Basics of Warfarin Management: Helpful Considerations

Author: Steve Lee, PharmD

Despite the availability of newer anticoagulants and serving as an alternative in prevention or treatment of DVTs, PEs or thromboembolic stroke due to atrial fibrillation (a-fib)—*warfarin is still critical* in modern cardiovascular health care.
Warfarin still remains the only oral treatment option for stroke prevention in valvular A-Fib, protection from thrombogenesis from various cardiac valve prosthesis and some hypercoagulable states.

Warfarin Dosing

Average daily dose of warfarin for patients (all ages) is roughly 5 mg. For patients over the age of 75, average daily dose is about 2.5 mg.

- Start elderly patients (≥ 65 years) on a lower dose.
- Avoid "loading doses" of warfarin if trying to speed up time for therapy effect. Generally, this doesn't improve time to stable anticoagulation status.
- Great inter-individual differences in dosing may exist in each group, but generally, aging yields a gradual decrease in the daily warfarin dose compared to younger patients.

Starting Warfarin

- Have a baseline INR prior to therapy.
- It can take 5 to 7 days, and even up to 2 weeks, for a full response to warfarin therapy.
- Daily INR monitoring should rarely be necessary for outpatient settings.
- After 3 days of warfarin consumption, check INR. Patients with INRs of 1.5 to 1.6 by this time are usually on a good trajectory for achieving therapeutic level of anticoagulation. No adjustments necessary.
- Adjust dosage if INR is elevating too fast or not elevating.
- Most patients, plan on twice-weekly INR monitoring for a short time, weekly for several weeks then every 2 weeks for several cycles after warfarin initiation. Thereafter, monthly INR checks for stable patients.
- After warfarin changes in stable patients, allow 2 weeks before reassessing and assuming a stable INR response from new regimen (Evaluate sooner for progress, if needed).

INR is Your Best Friend - The Importance of Monitoring

Always utilize the INR test. INR, in a nutshell, is a measurement on how long it takes for blood to coagulate (Higher INR number = longer it will take to clot). Educate patients on the value of understanding their INR and its effect on dosing adjustments.

PATIENTS WHO:

- Are stable (those requiring few adjustments to warfarin) → Monitor INR monthly
- Have extreme variability in warfarin response → increase INR monitoring frequency.
- Require few alterations in their warfarin and appear extremely stable,
  - An extended INR monitoring (6 to 8 weeks) may be reasonable OR
  - 2 to 3 months for more extreme monitoring intervals in patients considered as exceptionally stable, based on recent studies.

Generally, allow 2 full weeks to pass to see full effect from a warfarin dosing change.

Patient Compliance – Two Essential Tools

Highly encourage patients to use a pill bar in setting up their weekly warfarin regimen. Pill bars can serve two benefits: 1) correct dosage on the right day and 2) when a dose gets missed.

Consider developing a dosing card that matches the pill bar to use as written instructions each time a regimen is changed.

Diet Considerations – Think Vitamin K

Warfarin acts as an antagonist against the formation of Vitamin K dependent clotting factors. This activity can be significantly affected by enhanced Vitamin K consumption from foods or supplements. Therefore, stringent dietary restriction of Vitamin K foods are rarely necessary. Rather, good education up front.

- Educate patients on what foods have moderate-high Vitamin K.
- Encourage patients to stay moderate in consumption of these foods and to be consistent on a weekly basis.
- Stable dietary pattern on Vitamin K is the goal – not necessarily a restriction.
- Beware of OTC supplements can contain significant amounts of Vitamin K (e.g. Viactiv Chews®, Boost®, Ensure®)

Watch patients carefully when they relocate from their home to an assisted living center or nursing facility. Vitamin K consumption often increases due to the dietary services provided in these settings. Patients may need an increase in warfarin dosing over time to compensate for the added Vitamin K.

