as obtained by the June 2006 National Compensation Survey.[6] For warfarin treatment, these costs were determined by variables including the frequency and length of time related to pharmacy trips, time for diet and food preparation, time for pharmacy trips, time for blood draws, and time waiting for and attending outpatient clinic visits, including companion time and varying numbers of visits per year. We converted annual costs to monthly costs. For dabigatran, the

economic value of patient time was determined by variables such as the frequency and length of time related to pharmacy trips and waiting for and attending outpatient clinic visits, including companion time and varying number of visits per year. Indirect costs associated with adverse events were not calculated. Outpatient clinic visits occurred once every 3 months, with direct costs equal to the cost of 1 anticoagulation clinic visit.[15]

Medicare coverage in our model included estimates of Parts A, B, and D reimbursement rates. Medicare Part A covered 100% of inhospital costs beyond the first $1,184. Medicare Part B covered 80% of all outpatient clinic visits. Medicare Part D covered 75% of prescription drug costs with the assumption that patients did not fall within the Medicare Part D coverage gap. The cost of dabigatran was determined from wholesale price.[2] The cost of warfarin treatment was estimated as the cost of 20 annual INR draws and medication costs and 90-day anticoagulation management (Current Procedural Terminology code 99,363).[16] One-time event costs for ICH, MI, gastrointestinal (GI) hemorrhage, and IS were obtained from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project National Inpatient Sample Database and from previously established research (see Appendix Table 1). The cost of a major ECH event was estimated as the cost of diagnosis group–related cost (DGR: 378) for major GI bleed, given that major GI hemorrhages are the most frequent major ECH. The cost of a minor hemorrhage was estimated as the cost of an outpatient clinic visit (Current Procedural Terminology code 99,212). Costs were expressed in 2013 dollars.

In sensitivity analyses, cost ranges from previously published research were included (see Appendix Table 1). All costs are inflation adjusted to 2013 dollars. Division of costs by payer is provided in Appendix Table 2. Analyses were performed for the various perspectives across varying $CHADS_2$ scores and Medicare Part D coverage. Model parameters were varied over ranges established in the RE-LY substudy and other published studies (see Appendix Table 1). A probabilistic sensitivity analysis varied all parameters simultaneously using a Monte Carlo simulation of 10,000 iterations. Distributions for parameter inputs are described in Appendix Table 3. Threshold analysis was conducted to determine the value for the cost of dabigatran that would lead to a change in the base case results, under a willingness-to-pay (WTP) threshold of $100,000.[4,17] Stratified analyses were conducted to assess how the results may be sensitive to changes in the underlying patient population. These stratifications included different adverse event risks and treatment costs based on $CHADS_2$ score and Medicare Part D coverage, respectively.

Results

Costs, QALYs, and ICERs associated with the base case scenarios for the 3 payers are listed in Table 1. Figure 1 shows how the ICER changes depending on Medicare Part D coverage and payer type (society, Medicare, and patient). Under the base case scenario ($CHADS_2$ score ≥1 and Medicare Part D), dabigatran was a cost-effective alternative to warfarin from all perspectives (societal, Medicare, and patient). From Medicare's perspective, the ICER comparing dabigatran with warfarin was $35,311 per QALY gained for patients with Part D coverage and cost saving for patients without Part D coverage. From the patient perspective,

the ICER comparing dabigatran with warfarin was cost saving for patients with Part D coverage and $63,884 per QALY for those without Part D coverage.

All 3 stroke risk groups ($CHADS_2 \leq 1$, $CHADS_2 = 2$, and $CHADS_2 \geq 3$) accrued more QALYs with dabigatran. From Medicare's perspective, the ICER comparing dabigatran with warfarin was markedly lower in patients with higher $CHADS_2$ scores, as displayed in Figure 1. From the patient perspective, dabigatran improved health outcomes and saved money compared with warfarin, regardless of $CHADS_2$ score.

