

Drug Class Review

New Oral Anticoagulant Drugs

Preliminary Scan Report #1

April 2017

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Scan conducted by:

Elena Inouye, PharmD (c)
Brittany H. Lazur, MPH
Ryan Stoner, PhD
Marian McDonagh, PharmD

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator
Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director
Oregon Health & Science University

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses on new randomized controlled trials and comparative effectiveness reviews as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Original Report: May 2016 (searches through September 2015)

Date of Last Preliminary Update Scan Report

None since most recent report.

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. What is the evidence on the effectiveness and harms of the direct-acting oral anticoagulants compared with each other or with other anticoagulants for treatment of a venous thromboembolic event in adults?
2. What is the evidence on the effectiveness and harms of the direct-acting oral anticoagulants compared with each other or with other anticoagulants for extended treatment to prevent recurrence of thromboembolic events in adults at increased risk?
3. What is the evidence on the effectiveness and harms of the direct-acting oral anticoagulants compared with each other or with other anticoagulants for prevention of thromboembolic events in adults with atrial fibrillation or venous thromboembolic events in adults who have undergone orthopedic surgery?
4. What is the evidence on whether there are subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one

direct-acting oral anticoagulant is more effective or associated with fewer harms than another direct-acting oral anticoagulants or other anticoagulants?

Inclusion Criteria

Populations

Adult populations for:

- Treatment of DVT or PE
- Extension of treatment for DVT or PE, to prevent recurrence in patients at increased risk (as defined by study, or according to guidelines)
- Prophylaxis to prevent VTE in patients undergoing orthopedic surgery
- Prophylaxis in patents with atrial fibrillation (valvular or non-valvular), to VTE.

Interventions

Table 1. Interventions

Generic name	Trade name(s)	Forms
Direct Thrombin (Factor IIa) Inhibitors		
Dabigatran	Pradaxa®	Oral capsule
Direct Factor Xa Inhibitors		
Apixaban	Eliquis®	Oral tablet
Rivaroxaban	Xarelto®	Oral tablet
Edoxaban	Savaysa™ (US), Lixiana® (Japan)	Oral tablet

Comparators:

- Other Factor Xa inhibitors
- Other anticoagulants (oral or injectable; including, but not limited to, warfarin, unfractionated heparin, low molecular weight heparins)
- Aspirin for patients unable to take warfarin
- Placebo for extended treatment to prevent recurrence of VTE (only).

Outcomes

Effectiveness outcomes

- Mortality (all-cause and cardiovascular)
- Symptomatic thromboembolic event (ischemic stroke, recurrent/initial DVT or PE)
- Cardiovascular events (including, but not limited to, MI)
- Functional capacity (e.g., return to work, ability to work)
- Quality of life (e.g., SF-36).

Harms outcomes

- Overall adverse events reported
- Overall withdrawals due to adverse events
- Major adverse events (including, but not limited to, major bleeding, intracranial bleeding [including intracerebral hemorrhage] readmission, reoperation)
- Specific adverse events or withdrawals due to specific adverse events (including, but not limited to, any bleeding, gastrointestinal symptoms, hypersensitivity reactions, etc.).

Study designs

- Efficacy/effectiveness: head-to-head or active-controlled randomized trials and good-quality systematic reviews
- Harms: head-to-head or active-controlled randomized trials, good-quality systematic reviews, as well as cohort or case-control observational studies

METHODS FOR SCAN

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations from August 2015 through March 2017 using terms for specific included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan in addition to those included in Table 1. We also searched the FDA website (<http://www.fda.gov/medwatch/safety.htm>) for identification of new drugs and new serious harms (e.g., boxed warnings). To identify new drugs, we also searched CenterWatch (<http://www.centerwatch.com>), a privately-owned database of clinical trials information, and conducted a limited internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (<http://www.ahrq.gov/>) (<http://www.effectivehealthcare.ahrq.gov/>), the Canadian Agency for Drugs and Technology in Health (<http://www.cadth.ca/>), the VA Evidence-based Synthesis Program (<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>), and University of York Centre for Reviews and Dissemination (<http://www.york.ac.uk/inst/crd/crdreports.htm> - “Our Publications” and “Our Databases”). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

Study Selection

We included only potentially relevant randomized controlled trials and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan

None.

Note: Although reversal agents were not included in the scope of the report, for completeness we report here that idarucizumab (Praxbind®), the first reversal agent approved specifically for dabigatran, was approved on 10/16/2015.

Other reversal agents not yet approved, but in clinical trials:

1. Andexanet alfa (PRT4445, PRT064445): antidote to factor Xa inhibitors
2. Ciraparantag (PER977, aripazine): antidote to factor Xa and IIa inhibitors

Identified in previous Preliminary Update Scans

No scan since most recent report.

New Serious Harms (e.g., Boxed Warnings)***Identified in this Preliminary Update Scan***

None.

Identified in previous Preliminary Update Scans

No scan since most recent report.

Comparative Effectiveness Reviews***Identified in this Preliminary Update Scan***

We identified no potentially relevant comparative effectiveness reviews of newer anticoagulant agents published since the last report. We identified 1 protocol for an ongoing review conducted by the Agency for Healthcare Research and Quality (AHRQ) pertaining to venous thromboembolism prophylaxis in orthopedic surgery. This is an update of a report published in 2012 on this topic. The protocol for the ongoing review was published in February 2016. The key questions and analytic framework for this ongoing review is available in Appendix A.

Although not included in the current scope of this report, we have identified 1 potentially relevant review of the newly approved reversal agent for dabigatran, idarucizumab. This review was published by the Canadian Agency for Drugs and Technology in Health (CADTH) in January 2017. The key questions for this review are available in Appendix A.

