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Cost-Effective Medicines for Stroke Prophylaxis in Patients with Atrial Fibrillation

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Abstract

Non-valvular atrial fibrillation is the most common arrhythmia encountered in clinical practice and is associated with substantial healthcare costs. The risk of thromboembolic stroke is 3-5 times higher in patients with atrial fibrillation compared with the general population. Until the recent emergence of direct thrombin (factor IIa) and factor Xa inhibitors, antithrombotic therapy for atrial fibrillation was achieved with antiplatelet agents or vitamin K antagonists, which are considered cost-effective strategies when compared to no treatment. Now newer agents, such as the direct thrombin inhibitor dabigatran, can lower thromboembolic events and reduce the risk of fatal and intracerebral hemorrhage compared with warfarin, in addition to eliminating the need for costly therapeutic monitoring. Multiple analyses have shown that dabigatran, when compared with warfarin therapy that achieves a time in therapeutic range (TTR) consistent with previous large-scale trials, is a cost-effective approach to antithrombotic therapy in atrial fibrillation, ranging from $16,385 to $86,000 per quality-adjust life-year (QALY) gained. It has been shown to be especially cost-effective (QALY < $50,000) for high stroke-risk patients, those with a $CHADS_2$ score of > 3 (barring excellent INR control) and for lower-risk patients with a $CHADS_2$ of 2 but concomitant high risk of hemorrhage. In addition, factor Xa inhibitors, such as rivaroxaban (recently approved by the Federal Drug Administration [FDA]) and apixaban, may exhibit the same cost savings as dabigatran in terms of reduction of bleeding and elimination of therapeutic level monitoring costs. Going forward, the use of these agents and their role in thromboembolic stroke prophylaxis will need to be evaluated on a patient-by-patient basis, balancing consideration of the patient's stroke and bleeding risks, as well as quality of life post-therapy.

Introduction

Atrial fibrillation is the most common arrhythmia seen in clinical practice with a prevalence of over three million in the United States, a number that is estimated to rise to over 7.5 million by 2050.[1] It has a substantial impact on the healthcare delivery system and poses a significant economic, morbidity, and mortality burden.[2-4] In fact, 1 in every 4 people will be affected by atrial fibrillation during their lifetime.[5] The risk of thromboembolic stroke, perhaps the most feared com-

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plication of atrial fibrillation, is 3-5 times higher in patients with non-valvular atrial fibrillation than the general population.[6,7] Thromboemoblic events due to atrial fibrillation are more severe with respect to distribution of ischemic territory and duration of transient ischemic events than those caused by atherosclerotic carotid disease.[8, 9] The embolic source in atrial fibrillation begins with static blood in the left atrium or left atrial appendage which, along with endothelial dysfunction and altered hemodynamics, predisposes to clot formation and subsequent embolization, potentially resulting in ischemic stroke or systemic organ infarction.[10, 11] Atrial dimensions and hemodynamics lead to the formation of larger particles than those associated with shedding from atheroembolic carotid disease, and consequently higher mortality and disability.[8, 9]

The combination of high prevalence and morbid outcomes in atrial fibrillation has motivated a great deal of research in the area of antithrombotic therapies, which have been shown to significantly reduce the risk of thromboembolic stroke.[12, 13] Early trials investigating antithrombotic therapies for stroke prophylaxis found that they were very effective in patients with all forms of non-valvular atrial fibrillation: paroxysmal, persistent or permanent.[14] Interestingly, regardless of underlying arrhythmia treatment strategy (rate vs. rhythm control), antithrombotic therapies have shown a significant benefit with respect to reducing thromboembolic stroke; specifically, restoration of sinus rhythm alone has not been shown to reduce thromboembolic strokes in patients with atrial fibrillation. In fact, patients managed with a rhythm control strategy without antithrombotic therapy experienced the highest rates of thromboembolic events.[15, 16] With an aging population in the United States, the population-based need for antithrombotic therapy amongst patients with atrial fibrillation is substantial.[17] A cost-effective solution for decreasing the population-wide burden of thromboembolism, particularly in the current climate of efficient health care delivery, is increasingly important.

