

Oral Anticoagulant Agents

Executive Summary¹⁻⁷

- Four new oral anticoagulants (NOACs) are being marketed in the United States; edoxaban (Savaysa) is the newest agent on the market. Multiple new indications have been granted.
- The bulk of utilization in the Military Health System is for nonvalvular atrial fibrillation (NVAf).
- ACC/AHA/HRS and AAN guidelines for prevention of stroke in NVAf were updated in 2014.
- In patients with NVAf, NOACs are at least as effective as warfarin in preventing stroke, are easier to use and have a lower risk of intracranial hemorrhage.
- In patients with DVT/PE, NOACs, as maintenance therapy, are probably at least as effective as warfarin in preventing recurrent venous thromboembolism (VTE), while not increasing bleeding risk.

Background^{1-5,8}

Pradaxa, Xarelto, Eliquis, and Savaysa are newer oral anticoagulant medications. Pradaxa is a direct thrombin inhibitor; Xarelto, Eliquis, and Savaysa are Factor Xa inhibitors. Standard anticoagulation monitoring is not required. These agents are referred to as NOACs and Target-Specific Oral Anticoagulants (TSOACs). Warfarin, a vitamin K antagonist available since 1954, is indicated for prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism (PE); prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation (AFib) and/or cardiac valve replacement; and, reduction in the risk of death, recurrent myocardial infarction (MI), and thromboembolic events such as stroke or systemic embolization after MI.

Table 1: Oral Anticoagulant Agents Available in U.S.¹⁻⁵

| Generic Name | Brand Name (Mfg) | Formulations | FDA Approval | Patent Expiration |
|-----------------------------------|-----------------------------|--|--------------|-------------------------|
| Vitamin K Antagonists | | | | |
| Warfarin | Coumadin | 1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg tabs | Jun 1954 | multiple generics avail |
| Direct Thrombin Inhibitors | | | | |
| Dabigatran | Pradaxa (BI) | 75, 150 mg caps | Oct 2010 | 2018-2027 |
| Factor Xa inhibitors | | | | |
| Rivaroxaban | Xarelto (J&J) | 10, 15, 20 mg tabs | Jun 2011 | 2020-2021 |
| Apixaban | Eliquis (Pfizer/BMS) | 2.5, 5 mg tabs | Dec 2012 | 2019-2023 |
| Edoxaban | Savaysa (Daiichi-Sankyo) | 15, 30, 60mg tabs | Jan 2015 | 2021-2024 |

Table 2: FDA Indications—Anticoagulants¹⁻⁵

| Indication | Warfarin | Dabigatran | Rivaroxaban | Apixaban | Edoxaban | Enoxaparin |
|--|----------|--------------------------------|-----------------|-----------------|--------------------------------|---------------------------------|
| Stroke prevention assoc with AFib | X | X (Oct 2010) | X (Nov 2011) | X (Dec 2011) | X (Jan 2015) | |
| Stroke prevention assoc with cardiac valve replacement | X | | | | | |
| VTE prophylaxis hip and knee | X | | X (Jul 2011) | X (Mar 2014) | | *X |
| VTE treatment (DVT/PE) | X | X (Apr 2014) +LMWH 5-10d | X (Nov 2012) | X (Aug 2014) | X (Jan 2015) +LMWH 5-10d | X (STEMI & PE In-pt only) |
| ↓ risk of recurrent PE/DVT | X | X (Apr 2014) | X (Nov 2012) | X (Aug 2014) | | |
| ↓ death/recurrent MI/stroke or SE after MI | X | | | | | |

Table 3: FDA Dosing—Oral Anticoagulants^{1-5,9}

| Indication | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|----------------------------|--|-------------------------------------|--|--|
| AFib | 150 mg BID H2O | 20 mg QD food | 5 mg BID | 60mg QD CrCl >50mL/min and ≤ 95mL/min |
| AFib* alternate | 75 mg BID CrCl 15-30mL/min | 15 mg QD food CrCl 15-50 mL/min | 2.5 mg BID ≥80 yrs, ≤60kg SCr ≥1.5 mg/dL | 30mg QD CrCl 15-50mL/min |
| Hip | | 10 mg QD x 35 d | 2.5mg BID x 35 d | |
| Knee | | 10 mg QD x 12 d | 2.5mg BID x 12 d | |
| Treatment DVT/PE | 150 mg BID after 5-10 days parenteral anticoag | 15 mg BID x 21d, then 20 mg QD food | 10mg BID x 7 d, then 5mg BID | 60mg QD after 5-10days of parenteral anticoagulant; 30mg QD CrCl 15-50mL/min or ≤ 60kg |
| ↓ risk of recurrent PE/DVT | 150mg BID | 20mg QD food | 2.5mg BID x 6 mo | |

