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New Oral Anticoagulants: an Economic Analysis

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Oral anticoagulants are among the most commonly prescribed medications in the United States and may be used for thromboprophylaxis in atrial fibrillation (AF) or venous thromboembolism (VTE).[1] For many years, warfarin has been the preferred oral anticoagulant available for stroke prevention in AF or prophylaxis/treatment of VTE. However, 2010 marked the beginning of the expansion of therapeutic options for oral anticoagulation, which now includes dabigatran, rivaroxaban, and apixaban (Table 1).

These agents, commonly referred to as the new oral anticoagulants (NOACs), offer many advantages to traditional warfarin therapy. Unlike warfarin, which exerts its effect indirectly through depletion of vitamin K-dependent clotting factors in the liver, the NOACs utilize direct mechanisms of action, allowing for simplified pharmacokinetics and fewer drug, disease, and food interactions.[2] Not only do the new agents offer short onset and offset of therapeutic effect, but they also yield consistent therapeutic efficacy without the need for laboratory monitoring, in contrast to warfarin which requires regular international normalized ratio (INR) monitoring to assess for therapeutic efficacy. As a result, the NOACs have garnered attention regarding their possible replacement of warfarin as the mainstay of oral anticoagulant therapy.

Despite the many advantages to their use, the new NOACs come at a significantly higher cost to the patient than warfarin, which is available as a generic and boasts a cash price of less than $5 for a 30-day supply. In contrast, depending on prescription insurance the out-of-pocket costs for the three new agents may range from a copay of $40-60 for a 30-day supply to a cash price exceeding $300[3-4] (Table 2). Warfarin requires routine monitoring of the INR to ensure patients are adequately anticoagulated and to monitor for increased risk of bleeding associated with an elevated INR. In the average patient, the INR is monitored every 2-4 weeks,[5] which can be both costly and burdensome to the patient. As a result, it has been proposed that the NOACS present a more cost-effective therapeutic option from both a direct cost and patient quality of life perspective.[6]

Table 1: Oral Anticoagulant Options

Drug	FDA Approval	Mechanism
Warfarin (Coumadin)	1954	Vitamin K Antagonist
Dabigatran (Pradaxa)	2010	Direct Thrombin Inhibitor
Rivaroxaban (Xarelto)	2011	Factor Xa Inhibitor
Apixaban (Eliquis)	2012	Factor Xa Inhibitor

Review of the Current Economic Literature

Although the NOACs appear to be similar or more cost effective in a general sense, it is important to consider differences in efficacy or adverse event rates. Numerous trials have been completed to evaluate differences between the new and traditional agents.

A review of the current literature suggests that the NOACs are at least as effective as traditional warfarin therapy, when

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used for FDA-approved indications. Phase III clinical trials for the new agents demonstrated that dabigatran (RE-LY, 2009) and apixaban (ARISTOTLE, 2011) were more efficacious at preventing stroke in non-valvular atrial fibrillation than warfarin,[7,8] while rivaroxaban (ROCKET-AF, 2011) was shown to be non-inferior to warfarin.[9] A meta-analysis of these three trials demonstrated reduced risk of stroke and all-cause mortality with the new oral agents versus traditional warfarin therapy.[10] While it is difficult to assign a monetary value to this data, reduction in stroke and mortality is a significant cost benefit to the use of the new oral agents and, at the very least, allows the NOACs to be compared equally from a cost of efficacy perspective.

Adverse events also contribute significantly to the overall cost of a therapeutic agent. Anticoagulants of any type are associated with bleeding events, such as gastrointestinal (GI) bleeding or intracranial hemorrhage (ICH). Although rare, hospitalization and associated costs from these bleeding events can range from $24,129 per patient for a mild GI bleed to $41,903 per patient for a major ICH.[11] However, the NOACs have been shown to all have a reduced risk of ICH, which is the adverse effect associated with the highest cost.[12] Despite improved rates of ICH, dabigatran is associated with an increased risk of dyspepsia and GI bleed by as much as 10%,[2] which may increase adverse event-related cost, while apixaban is associated with an overall lower rate of major bleeding, both intracranial and extracranial.[8] Rivaroxaban shares a lower rate of ICH with the other NOACs but does not offer any unique advantages or disadvantages related to adverse effects that have been identified.[9]