Determining whether a therapy is "cost-effective" historically involved estimating the "cost per year of life saved" by calculating the cost to save a life, estimating how many years that person will live, and dividing the cost to save the life by the number of years the person will live.[18] In general, an estimate of what society is willing to pay for, and therefore what is determined to be cost-effective, is $50,000 per year of life saved.[19] To put this in perspective historically, hemodialysis costs approximately $129,000 per year of life saved.[20] Given the substantial patient-level morbidity and population-level costs associated with embolic stroke (permanent disability, intensive rehabilitation, and risk of hospitalization for co-morbidities related to stroke), a more useful measurement of a cost-effective therapy in atrial fibrillation may be the "quality-adjusted life-year" (QALY), first used in 1976 by Zeckhauser and Shepard to indicate a health outcome measurement unit that combines duration and quality of life.[21, 22] QALYs adjust a patient's life expectancy based on the levels of health-related quality of life they are predicted to experience throughout the course of their life, or part of it. In general, it is calculated by obtaining quality-of-life estimates, known as "utilities," and by interviewing patients using the "trade-off method" to determine utilities for various scenarios, health outcomes, and deficits. Each expected life year is then multiplied by this "utility" factor, the sum of which are QALYs.[22] In the case of atrial fibrillation and thromboembolic disease, where the burden of neurological disability can be high, utilities for neurologic deficits can be compared to the consequences of taking antithrombotic therapy and multiplied by life expectancy to determine QALY. This method has been previously employed for atrial fibrillation by Gage, et al.[23] Similar methods have been used to analyze the cost-effectiveness of novel antithrombotic therapies and can be used for emerging therapies.

Aspirin and Anti-Platelet Therapies – Inexpensive, but Are They Effective?

Until the recent emergence of direct thrombin inhibitors and factor Xa inhibitors, antithrombotic therapy in atrial fibrillation was achieved with aspirin or warfarin, and in some cases aspirin with another antiplatelet therapy, including a thienopyridine such as clopidogrel, or a thromboxane synthase inhibitor such as dipyridamole. Aspirin had been shown in early studies to reduce thromboembolic stroke when compared to placebo.[12,24-26] In the early clinical trials, which compared the

efficacy of aspirin against no therapy in stroke prophylaxis for atrial fibrillation, only one trial achieved statistical significance in lowering thromboembolic stroke. A subsequent landmark meta-analysis concluded the risk of thromboembolic stroke was reduced by twenty percent with aspirin vs. placebo in patients with atrial fibrillation.[25] Because the relative risk of stroke from atrial fibrillation increases long-term when additional comorbidities are present, patients can be stratified to aspirin therapy using the $CHADS_2$ risk score. The $CHADS_2$ risk score is a multivariate risk model that has been validated in various patient populations for primary prevention of stroke in patients with atrial fibrillation.[14, 27] The presence of each of the following risk factors proportionally adds one point to the future stroke risk score, including chronic heart failure (the "C" in the $CHADS_2$ acronym), hypertension ("H"), advanced age ≥75 ("A"), diabetes mellitus ("D"), and prior stroke or TIA (which carries twice the weight of the other risk factors, hence the "S2"). Future risk of ischemic stroke is expressed in number of events per 100 person years of follow-up, with or without antithrombotic therapy, and increases as one's score increases from 0 to 6. Those with a score of 0 or 1, and therefore a low stroke risk, were deemed more appropriate for aspirin therapy because the risk of stroke is low as compared with the risk of bleeding from antithrombotic therapy (which also increases with additional comorbidities).Contemporary analyses demonstrate that $CHADS_2$ may not be comprehensive enough to accurately estimate stroke risk, particularly in the $CHADS_2$ low-range of a morbid population; as a result, the $CHADS_2$VASc score was developed. The $CHADS_2$VASc score can further risk stratify patients with a $CHADS_2$ score of 0 or 1 adding an additional point each in the presence of atherosclerotic vascular disease ("V"), age between 65-74 years (the second "A"), or female sex category ("Sc"). [28] This revised score not only refines the selection of patients appropriate for antiplatelet therapy, but also allows for more accurate risk stratification in this population.

When compared to other antithrombotic therapies, aspirin is quite inexpensive; in fact it costs only $35.97 for a one-year supply. However, its effectiveness in stroke prophylaxis in atrial fibrillation on a population level is diminishing. Olesen, et al. have shown that the benefit of warfarin therapy outweighs complications in all patients with atrial fibrillation except those at lowest risk of thromboembolic events (i.e. $CHADS_2$VASc of 0).[24, 29] Another cost-effectiveness analysis of aspirin performed by Gage, et al. similarly demonstrated that aspirin is only as cost-effective as warfarin in low-risk populations (i.e. $CHADS_2$ score of 0). Specifically, in a low-risk population, the quality-adjusted life expectancy was estimated to be 6.70 years with warfarin therapy, 6.69 years with aspirin therapy, and 6.51 years with no therapy. Warfarin was not cost-effective in this population but aspirin actually saved money, at a 10-year cost (including the cost of prophylaxis, stroke, transient ischemic attacks, hemorrhage, and death in 1994 dollars) of $5400 versus $6300 for no therapy. This strategy did not prove cost-effective in other higher risk groups.[23]