One-way sensitivity analyses were conducted for multiple variables related to costs, utilities, and age from a societal perspective. The financial value of patient time for both warfarin therapy and dabigatran therapy included minimums of 0 given the uncertainty of how patients value time. Varying the cost of dabigatran and the economic value of patient time for warfarin therapy had the greatest impact on the cost-effectiveness of dabigatran from a societal perspective, as shown in Appendix Figure 3. Varying the cost of dabigatran had the greatest impact on the cost-effectiveness of dabigatran for patients with Medicare Part D coverage from Medicare's perspective. Varying the cost of ICH events had the greatest impact on the cost-effectiveness of dabigatran versus warfarin for patients with Medicare Part D coverage from Medicare's perspective. At a cost <$7.43 per capsule ($445.70 per month), dabigatran 150 mg twice daily has a total health care cost less than warfarin with greater QALYs (negative ICER) for patients with Medicare Part D coverage from the patient perspective. Varying the economic values of patient time for warfarin and dabigatran therapies had the greatest impacts on the cost-effectiveness of dabigatran versus warfarin from the patient perspective for patients with Medicare Part D coverage. Varying the monthly cost of dabigatran had the greatest impact on the cost-effectiveness of dabigatran versus warfarin for patients without Medicare Part D coverage from the patient perspective (ICER of $22,900 to $77,200 per QALY). Varying the economic value of patient time for warfarin and dabigatran therapies also had significant impacts on the cost-effectiveness of dabigatran versus warfarin.

The highest price at which dabigatran 150 mg twice daily remains cost effective compared with warfarin from a societal perspective ranges from $515 ($CHADS_2 \leq 1$) to $789 ($CHADS_2 \geq 3$) per month ($8.59 to $13.16 per capsule) at a WTP threshold of $100,000 (Figure 2).

The probabilistic sensitivity analysis varied all parameters simultaneously. With a WTP threshold of $100,000 per QALY, dabigatran 150 mg twice daily was cost effective in 100% of simulations in the base case scenario from a societal perspective (Figure 3) and from the patient perspective. Dabigatran 150 mg twice daily was cost effective for 95.3% of simulations in the base case scenario from Medicare's perspective. With a WTP threshold of $100,000 per QALY, dabigatran 150 mg twice daily was cost effective in 99.7% of simulations for patients without Medicare Part D coverage from the patient perspective (Figure 3) and 100% of simulations from Medicare's perspective.

Discussion

This study demonstrates that for patients ≥65 years with NVAF at an increased risk of IS, dabigatran 150 mg twice daily is a cost-effective alternative to dose-adjusted warfarin for IS prophylaxis from societal and Medicare perspectives in all scenarios at a WTP of $100,000. Of unique interest, at a WTP threshold of $100,000, dabigatran remains a cost-effective alternative to warfarin therapy for society and payers irrespective of prescription coverage, but the cost per QALY varies greatly depending on prescription coverage. The availability of prescription drug coverage has significant impact in the cost trade-off between dabigatran and warfarin from the patient perspectives. For patients with Medicare Part D prescription drug coverage, dabigatran was cost saving, but for patients without Medicare Part D coverage, dabigatran therapy was costly ($63,884 per QALY), showing the considerable effect prescription coverage may have on cost-effectiveness for patients. In particular, adults without Medicare Part D coverage represent a vulnerable population that may have reduced financial resources and, therefore, may be more sensitive to the higher relative cost of dabigatran.

This high cost per QALY may affect short-term prescription coverage choices and long-term medical therapy for this population. Prescription drug coverage has noteworthy effects on the cost-effectiveness from the patient perspective. This situation is unusual: a recently developed medication became cost saving from the patient perspective compared with a generic drug. This held under a variety of assumptions.

IS risk, as estimated by the $CHADS_2$ score, had a noticeable effect on the ICER of dabigatran. With increasing risk of IS, dabigatran becomes even more cost effective from societal and Medicare viewpoints. Models by Davidson, Rognoni, Sorenson, and Pink reported similar results from societal perspectives in Swedish, Italian, Canadian, and UK health care systems, respectively.[18–20] As the incidence of IS increases with $CHADS_2$ scores, the societal and Medicare costs associated with these events rise. Dabigatran remained cost effective at WTP thresholds of $100,000 and $50,000 across the spectrum of $CHADS_2$ scores.