In addition to comparable or potentially improved efficacy, evaluation of the economic cost between the agents indicates that the NOACs offer reduced ICH bleeding events (though increased dyspepsia and GI bleed with dabigatran) and improved overall quality of life. According to Harrington et al., the new oral anticoagulant agents are more cost effective alternatives to warfarin therapy; specifically, the trial concluded that apixaban was the most cost effective anticoagulant therapy option with respect to quality adjusted life years (QALY) due to lack of monitoring and fewer adverse bleeding events.[6]

This review of the current economic literature suggests that use of the NOACs is supported by efficacy, safety, and for some patients economic considerations. As with all medication therapy, the choice of an anticoagulant should be determined by considering the individual patient. A patient with a history of dyspepsia or GI bleed may be at a higher risk of having an adverse event with dabigatran. This may result in increased direct health care cost or in a patient who is noncompliant with therapy leading to a thrombotic event that could result in extensive healthcare and social costs. It is important for the prescriber to be familiar with the overall features of each of the available oral anticoagulants in order to have a candid conversation with their patients regarding efficacy, adverse effects, and associated costs.

Other Considerations

Although NOACs have been touted as not requiring therapeutic monitoring, parameters must still be followed to ensure safety. Patients prescribed any anticoagulant should have a complete blood count (CBC) every 6 months to monitor for bleeding. Due to the elimination of the new oral agents, renal and hepatic function monitoring is recommended as clinically indicated (generally once annually) depending on the agent (Table 3). While renal and hepatic function tests are often performed regardless of anticoagulation therapy, it is important to consider this additional cost to an otherwise healthy patient who may not

Table 2: Cost Comparison of Oral Anticoagulants

Drug	Warfarin (Coumadin)	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)
Average Wholesaler Price (30-day-supply)	$22.12	$349.99	$343.33-$561.25	$349.99
Annual Monitoring	$626.72	N/A	N/A	N/A
Estimated Total Annual Cost	$892.16	$4,199.88	$4,341.07†	$4,199.88

†Based on a 21-day supply of two tablets per day followed by 1 tablet for day

New Oral Anticoagulants: an Economic Analysis (continued)

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Table 3: Recommended Monitoring Parameters				
Drug	**CBC**	**INR**	**Renal**	**Hepatic**
Warfarin	✓	✓		
Dabigatran	✓		✓	
Rivaroxaban	✓		✓	✓
Apixaban	✓		✓	✓

require such monitoring.

Lack of adherence to prescribed therapy can result in a greater risk for adverse events with the NOACs. The half-lives of these agents are significantly shorter than warfarin,[2] which means the therapeutic effect of the drug is faster to decline following a missed dose. Unlike warfarin, which takes an average of 4-5 days to return to baseline following discontinuation,[13] a single missed dose of the NOACs could increase the patients risk for a thromboembolic event. Conversely, warfarin requires bridge therapy with a low molecular weight heparin (LWMH) such as enoxaparin for the first 5 days of warfarin therapy, which results in added costs to the patient.

Additionally, a patient who takes more than the prescribed dose of the NOACs will not have an available reversal agent in the case of a bleeding event. Similarly, if a patient experiences an emergency bleeding event, such as trauma, or requires emergency surgery, a specific reversal agent is not available to return the patient to a normal coagulation level. While warfarin is easily reversed with vitamin K, overdose or bleeding events while taking one of the NOACs can only be treated with prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP), which are costly agents that may not be associated with beneficial outcomes (Table 4). Dabigatran specifically is only removed via dialysis and apixaban may be reversed with the use of activated Factor VII, however, clinical trials have not been performed to date to evaluate this association. Each of these reversal options is costly and may require hospitalization, while supratherapeutic warfarin levels can be easily treated with low cost vitamin K tablets.