Dual antiplatelet therapy with aspirin and clopidogrel, estimated to cost $1799.88 for a one-year supply until clopidogrel becomes generic as expected in May 2012, was assessed in the ACTIVE trial for stroke prophylaxis in atrial fibrillation. ACTIVE A, which compared clopidogrel with placebo in patients already receiving aspirin, showed combined therapy with aspirin and clopidogrel further reduced thromboembolic stroke in patients with atrial fibrillation, but at a trade-off of higher bleeding risk when compared to aspirin alone.[30] Alternatively, ACTIVE W, which compared a strategy of clopidogrel plus aspirin to oral anticoagulation therapy, established that warfarin was superior thromboembolic prophylaxis compared to aspirin/clopidogrel without a significant difference in bleeding complications.[31] As noted by Hankey, et al., while aspirin/clopidogrel may be superior to aspirin alone in terms of thromboembolic stroke prevention, it is unlikely to be more cost-effective until clopidogrel loses patent protection.[32] Other reports have confirmed that dual-antiplatelet therapy does not appear to be a cost-effective strategy.[33]

Warfarin – Effective, But What is the Total Cost?

Warfarin has been established as effective therapy for the prevention of thromboembolic stroke in patients with atrial fibrillation. Indeed, stroke prophylaxis with warfarin is superior to aspirin in sev-

eral clinical trials.[12, 26, 34] Warfarin has subsequently been the therapy of choice for stroke prophylaxis in non-valvular atrial fibrillation in those who can tolerate its associated side effects, drug interactions, and INR monitoring. However, because warfarin is associated with increased risk of bleeding, patients and clinicians have had to face difficult decisions regarding the safety of anticoagulation therapy in clinical practice. In addition, warfarin requires frequent monitoring to maintain a narrow therapeutic window, has a slow onset of action with several days required to reach therapeutic levels, has significant medication interactions, and adversely affects quality of life by requiring lifestyle modifications to avoid injury and interaction with meals.

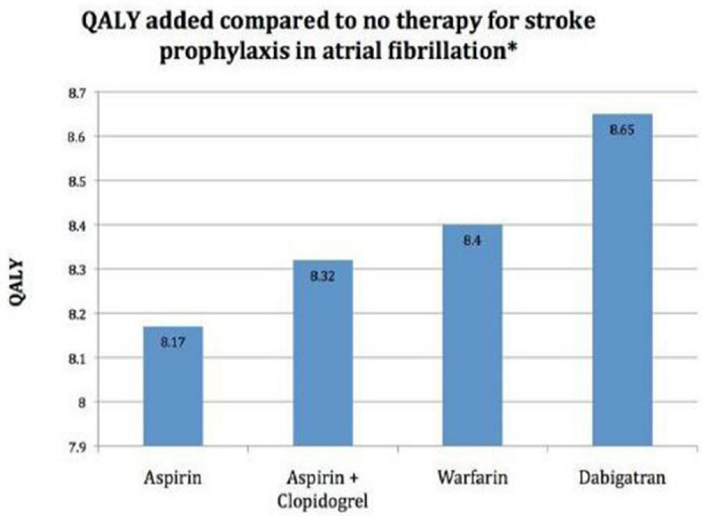
Although the annual cost of warfarin is only $109.50, the cumulative cost including therapeutic level monitoring must also be considered in its total cost. The cost of monitoring includes the number of annual visits (an average of 16), registered nurse's (RN) and general practitioner's (GP) time, home testing, and blood sample collection, analysis and transportation. Inclusive of all costs, the cost of monitoring is estimated to be $2,134 per patient per year in the first year, with a subsequent drop to $1,170 per year as long as a stable level of therapeutic level is maintained.[35] When compared to aspirin, Gage, et al. demonstrated in 1994 that warfarin is more cost-effective in both moderate- and high-risk patients with atrial fibrillation.[23] Specifically in moderate-risk patients, the cost-effectiveness of warfarin therapy compared with aspirin therapy was $8000 (range, $200 to $30000) per QALY gained. Warfarin was also more cost-effective compared to no therapy in the moderate- and high-risk patient groups.