*Alternate dosing:

- Dabigatran: 75 mg dose never studied clinically; no pts CrCl <30mL/min
- Rivaroxaban: 8 patients had CrCl <30 mL/min in ROCKET-AF trial
- Apixaban: no data in patients with CrCl of 15–30 mL/min
- Edoxaban: 75–90mg (45mg) may have improved efficacy with acceptable safety in patients with CrCl ≥80 (≤50mL/min)

Table 4: Current Formulary Status—Anticoagulants, LMWHs, Antiplatelet Agents

| Basic Core Formulary (BCF) | Uniform Formulary (UF) | Nonformulary (NF) |
|--|---|-------------------|
| Feb 2013 Warfarin (BCF since 1998) | Dabigatran (Pradaxa) Rivaroxaban (Xarelto) Apixaban (Eliquis) | None |
| Aug 2012 Enoxaparin (generic Lovenox) | Dalteparin (generic Fragmin) Fondaparinux (generic Arixtra) | None |
| Feb 2012 Clopidogrel (generic Plavix) | Prasugrel (Effient) Ticagrelor (Brilinta) | None |

Edoxaban (Savaysa), a factor Xa inhibitor, has been approved but not yet reviewed. No generic NOACs are available.

Summary of the Evidence¹⁻²⁰

- Pradaxa is a direct thrombin inhibitor. Xarelto, Eliquis, and Savaysa are Factor Xa inhibitors.
- All agents are indicated to reduce the risk of stroke and systemic embolism in patients with NVAF; for the treatment of deep vein thrombosis (DVT) and PE. However, Savaysa should not be used in NVAF in patients with a creatinine clearance (CrCL) > 95 mL/min. For the treatment of DVT and PE, Xarelto and Eliquis may be used as initial therapy. All agents, except Savaysa, are indicated for reducing the risk of occurrence of DVT and PE. Xarelto and Eliquis are also approved for the prophylaxis of DVT, which may cause PE, after hip or knee replacement surgery.
- Dosing with Pradaxa and Eliquis is twice daily (BID). With Xarelto, most dosing is once daily (QD), except for the treatment of DVT and PE for the first 21 days in which dosing is BID. Savaysa is dosed QD.
- The agents vary in some key pharmacokinetic parameters. Eliquis has less renal clearance than dagabritan and rivoroxiban and may be preferred for use in patients that have decreased renal function. Renal clearance accounts for approximately 50% of the total clearance of Savaysa.
- Direct and/or comparative trials between Pradaxa, Xarelto, Eliquis and Savaysa have not been performed. All agents have been compared with warfarin in NVAF. Only Eliquis has been compared with aspirin in NVAF. Pivotal trial data for each medication in NVAF are summarized below. Also, a brief synopsis is provided for the uses in other indications.
- In RE-LY, which involved patients with NVAF (n = 18,113), Pradaxa 150 mg BID significantly reduced the primary composite endpoint of stroke and systemic embolism (2.2%) versus Pradaxa 110 mg BID (3.0%) and warfarin (3.4%). Pradaxa was superior in reducing ischemic and hemorrhagic strokes. The median follow-up was 2 years.
- In ROCKET AF, which involved patients with NVAF (n = 14,264), Xarelto was noninferior to warfarin for the primary composite endpoint of time to first stroke or non-central nervous system embolism (3.8% versus 4.3%); superiority to warfarin

was not noted. The median follow-up was 590 days. There are limited data regarding the effectiveness of Xarelto and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled.