Conclusion

With these considerations, it is important for the prescriber to consider the patient as a whole when choosing an appropriate anticoagulant therapy. Patients who have demonstrated compliance with therapy and are at a lower risk for stroke ($CHADS_2$-VASc score) may be more likely to benefit from NOACs therapy. However, in a patient with demonstrated non-adherence or high risk of stroke, the risk of adverse events may outweigh the benefit of no laboratory monitoring. As with all medications, it is vital that the prescriber and pharmacist provide detailed counseling for the patient regarding the therapy prescribed to ensure patient compliance. Patients should be alerted to the risk of stroke and bleeding. Patients taking NOACs should particularly be counseled on the lack of reversal agent.

<Click here for references>

Table 4: Reversal Options for Oral Anticoagulants					
Drug	**Est Cost**	**Warfarin**	**Dabigatran**	**Rivaroxaban**	**Apixaban**
Vitamin K	Low	✓			
PCC/FFP	Mod	✓		✓	✓
Factor VIIa	Mod	✓			✓*
Hemodialysis	High		✓		
***Not evaluated by clinical trials to date**					

Etidronate for the prophylaxis of heterotopic ossification following total hip arthroplasty

Justin Scholl, PharmD, BCACP

Total hip arthroplasty or hip replacement surgery can result in a painful new bone formation known as heterotopic ossification. The incidence of heterotopic ossification following total hip arthroplasty is estimated to be approximately 53%, especially when risk factors, including a prior history of heterotopic ossification, prior trauma/ operations, ankylosing spondylitis, Paget's disease or rheumatoid arthritis are present.[1,2] The pathophysiology is believed to involve the migration of pluripotent mesenchymal cells into tissues surrounding the joint which then differentiate into osteoblasts, which in turn form mature bone. [1] This formation results in loss of range of motion of the affected joint as well as pain and inflammation experienced by the patient.

In patients with high risk for the development of this condition, prophylactic approaches include local radiation of the surgical area, indomethacin or other NSAIDS for two to six weeks following surgery or the use of bisphosphonate therapy such as etidronate. [1, 2]

Etidronate is indicated for the prevention of heterotopic ossification following total hip arthroplasty or spinal cord injury.[3]

Etidronate Drug Information:

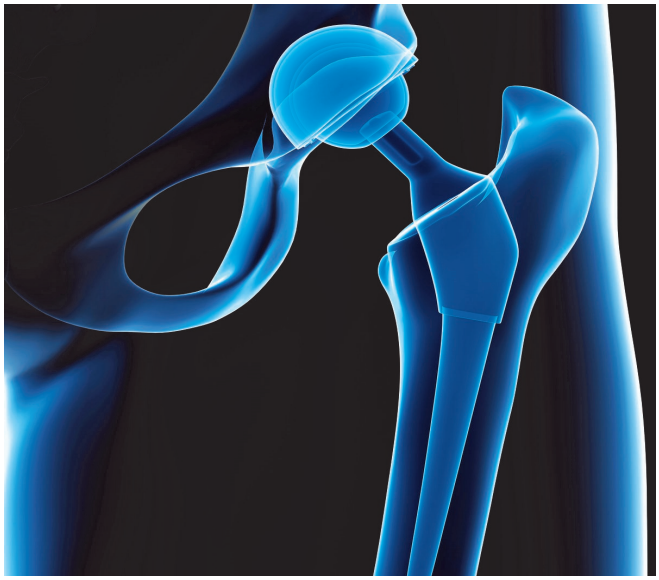
Dose: 20mg/kg/day given on an empty stomach with at least 8 ounces of water.