Over the last two years, there have been significant developments in antithrombotic therapy (i.e. direct thrombin inhibitors and factor Xa inhibitors), which now provide an alternative and potentially more cost-effective therapy for stroke prophylaxis without the burden of therapeutic level monitoring or slow onset of action.

Direct Thrombin Inhibitors - A New Potential Cost-Effective Strategy

Novel direct thrombin inhibitors have recently emerged as an alternative to warfarin for stroke prophylaxis in atrial fibrillation. Dabigatran is a potent, direct, competitive inhibitor of thrombin, which has an absolute bioavailability of 6.5%, a serum half-life of 12 to 17 hours, and does not require regular therapeutic monitoring. The RE-LY trial, which compared dabigatran to warfarin in patients with atrial fibrillation, showed that dabigatran 150 mg twice daily was superior to warfarin therapy by reducing thromboembolic events, and

Figure 1: QALY Added Compared to No Therapy for Stroke Prophylaxis in Atrial Fibrillation.*Data presented is for Base Case as Analyzed by Shah et al, and Represents the Typical Patient in the RE-LY Study



fatal and intracerebral hemorrhage.[36] Subsequent cost-effectiveness analyses have demonstrated that when the total cost of administering warfarin is taken into account, and the cost savings associated with dabigatran's reduction in stroke are factored in, dabigatran may be a more cost-effective therapy for stroke prophylaxis in atrial fibrillation and may offer more quality-adjusted life-years than other alternatives (see Figure 1).[33]

A "back of the envelope" analysis has demonstrated the cost-effectiveness of dabigatran compared to warfarin in atrial fibrillation.[37] Compared to warfarin, with an annual cost of drug acquisition and monitoring of approximately $1,761 per year, the annual cost of dabigatran comes at $2,884 per year[38], which makes the annual additional cost of dabigatran over warfarin approximately $1,123 per year. However, the rate of stroke per year in RE-LY was 1.57% for warfarin and 1.01% for 150 mg of dabigatran; therefore, there is a 0.56% lower annual rate of stroke.[36] It should also be noted that there was a small but statistically significant reduction in mortality (0.5% per year) associated with dabigatran therapy, and there were also numerically (but not statistically significantly) fewer major bleeds (3.4% vs 3.1% per year). With this mortality benefit, 200 patients will have to be treated with dabigatran instead of warfarin per year to save one life. For a population sample of 200 patients, extra medication cost of dabigatran would be $224,600, and dabigatran would be expected to reduce yearly incidence of stroke by 1.12 compared to warfarin (200 patients x 0.56%), which would equate to a cost saving of $112,000 if Center for Disease Control (CDC) estimates for cost of stroke ($100,000 per year) are maintained.[37, 39] Similarly, dabigatran would be able to reduce yearly personal incidence of major GI bleed by 0.6 events per year or $4800 per year (estimated cost of bleeding event $8000).[37,40,41] Dabigatran would increase the yearly incidence of MI by 0.42 in a 200 patient population, which would cost an additional $2800 per year (estimated cost of MI $7000).[37] The overall cost of dabigatran treatment in 200 patients, to save one life, would therefore be $110,600. It would therefore take 2.2 years to reach the $50,000 per life saved per year threshold for dabigatran to be cost-effective (unpublished data Dr. C. Michael Gibson).[37]

Separate analyses have been performed by Freeman, et al. and Shah, et al., which estimated cost per QALY gained with dabigatran 150mg to be $45,372 and $86,000, respectively.[33, 42] The latter may be a more accurate estimate as the authors explicitly modeled dyspepsia, calibrated their mortality rates to those of RE-LY, and stratified their results by INR control, the $CHADS_2$ score, and the HEMORR2HAGES bleeding risk score.[43] Both studies found that dabigatran 150 mg would be cost-effective (QALY < $50,000) for high-risk patients with a $CHADS_2$ score of > 3 (unless INR control was excellent) and for patients with a $CHADS_2$ of 2 and high estimated risk of hemorrhage with warfarin. Overall, it appears that while there is some variability in QALY, there is a consensus that dabigatran is a

Figure 2: Dollars Spent on various Therapies per QALY in the United States.**Data Ranges presented are Based on Analyses by Gage et al, Shah et al, and Gibson et al.