We determine dabigatran to have an ICER of $21,980 per QALY from a societal perspective for the base case. Two recent studies support our finding that, from a societal viewpoint, dabigatran is a cost-effective alternative to warfarin at a WTP threshold of $100,000. In a study published by Kamel et al,[4] the ICER for dabigatran 150 mg twice daily compared with warfarin was $25,000 per QALY from a societal perspective. Similarly, Freeman et al[3] estimated an ICER of $12,386 per QALY when American market cost of dabigatran was included. However, neither study used indirect costs of patient time or costs of anticoagulation clinic visits, and these studies included patients initiating warfarin at age 70. A separate model developed by Shah and Gage[5] yielded an ICER of $86,000 per QALY, far greater than the values seen by Kamel and Freeman, perhaps because the former models stratified results by the effectiveness of INR control, modeled dyspepsia as a side effect of dabigatran, and included bleeding risks and stroke risk scores. We did not stratify results by the effectiveness of INR control because we compared the probability of adverse events for the entire cohort of patients receiving warfarin therapy in the RE-LY trial.

Alternatively, previous research by Pink et al[19] under a UK health care perspective demonstrated an ICER of ε26,700 ($35,700) per QALY, with dabigatran only being cost effective in patients at high risk of IS. Our results may differ for several reasons. Pink's model did not include the economic value of patient time on either therapy option, which may account for the increased ICER. Furthermore, in Pink's model, the treatment cost for an ICH was assumed to be higher because of the lack of an appropriate reversal agent.

Although our research used broadly similar model structure and estimates as previous research, our inclusion of recently published costs and the economic value of patient time had significant effects on dabigatran's cost-effectiveness. This may account for the differences in our findings from previous studies.[3–5] Including the economic value of patient time, the frequency of INR laboratory draws and anticoagulation clinic visits increased the cost of warfarin therapy relative to dabigatran. Similarly, given overestimation of the cost of dabigatran in previous studies, overall cost of dabigatran therapy was improved in our study.

This model had a few limitations. Notably, the efficacy of medical therapy in the RE-LY clinical trial may vary from therapy in real-world settings, which generally have reduced adherence, reduced monitoring, and increased probability of co-morbidities. In particular, bleeding rates may be higher in older, unselected adults treated with dabigatran compared with the bleeding rates observed in the RE-LY trial.[21] Furthermore, important information related to the proportion of patients, average cost, and average length of stay for skilled nursing facilities and nursing home care for each adverse event was unavailable. Other models, similarly, did not include this information in their analysis.[3–5,18–20] Another limitation is the division of Medicare Part D coverage to either complete or incomplete coverage without including scenarios with Medicare supplemental (Medigap) plans, which could create significant variations in costs of medications, medical services, and medical supplies. Similarly, we did not assess the effects of patients who enter into the Medicare Part D prescription coverage gap. However, the Affordable Care Act has established plans to eliminate this coverage gap by 2020. Last, our analysis assumes a baseline age of 65, which may not replicate clinical scenarios when NVAF develops in younger patients.