- In ARISTOTLE, which involved patients with NVAF (n = 18,201), Eliquis was superior to warfarin in reducing the primary endpoint of the risk of stroke and systemic embolism (n = 212 events with Eliquis [1.27% per year] versus 265 events with warfarin [1.60% per year]) [P = 0.01]. The superiority was mainly due to a reduction in hemorrhagic stroke. Eliquis also was associated with a lower rate of all-cause death compared with warfarin (P = 0.046). Patients were followed for a median of 89 weeks.
- In ENGAGE AF-TIMI 48, which involved patients with NVAF (n = 21,105), Savaysa was non-inferior to warfarin for the occurrence of first stroke or of a systemic embolic event (1.2% per year with Savaysa 60 mg QD versus 1.5% per year with warfarin). Treatment was for a median of 2.5 years.
- For the treatment of DVT and PE, all agents generally appear noninferior to parenteral anticoagulants (e.g., enoxaparin subcutaneous [SC], heparin) followed by warfarin and better than placebo for the risk of recurrence. The relative risk for major bleeding was significantly less for TSOACs versus warfarin. For prophylaxis after hip or knee surgery, in general, Xarelto was superior to enoxaparin SC and Eliquis was at least as good as enoxaparin SC.
- All of these agents have been studied off-label for other indications. Pradaxa and Savaysa have published data for the prophylaxis of VTE post orthopedic surgery. Some agents have been studied in patients who have had a recent acute coronary syndrome.
- The 2014 guidelines for the management of AFib from the American Heart Association (AHA), American College of Cardiology (ACC), and the Heart Rhythm Society (HRS) recommend oral anticoagulants for patients with NVAF with a prior stroke, transient ischemic attack (TIA), or a CHA2DS2-VASc score ≥ 2 with the options being warfarin, Pradaxa, Xarelto, or Eliquis. Savaysa was not addressed.
- In 2012, the American College of Chest Physicians (ACCP) published guidelines regarding antithrombotic therapy and prevention of thrombosis. For some clinical scenarios Pradaxa, Xarelto, and Eliquis are recommended as options. Since publication of these guidelines, several of the newer oral anticoagulants received approval for treatment in these situations. Savaysa was not addressed.
- All agents are contraindicated in patients with active pathological bleeding. Pradaxa is contraindicated in patients with prosthetic heart valves.
- All agents have similar Boxed Warnings regarding premature discontinuation and spinal/epidural hematomas. Savaysa has a unique warning regarding reduced efficacy in NVAF among patients with a CrCl > 95 ml/min; use should be avoided in such patients due to an increased risk of ischemic stroke compared with warfarin.
- The main adverse events (AEs) are bleeding with all three agents. Warfarin has a Boxed Warning for major or fatal bleeding. Pradaxa is associated with more frequent gastrointestinal (GI) AEs. Pradaxa and warfarin had similar rates of major bleeds in NVAF. However, Pradaxa was associated with a higher rate of GI bleeds. Pradaxa is also uniquely associated with more frequent gastritis-like symptoms. Major bleeding events in the DVT/PE indications were similar to warfarin.
- Xarelto and warfarin had a similar incidence of major bleeding in NVAF. However, Xarelto had a lower rate of fatal bleeding. Bleeding rates in use for thromboprophylaxis were generally similar between Xarelto and enoxaparin given SC.
- Eliquis led to significantly fewer major bleeds compared with warfarin in NVAF, including intracranial bleeding. Eliquis was associated with a modest increase in major bleeding versus aspirin in this patient population. In thromboprophylaxis DVT, bleeding was similar between Eliquis and enoxaparin. In the treatment of DVT/PE, Eliquis led to fewer major bleeds compared with enoxaparin/warfarin.
- Savaysa led to less major bleeding compared with warfarin in NVAF. For treating VTE, bleeding rates were lower with Savaysa versus warfarin.

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References

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| ACC | – American College of Cardiology |
| AE | – adverse event(s) |
| AFib | – atrial fibrillation |
| AHA | – American Heart Association |
| BID | – twice daily |
| CrCl | – creatinine clearance |
| DVT | – deep vein thrombosis |
| GI | – gastrointestinal (GI) |
| HRS | – Heart Rhythm Society |
| LMWH | – low-molecular-weight heparin |
| MI | – myocardial infarction |
| NOACs | – new oral anticoagulants |
| NVAF | – nonvalvular atrial fibrillation |
| PE | – pulmonary embolism |
| QD | – once daily |
| SC | – subcutaneous |
| SE | – systemic embolization |
| TSOACs | – Target-Specific Oral Anticoagulants |
| VTE | – venous thromboembolism |