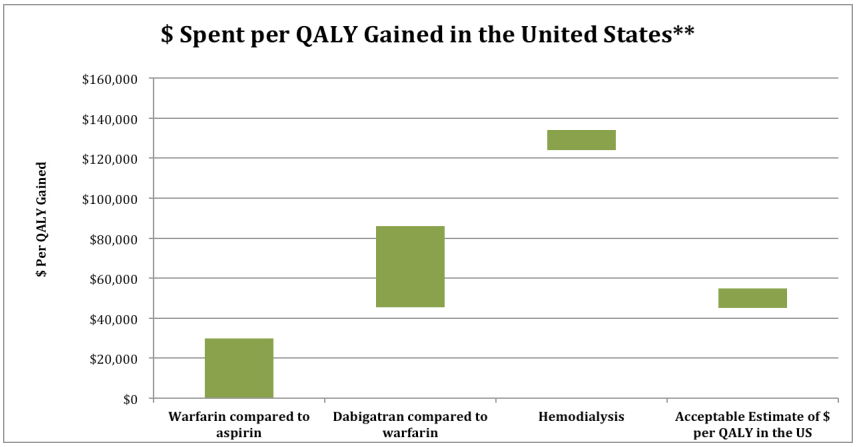


Table 1 Clinical studies of alcohol and atrial fibrillation

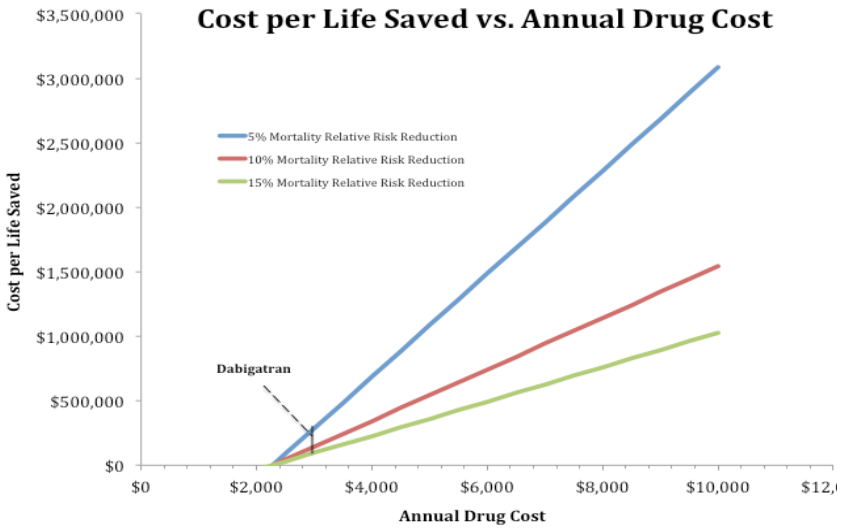
Therapy	Recommened $CHADS_2$ Score	Advantages	Disadvantages
Aspirin	0	Inexpensive Secondary prevention of CAD or CVD	Effectiveness not clearly demonstrated
Aspirin+ Clopidogrel	>0	Superior to aspirin in stroke prophylaxis for atrial fibrillation	Inferior to warfarin in stroke prophylaxis for atrial fibrillation Similar bleeding risks compared to warfarin
Warfarin	>0	Long track record of stroke prophylaxis in atrial fibrillation Low medication cost	Narrow therapeutic window Slow onset of action Increased risk of bleeding compared to aspirin and dabigatran Significant cost associated with drug acquisition and therapeutic monitoring
Dabigatran	>1	Superior stroke prophylaxis and lower intracranial bleeding compared to warfarin No need for monitoring Immediate onset o therapeutic effect	Higher risk of gastrointestinal bleeding when compared to warfarin High medication cost Relatively unproven long term outcomes
Rivaroxaban	>1	Similar efficacy compared to warfarin Lower intracranial and fatal hemorrhage compared to warfarin	High medication cost Relatively unproven long term outcomes
Apixaban	>1	Lower thromboembolic stroke and intracerebral hemorrhage compared to warfarin	High medication cost Relatively unproven long term outcomes

cost-effective stroke prophylaxis therapy strategy for patients at high risk of a thromboembolic event with atrial fibrillation (see Figure 2). It should be noted that these conclusions assume a time in therapeutic range (TTR) in the warfarin-treated arm that is consistent with previous literature. Several prospective trials have shown that patients with atrial fibrillation treated with warfarin stay in therapeutic range only 61-68% of the time.[44, 45] Patients with a TTR over 75% have a thromboembolic event rate of only 1.07% per year, which is similar to the thromboembolic event rate in patients treated with dabigatran 150 mg in RE-LY.[36, 46] This was reinforced by Wallentin, et al., who demonstrated that 150 mg dabigatran was not superior to warfarin at reducing the risk of non-hemorrhagic stroke at higher TTR quartiles.[47] These results highlight the importance of considering TTR for a given patient population when making cost-effectiveness comparisons between novel therapies and warfarin.