Doses should be reduced in patients with renal dysfunction due to risk of hyperphosphatemia

Formulation: 200mg & 400mg tablets commercially available (tablets cannot be split)

Duration: Initiation 1 month prior to surgery and continuing for 3 months following surgery

Safety: Complaints of GI upset including ulcers & esophagitis, musculoskeletal pain, hyperphosphatemia; rare instances of osteonecrosis of the jaw and agranulocytosis



Efficacy data from clinical trials of etidronate in this setting is conflicting. Data from animal and *in vitro* models demonstrates the ability of etidronate to suppress the formation of mature bone in non-osseous environments; it does not reverse already established heterotopic bone. [4, 5] However, human trials have demonstrated that the use of etidronate in long term prevention of heterotopic ossification following discontinuation does not differ significantly from placebo.[4] Moreover, once the medication is removed, normal bone formation will resume in approximately three to six months. [3,4] A more recent study by Vasileiadis and colleagues demonstrated that clinical outcomes in 56 total hip arthroplasty patients followed over 12 months did not differ significantly in either Harris Hip Score or radiographic evidence of heterotopic ossification between groups treated with etidronate or indomethacin.[2] Significant differences were noted with a greater incidence of adverse reactions (mostly GI upset) in the indomethacin group and increased cost of therapy in the etidronate group.

In summary, etidronate is indicated for the prophylaxis of heterotopic bone formation following total hip arthroplasty and appears to be at least as effective as the use of indomethacin. However, long term data are equivocal between the two groups and etidronate has a significantly greater cost.

<Click here for references>

Pradaxa® (dabigatran) vs. Warfarin: Reported bleeding and adverse events

Adolfo Suarez, PharmD candidate; Marcus W. Campbell, PharmD, BC-ADM

Warfarin is an oral anticoagulation drug which inhibits blood clotting by preventing the production of clotting factors II, VII, IX, X, as well as proteins C and S, all of which are synthesized by the liver. The assembly of these factors is dependent on vitamin K, which is antagonized by warfarin through the inhibition of vitamin K epoxide reductase. Warfarin is used in the prevention and treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), as well as complications secondary to cardiovascular conditions arising from valve replacement, atrial fibrillation (Afib), myocardial infarction (MI), and stroke. The use of warfarin is limited by its narrow therapeutic index, as well as its requirement for frequent monitoring. Adverse drug reactions include bleeding, rash, abdominal pain, diarrhea, hepatitis, etc. Warfarin-induced bleeding can be reversed with the administration of vitamin K.[1]

Pradaxa® (dabigatran exilate) is a direct thrombin inhibitor approved by the FDA in October of 2010 as an alternative to warfarin in patients with nonvalvular Afib. Its approval was based on the results of the phase III Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial. Dabigatran specifically targets thrombin (factor IIa) in both, its free and fibrin-bound form. The mechanism of action of this medication inhibits clot formation by blocking thrombin-mediated functions, such as the conversion of fibrinogen to fibrin, thrombin-induced platelet aggregation, and activation of factors V, VIII, XI, and XIII. Dabigatran is used for the prevention and treatment of DVT, PE, and other embolic complications from Afib. It is also readily utilized to minimize recurrence of MI and strokes after a cardiovascular event. Unlike warfarin, dabigatran does not currently have an antidote on the market. The agent idarucizumab, a fully humanized agent has shown positive results in development research and has received FDA approval to be expedited.[2,3]

Alternative agents to warfarin have proven efficacy in the management of disease states requiring anticoagulation therapy. These new drugs offer ease in prescribing and monitoring, as well as a more favorable interaction profile. However, experts and prescribers alike have questioned the long-term adverse effects associated with these novel anticoagulants. A retrospective review of the FDA Adverse Event Reporting System (FAERS) database was conducted from October 2010 to December 2011, the year following the release of dabigatran. Information regarding reported bleeding adverse events and/or fatal outcomes associated

with the use of dabigatran was gathered and compared to similar reported events involving warfarin.[4]

FAERS is a voluntary surveillance system made up of reports of adverse effects and related outcomes provided by manufacturers, healthcare providers, and consumers. Researchers conducted a query listing dabigatran or warfarin as primary suspecting agents. Drug information such as dose, indication, and duration of therapy were also included in the search. Bleeding events were classified as general hemorrhage, GI bleeds, or intracranial bleeds. Of note, numerous reported events for both dabigatran and warfarin were incomplete missing key covariates such as age, gender, and weight.[4]

