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From Antidotes to Edoxaban: An Oral Anticoagulation Update

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Anticoagulation is required for a multitude of indications, from atrial fibrillation (AF) to pulmonary embolism (PE) and deep vein thrombosis (DVT). Four new oral agents, now being referred to as "direct oral anticoagulants (DOACs)" are available for patients whom warfarin is not a preferred option. The newest drug to enter the market is edoxaban (Savaysa®) an oral direct factor Xa inhibitor.¹ The focus of this newsletter will be to highlight the evidence for the use of edoxaban and how it compares to the already approved agents. An update on the development of antidotes for the DOACs will also be discussed.

Edoxaban (Savaysa®)

Edoxaban is approved for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and for the treatment of DVT and PE in patients already treated with a parenteral anticoagulant.¹ Unlike the other DOACs, edoxaban is not recommended in NVAF patients with high functioning renal clearance ($\text{CrCl} > 95 \text{ mL/min}$) due to an increased risk of ischemic stroke, compared to warfarin, found in this subgroup.¹

Atrial Fibrillation

The NVAF trial (ENGAGE AF-TIMI 48) was a good quality study comparing edoxaban 30 mg daily and edoxaban 60 mg daily to warfarin in over 21,000 patients for approximately 2.5 years.² Patients had a CHADS₂ score of ≤ 3 , putting them at low to moderate risk of embolism. Patients randomized to warfarin were in therapeutic range an average of 65% of the time. Both doses of edoxaban were found to be noninferior to warfarin (table 1). Similar to the other factor Xa inhibitors the incidence of intracranial hemorrhages was lower in both edoxaban groups compared to warfarin, which was driven by hemorrhagic stroke reduction. All-cause mortality was lower in the low dose edoxaban group compared to warfarin ($p=0.006$) and similar between high dose edoxaban and warfarin [hazard ratio (HR) 0.92, 95% CI 0.83 to 1.01, $p=0.08$].²

Table 1. Key Efficacy Outcomes of ENGAGE-TIMI 48 Trial.²

Outcome†	Edoxaban 30 mg (E30)	Edoxaban 60 mg (E60)	Warfarin (W)	Hazard Ratios and P-values
Composite of stroke or systemic embolism	253 (3.6%)	182 (2.6%)	232 (3.3%)	E30 vs. W: 1.07 (97.5% CI, 0.87 to 1.31; $p=0.005^*$) E60 vs. W: 0.79 (97.5% CI, 0.63 to 0.99; $P<0.001^*$)
Ischemic stroke	333 (4.73%)	236 (3.35%)	235 (3.33%)	E30 vs. W: 1.41 (95% CI 1.19 to 1.67; $p<0.001$) E60 vs. W: 1.00 (95% CI 0.83 to 1.19, $p=0.97$)
Hemorrhagic stroke	30 (0.43%)	49 (0.70%)	90 (1.3%)	E30 vs W: 0.33 (95% CI 0.22 to 0.50; $p<0.001$) E60 vs W: 0.54 (95% CI 0.38 to 0.77; $p<0.001$)
All-cause mortality	737 (11%)	773 (11%)	839 (12%)	E30 vs W: 0.87 (95% CI 0.79 to 0.96; $P=0.006$) E60 vs W: 0.92 (0.83 to 1.01; $p=0.08$)

* For noninferiority analysis; † data from overall study period

VTE Treatment

The approval of edoxaban for the use in VTE treatment was based on a good quality, phase 3, randomized controlled trial that compared edoxaban 60 mg daily to warfarin (adjusted INR of 2-3).³ Edoxaban 30 mg daily was given to subjects with the following characteristics: CrCl 30-50 mL/min, body weight ≤ 60 kg and/or use of potent P-glycoprotein inhibitors. Patients were required to have been treated with at least 5 days of parenteral anticoagulant to be included. The median treatment duration was 7 days. Patients taking warfarin were therapeutic 64% of the time, which is consistent with other studies. The primary endpoint was occurrence of adjudicated symptomatic recurrent VTE, which included DVT or fatal or non-fatal PE. Edoxaban was found to be noninferior to warfarin for the primary endpoint, HR 0.89 (95% CI 0.70 to 1.13, $p<0.001$ for noninferiority).³ Mortality rates were similar between groups.

Safety

Bleeding and anemia were the most common adverse effects seen with edoxaban use in clinical trials.¹ As with other DOACs used in patients with AF, major bleeding rates were significantly less in edoxaban groups compared to warfarin.² Intracranial bleeding was also significantly less in edoxaban treated subjects. The incidence of gastrointestinal bleeds (GI) was similar between low dose edoxaban and warfarin but significantly higher in the high dose edoxaban group compared to warfarin (HR 1.23; 95% 1.02 to 1.50; $p=0.03$, NNT 167) in the ENGAGE trial.² Major bleeding rates were similar between edoxaban and warfarin in patients treated for VTE.³

Place in Therapy

Anticoagulation is a delicate balance between embolism prevention and bleeding while also preventing mortality. All the DOACs have been shown to be noninferior to warfarin for the prevention of stroke and systemic embolism in patients with NVAF, with dabigatran and apixaban also demonstrating superiority.⁴⁻⁶ DOACs have been shown to perform significantly better than warfarin for preventing hemorrhagic strokes. No significant differences in ischemic stroke rates have been demonstrated between the DOACs and warfarin, except for dabigatran which was found to be superior to warfarin ($p=0.03$).⁴ Evidence has shown edoxaban and apixaban to have significantly less major bleeding compared to warfarin, however, warfarin is associated with less risk of GI bleeds compared to all DOACs.^{2,4-6} Only apixaban is associated with lower all-cause mortality rates compared to warfarin (when comparing high dose treatment regimens).⁶