Identified in previous Preliminary Update Scans

No scan since most recent report.

Randomized Controlled Trials***Trials identified since the most recent Full Report***

Medline searches resulted in 182 citations. Of those, 3 new active-controlled trials and 22 new secondary analyses of active-controlled trials were considered potentially relevant (see Appendix B for abstracts).

Two new active-controlled trials compared rivaroxaban with enoxaparin (1 study in patients undergoing total hip arthroplasty, 1 study in patients with pulmonary embolism with or without deep vein thrombosis). The third active-controlled trial compared edoxaban with enoxaparin/warfarin in atrial fibrillation patients undergoing electrical cardioversion.

The majority of the secondary analyses of active-controlled trials were in patients with atrial fibrillation (6 publications of ENGAGE AF-TIMI 48, 5 of ARISTOTLE, 4 of ROCKET AF, 3 of RE-LY, and 2 of AVERROES). The other 2 secondary analyses were of patients with venous thromboembolism (1 publication of Hokusai-VTE) and patients on extended treatment for venous thromboembolism (1 publication of EINSTEIN). The secondary analyses were focused on various subgroups of their parent trials.

Characteristics of the aforementioned trials are shown in Table(s) 2 and 3, below.

Table 2. New active-controlled trials

Study	N	Population	Comparison	Focus
Goette, 2016 ENSURE-AF	2,199 2 months	Atrial fibrillation (non-valvular)	Edoxaban vs. enoxaparin-warfarin	Efficacy and safety in patients undergoing electrical cardioversion
Kim, 2016	351 2 weeks	Orthopedic surgery (total hip arthroplasty)	Rivaroxaban vs. enoxaparin	Bleeding and VTE events stratified by age (<60 y vs. >60 y)
Duan, 2016	62 6 months	Pulmonary embolism (± DVT)	Rivaroxaban vs. enoxaparin (followed by VKAs)	Efficacy (e.g. major bleeding) with respect to CYP2C9 and VKORC1 genotypes

Abbreviations: DVT, deep vein thrombosis; VKA, vitamin K antagonist; VTE, venous thromboembolism; y, years

Table 3. Secondary analyses of active-controlled trials

Study	Population	Primary Trial	Comparison
Avezum, 2015	Atrial fibrillation	ARISTOTLE	Apixaban vs. warfarin
Durheim, 2016	Atrial fibrillation	ARISTOTLE	Apixaban vs. warfarin
Jasper Focks, 2016	Atrial fibrillation	ARISTOTLE	Apixaban vs. warfarin
Rao, 2015	Atrial fibrillation	ARISTOTLE	Apixaban vs. warfarin
Vinereanu, 2015	Atrial fibrillation	ARISTOTLE	Apixaban vs. warfarin
Lip, 2015	Atrial fibrillation	AVERROES	Apixaban vs. aspirin
Ng, 2016	Atrial fibrillation	AVERROES	Apixaban vs. aspirin
Eisen, 2016	Atrial fibrillation	ENGAGE AF-TIMI 48	Edoxaban vs. warfarin
Geller, 2015	Atrial fibrillation	ENGAGE AF-TIMI 48	Edoxaban vs. warfarin
Bohula, 2016	Atrial fibrillation	ENGAGE AF-TIMI 48	Edoxaban vs. warfarin
O'Donoghue, 2015	Atrial fibrillation	ENGAGE AF-TIMI 48	Edoxaban vs. warfarin
Steffel, 2015	Atrial fibrillation	ENGAGE AF-TIMI 48	Edoxaban vs. warfarin
Yamashita, 2016	Atrial fibrillation	ENGAGE AF-TIMI 48	Edoxaban vs. warfarin
Ezekowitz, 2016	Atrial fibrillation	RE-LY	Dabigatran vs. warfarin
Hori, 2015	Atrial fibrillation	RE-LY	Dabigatran vs. warfarin
Nagarakanti, 2015	Atrial fibrillation	RE-LY	Dabigatran vs. warfarin
Fordyce, 2016	Atrial fibrillation	ROCKET AF	Rivaroxaban vs. warfarin
Pokorney, 2016	Atrial fibrillation	ROCKET AF	Rivaroxaban vs. warfarin
Sherwood, 2015	Atrial fibrillation	ROCKET AF	Rivaroxaban vs. warfarin
Steinberg, 2015	Atrial fibrillation	ROCKET AF	Rivaroxaban vs. warfarin
Eerenberg, 2015	Extended VTE treatment	EINSTEIN	Rivaroxaban vs. LMWH/VKA
Nakamura, 2015	VTE	Hokusai-VTE	Edoxaban vs. warfarin

Abbreviations: LMWH, low molecular weight heparin; VKA, vitamin K antagonist VTE, venous thromboembolism

SUMMARY

Since the last report on this topic, we have identified no newly approved drugs, no new serious harms, and no completed comparative effectiveness reviews of newer anticoagulant agents. While there are no recently completed systematic reviews of the oral anticoagulants, we have identified the protocol for an ongoing AHRQ review of venous thromboembolism prophylaxis in orthopedic surgery. In terms of new evidence, we have identified 3 new active-controlled trials (2 of rivaroxaban vs. enoxaparin in orthopedic surgery and pulmonary embolism and 1 of edoxaban vs. enoxaparin/warfarin in atrial fibrillation patients undergoing electrical cardioversion). We have also identified 22 new secondary analyses of active-controlled trials that were included in the last DERP report (6 publications of ENGAGE AF-TIMI 48, 5 of ARISTOTLE, 4 of ROCKET AF, 3 of RE-LY, 2 of AVERROES, 1 of Hokusai-VTE, and 1 of EINSTEIN). The bulk of this evidence provides more evidence on subgroups of patients.