Factor Xa Inhibitors – The Next Frontier

Another promising class of antithrombotic drugs are the factor Xa inhibitors. These therapies are similar to direct thrombin inhibitors in that they do not require laborious therapeutic monitoring and have a relatively fast onset of action. Rivaroxaban, a factor Xa inhibitor, was recently ap-

Figure 3: Cost per life saved based on annual drug costs when compared to warfarin therapy



Mortality is varied based on emerging data on direct thrombin and factor Xa inhibitors. Stroke and major bleeding benefit is held constant. Current dabigatran pricing is $2884 per year, making the cost per life saved with a 10% relative risk reduction in mortality $110,600. Rivaroxaban and apixaban pricing based on European estimates for treatment of DVT may fall below the ~$2300 threshold for actual cost-savings, but final pricing is still pending for these drugs. All costs are presented in US dollars

proved for use in atrial fibrillation by the FDA.[48] This agent was shown in the ROCKET-AF trial to be non-inferior to warfarin in thromboemoblic stroke prophylaxis, while having lower rates of fatal and intracerebral bleeding.[49] To date, rivaroxaban has been shown to be a cost-effective therapy in the reduction of venous thromboembolism after total hip replacement in Canada; in fact the therapy was shown to provide quality-of-life benefit at a lower cost than enoxaparin, and this may translate to stroke prophylaxis in atrial fibrillation.[50] In the United Kingdom (UK) and Europe, the National Institute for Health and Clinical Excellence (NICE) are deliberating whether rivaroxaban is cost-effective utilizing a provisional cost in the UK of once daily rivaroxaban ($3.24 per day), or an annual cost of $1200.[51]

Apixaban, another novel factor Xa inhibitor, may prove to be the most cost-effective antithrombotic for use with atrial fibrillation given the overwhelming efficacy and safety reported in the ARISTOTLE trial. ARISTOTLE evaluated apixaban compared with warfarin for stroke prophylaxis in atrial fibrillation and noted significantly lower rates of all-cause mortality, thromboembolic stroke, and intracerebral hemorrhage.[52] The emerging data on this novel therapy and its potential utility in atrial fibrillation is very favorable; however the cost associated with apixaban has not yet been announced by its manufacturer making any cost-effectiveness estimates premature.

In the absence of finalized cost data in the United States, Figure 3 demonstrates what the cost per life saved vs. annual drug cost for this class of medications would be with variable mortality benefits (ranging from 5-15% relative risk reduction). The ROCKET-AF, RE-LY, and ARISTOTLE[52] trials all demonstrate similar mortality, stroke, and major bleeding benefit over warfarin therapy; as a result, the "back of the envelope" analysis used to generate Figure 3 makes the same cost assumptions presented for the dabigatran analysis and holds bleeding and stroke rate reductions constant. This analysis highlights the approximate $2300 threshold for annual drug cost leading to actual cost saving based on reduction of mortality, stroke, and major bleeding over warfarin.

Conclusions

As the burden of atrial fibrillation and its morbidity continue to grow, so will the need for cost-effective novel therapies. Until recently, the most effective therapy for thromboembolic stroke prophylaxis in nonvalvular atrial fibrillation has been warfarin.

While warfarin does add quality-adjusted life-years when compared to aspirin or no therapy, its many shortcomings including slow-onset of action and tedious therapeutic level monitoring, are finally being overcome by the novel direct thrombin inhibitors and factor Xa inhibitors. Questions remain regarding the performance of these drugs when applied to the general population as opposed to those represented in large clinical trials. In addition, the cost-effectiveness of these antithrombotic therapies will weigh heavily on their price and "real-world" effectiveness. As a result, the use of these agents and their role in thromboembolic stroke prophylaxis will need to be evaluated on a patient-by-patient basis, taking into consideration the patient's stroke risk, risk of bleeding, medication compliance, and quality of life post-therapy (see Table 1). If these agents emerge as safe and cost-effective therapies after the benefit of post-marketing surveillance data, they will pave the way for further innovation in the medical care of this expanding population.

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