When evaluating indirect treatment comparisons, it is important to consider key trial differences that may have impacted the results. Studies of DOACs in patients with NVAF were blinded trials, except the RE-LY study.^{2,4-6} RE-LY compared dabigatran to warfarin using an open-label design. Open-label studies may bias results in favor of the study treatment. The time in therapeutic range (TTR) can greatly influence the efficacy of treatment in patients randomized to warfarin. TTRs were consistent between the studies except for the ROCKET-AF study which had a mean TTR of 55% compared to an average of 65% for the other studies.^{2,4-6} TTR variability can translate into fewer patients taking an effective dose of warfarin which may worsen outcomes and bias the results in favor of the comparator. The CHADS₂ score estimates the risk of stroke based on patient comorbidities. The CHADS₂ score was similar between the studies (2.1-2.8) except for the ROCKET-AF trial.^{2,4-6} In ROCKET-AF rivaroxaban and warfarin patients had a higher CHADS₂ score, with a mean score of 3.5.⁵ A higher CHADS₂ score puts patients in a higher risk category for stroke and consequently more likely to experience a higher incidence of stroke or systemic emboli compared to other DOACs. Clinical trials directly comparing the DOACs is the only way to determine the true differences between efficacy outcomes.

For VTE treatment, systematic reviews and meta-analyses have found no significant difference between efficacy of the DOACs compared to standard therapy (enoxaparin and warfarin).^{7,8} Major bleeding rates were found to be less with the DOACs compared to standard therapy, with the lowest rates seen with rivaroxaban and apixaban.^{7,8}

Antidotes

Clinical studies have not recognized the lack of a reversal agent as a major barrier to the use of DOACs. However, having access to an antidote in the event of a bleeding emergency is desired. Effectiveness of potential antidotes depends on the specific pharmacokinetics of each individual DOAC. Activated charcoal can be considered in the event of an acute dabigatran ingestion.⁹ It is unclear if it would be helpful for edoxaban or apixaban and not likely to work for rivaroxaban. Dialysis may be useful for dabigatran in an emergency situation. The efficacy of dialysis for apixaban and edoxaban drug removal is unknown. The highly protein bound nature of rivaroxaban would make it not dialyzable.⁹ The use of prothrombin complex concentrate (PCC) and activated PCC (aPCC) as a dabigatran and rivaroxaban antidote has been contradictory. Some studies have demonstrated improvement in lab parameters (i.e., prothrombin and thrombin potential) and exogenous thrombin potential while other studies showed no benefit. PCC and aPCC have not shown to be effective in the reversal of apixaban in animal studies. Limited evidence has demonstrated PCC and aPCC to be helpful as an edoxaban antidote.⁹ Supportive care and removal of antithrombotic is the standard of care in a bleeding emergency until an antidote becomes available.

There are three new DOAC antidotes being studied in trials. Idarucizumab (aDabi-Fab) is being developed to inactivate dabigatran and is currently being studied in a phase 3 trial (RE-VERSE AD).⁹ A phase 3 trial of an antidote to inactivate rivaroxaban, by binding to factor Xa inhibitors and heparin-activated antithrombin, is in the recruitment stage.⁹ This recombinant protein, andexanet alfa (Annexa), has also proven to be useful in apixaban reversal and may have a role in edoxaban reversal but no studies have been reported. A universal anticoagulant reversal agent in development is PER977 (arapazine/ciraparantag). PER977 binds to the anticoagulant and causes inactivation. In addition to antidote concerns, there is no standardized, reproducible way to measure coagulation effects of the DOACs.⁹

Change in Oregon Health Plan (OHP) Policy

A review of the oral anticoagulant class was presented to The Oregon Pharmacy and Therapeutics Committee in May of 2015.¹⁰ The Committee recommended that Oregon Health Plan (OHP) Fee-For-Service patients have access to all DOACs by discontinuing the clinical prior authorization (PA) requirement. A Retrospective DUR program will be conducted to monitor appropriate use.

Removal of the PA requirement was done as a result of findings of a recent policy evaluation of the anticoagulants.¹¹ The evaluation found <10% of patients with claims for anticoagulants were for DOACs. But, there was a low rate of (56.3%) of PAs requested by providers and 41 patients encountering a PA did not receive subsequent anticoagulation, putting them at risk for thrombosis. The potential safety risk to members prompted revisions to the PA policy. These changes were also supported by evidence from guidelines and systematic reviews that demonstrated similar efficacy and safety results for most anticoagulants, when used for their approved indications.¹²⁻¹⁸ Tolerability, dosing, route of elimination, drug/food interactions and monitoring requirements are just a few of the characteristics that differentiate the anticoagulants from each other. Clinical relevance of these differences still needs to be determined.

Conclusion

With the approval of the fourth new oral anticoagulant, there are an increasing number of alternatives to warfarin for patients requiring anticoagulation. Studies have demonstrated similar efficacy between the DOACs and warfarin when used in patients with NVAF and VTE. Clinically relevant differences

between the agents remain small. The optimal anticoagulant choice is influenced by patient specific characteristics, which will be aided by additional studies as the DOACs are prescribed on a broader scale.

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