The analysis outcomes were defined as number of bleeding events and number of bleeding cases that resulted in death. Investigators utilized a study found in the National Disease and Therapeutic Index to estimate treatment patterns for dabigatran in the US in the year following its release. This information provided a basis for comparison, as it estimated the population risk of bleeding fatalities in patients on dabigatran. Additionally, dabigatran-related fatality data was extracted from the RE-LY trial. Of the 966,536 initial case reports and follow-ups identified, 9,029 dabigatran cases and 2,038 warfarin cases were included in the analysis. In general, dabigatran adverse events were seen in older patients when compared to warfarin, 75.5 vs. 70.5 years, respectively. Dabigatran patients were less likely to be hospitalized (28% vs 46%) and included higher male population (56% vs. 47%) when compared to warfarin

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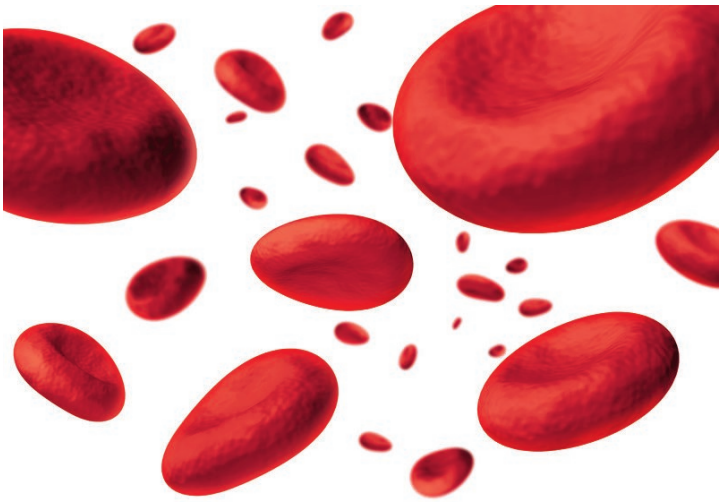
Pradaxa® (dabigatran) vs. Warfarin: Reported bleeding and adverse events (continued)

cases. The overall fatality rates from reports were similar for both dabigatran and warfarin (5.8% vs. 4.2%). In terms of classification of bleeds, a higher proportion of GI bleeds were seen with dabigatran (53% vs. 26%); conversely, a higher number of intracranial bleeds were reported in patients on warfarin (12.8% vs. 9.1%). While dosing information was often incomplete, in those reported, 51.6% of dabigatran bleeding reported cases were on the 150 mg twice daily dosing. Reported cases of bleeding, which resulted in death, predominated with dabigatran patients as compared to warfarin (14.8% vs. 7.1%), from October 2010 to December 2011, there were 348 deaths reported due to bleeding associated with dabigatran therapy.[4,5]

An additional stratified analysis was conducted comparing reporting odds ratio (ROR) of age, gender, and weight for dabigatran vs. warfarin. Dabigatran odds were higher in the age range 75-84 years of age compared to warfarin (ROR 1.4, 95% CI 1-1.9), as well as in patients weighing less than 100 kg (ROR 1.5, 95% CI 1.2-1.9), and women (ROR 2.7, 95% CI 1.9-3.6). Bleeding fatality RORs were higher with dabigatran across all stratification groups.[4]

While results of this retrospective analysis indicate higher incidents of adverse bleeding events resulting in fatalities with dabigatran, a number of limitations were identified. For instance, well-known underreporting associated with the FAERS. Since dabigatran is the newer agent, it is likely that bleeding events were reported more frequently as compared to warfarin. There is also a high possibility of duplicate cases, unavailable dosing information, and disproportionate distribution as it relates to patient demographics. The latter may have potentially had a profound impact on the results, as odds of adverse events are known to vary with age, gender, body weight and comorbidities. As a result, further studies of the bleeding events with dabigatran are merited. Furthermore, it will be interesting to see the impact of the antidote idarucizumab on the rate of dabigatran related fatalities.

<Click here for references>



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