Our study had multiple notable strengths. This analysis is the first to examine multiple payer perspectives across a range of $CHADS_2$ scores while also examining the impact of Medicare Part D coverage. Furthermore, this study's model allows for future manipulation of multiple variables, notably the frequency of clinic visits, INR blood draws, and anticoagulation follow-up. This model also allows for future stratification of the study population by socioeconomic status, gender, and a multitude of patient-related factors. Our model includes current, updated medical therapy costs and a mixture of previously published research models. Finally, this model can be used to compare warfarin and dabigatran therapy with other direct oral anticoagulants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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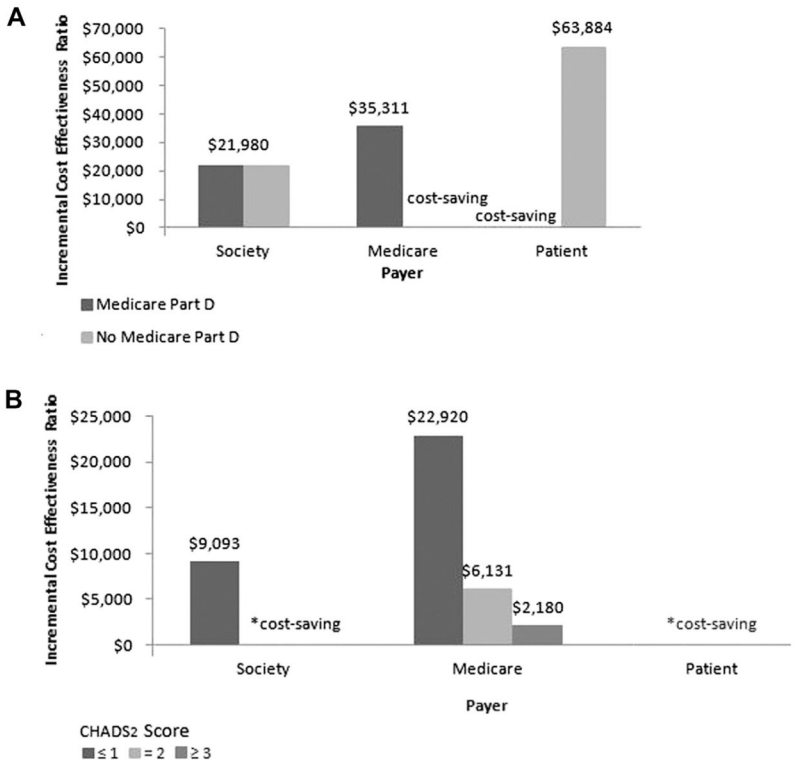

Figure 1.

(A) ICER for dabigatran versus warfarin, with and without Medicare Part D, by payer. ICER of dabigatran versus dose-adjusted warfarin for patients with and without Medicare Part D insurance, assessed by paper type (society, Medicare, and patient). Cost-saving describes a scenario with higher QALYs gained and lower overall costs when receiving treatment A versus receiving treatment B. *(B)* ICER for dabigatran versus warfarin, across varying $CHADS_2$ scores and payers. ICER of dabigatran versus dose-adjusted warfarin for patients with Medicare Part D insurance across varying CHADS2 scores. Cost saving describes a scenario with higher QALYs gained and lower overall costs when receiving treatment A versus receiving treatment B. Assume Part D coverage.

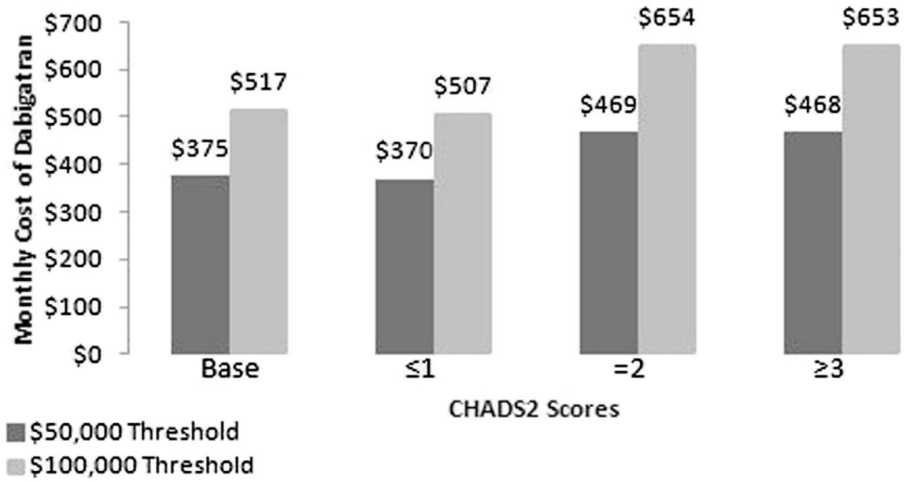

Figure 2.

Maximal societal value of dabigatran, by WTP threshold. Dollar value represents that maximum monthly cost of dabigatran at which dabigatran 150 mg twice daily remains cost effective compared with warfarin from a societal perspective, using both $50,000 and $100,000 WTP thresholds. Base CHADS2 score reflects the mean CHADS2 score of patients in the RE-LY trial.

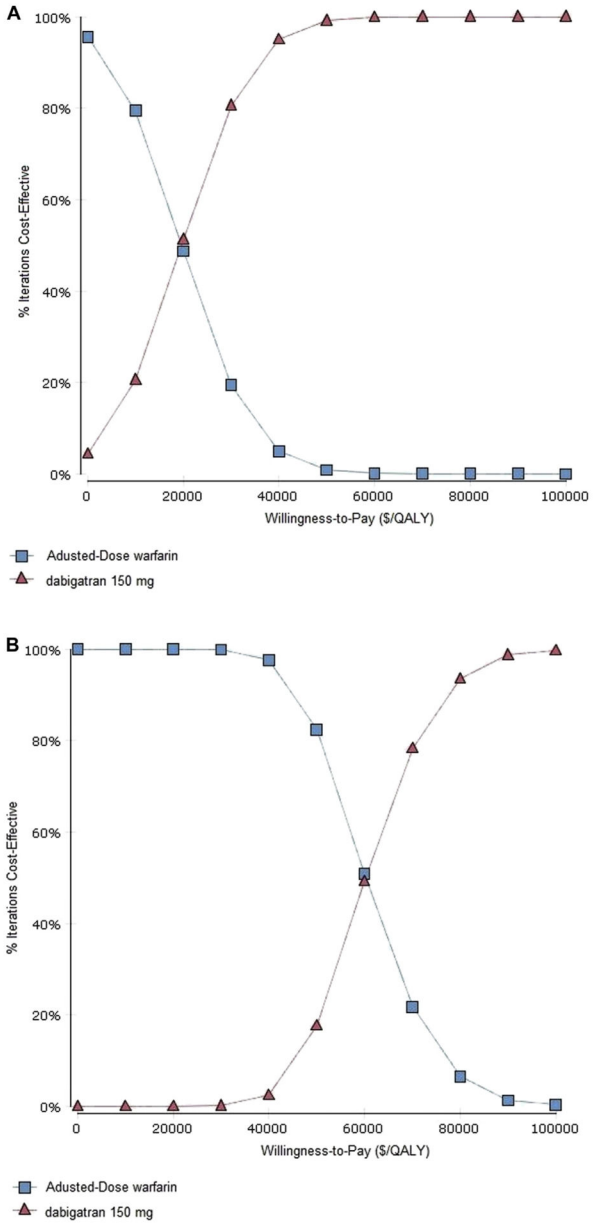

Figure 3.

(A) Cost-effectiveness acceptability curve—patient with Medicare Part D, societal perspective. *(B)* Cost-effectiveness acceptability curve—patient without Medicare Part D, patient perspective.

Table 1

Projected costs and QALYs for patients with nonvalvular atrial fibrillation, patient with Medicare Part D coverage, by varying perspective

Payer	Therapy	Cost, $	QALYs	Marginal Cost per QALY, $
Society	Warfarin	95,528	8.998	
	Dabigatran	104,186	9.392	21,980
Medicare	Warfarin	61,586	8.998	
	Dabigatran	75,496	9.392	35,311
Patient	Warfarin	33,942	8.998	
	Dabigatran	28,691	9.392	Cost-saving*

QALY = quality-adjusted life year.

*Cost-saving = higher quality-adjusted life years gained and lower overall costs when receiving treatment A versus receiving treatment B.