Warfarin Tablets (9)

Avera

Helpful Mnemonic:
Please **L**et **G**ranny **B**rown **B**ring **P**eaches **T**o **Y**our **W**edding

Therapy "Disruptors"

Patient's responsiveness to warfarin can be affected by the development or exacerbation of other health conditions, such as:

- Major GI illness affecting overall food consumption or the decrease in GI transit time affecting Vitamin K consumption/absorption, thus a gradual INR rise.
- Worsening heart failure or conversion from primarily normal sinus rhythm to predominantly A-Fib may cause a rise in INR.

Intensify INR monitoring in this environment or when other significant health changes occur.

Drug Interactions: Some BIG, but Mainly Small

Warfarin has characteristics subject to a host of drug interactions. Mechanisms for these interactions involve drug binding sites, metabolism and elimination pathways, including Vitamin K-related impacts. Some interactions can be catastrophic, but the majority are modest; thus, requiring only intensified INR monitoring and minimal dosing adjustments. In most instances, intensified INR monitoring is indicated.

COMMON INTERACTIONS TO BE AWARE OF:

Antibiotics

- Trimethoprim/Sulfamethoxazole: increases anticoagulant effect/INR → Avoid combination if at all possible; if used in combination monitor INR closely and anticipate a warfarin dose reduction.
- Fluoroquinolones & Tetracyclines: potential to increase anticoagulant effect/INR → Monitor INR after 3 days of therapy and assess response.
- Beta-lactams (e.g. penicillin, cephalosporin): Often no impact on INR.

Fluconazole

- Larger dose regimens over multiple days may increase anticoagulant effect/INR → Monitor INR closely and anticipate potential warfarin dose reduction (generally not a concern with one-time dosing).

Corticosteroids

- Doses of corticosteroids that seem to approximate a prednisone dose in excess of 20mg/day can increase anticoagulant effect/INR → closely monitor INR during concomitant therapy.

Statins

- Majority of statin medications have little/no effect on warfarin. Rosuvastatin may increase anticoagulant effect/INR → Monitor INR after initiation and anticipate a warfarin dose reduction.

Amiodarone

- Increases anticoagulant effect/INR Monitor patients extra closely following initiation of drug or following a dose increase; can consider an empiric warfarin dose adjustment of 10-20% when initiating amiodarone.
- Has a long half-life. If discontinued or dose decreased → Interaction may persist for weeks to months; anticipate a slow, upward climb in warfarin dosing after discontinuation.

Dosing Adjustments- Don't Overdo it!

Once patients are warfarin-saturated, INR response to dosage changes occur gradually, but not necessarily in a linear fashion. INR changes can almost appear exponential at times. In most cases, avoid aggressive dosage adjustments.

There are nine dosages of Warfarin, starting at 1 mg up to 10 mg tablets. Despite this, there may be patients who end up needing dosing between two available strengths. If this occurs, simply prescribe two separate tablet strengths to "produce" the needed regimen. Thus, allowing more flexibility for adjustment in fine increments by giving them instructions to consume a combination of each strength, with the goal of fine tuning a weekly dose.

Example: 5 mg daily is not quite adequate (INR 1.8 in an A-fib patient) AND 6 mg daily is too much (INR 4.5). Consider 6 mg for 2 days and 5 mg for 5 days as a weekly regimen (e.g. 6 mg on Monday and Friday and 5 mg all of the other days). Reassess in two weeks, titrating as little as 1mg/week by adjusting regimen as needed.

When a patient is nearly saturated with warfarin, a small amount can yield much more "free drug" for systemic effect. Avoid significant dosing changes in patients who may need a small increase or decrease in INR.

Hold It?

- Avoid holding warfarin doses for patients slightly out of the desired INR range. Simply readjust and monitor.
- Significant elevated INRs can be reduced more rapidly by holding a daily dose or two of warfarin.
- Each missed dose can yield an INR drop of 0.8 to 1.0 full INR point with the nadir occurring 3 to 4 days after missed dose (Remember important lag time for response).

Missed Doses? Always Ask the Patient

- Prior to labs, always ask for potential/missed warfarin doses within the last 7 to 10 days. This can have a major impact on therapeutic decision.
- Skipped doses can yield INR drop maximal at 3 to 4 days and slowly rising.

Identifying missed doses can help prevent over-anticoagulation when dosage increases are made that might be unnecessary.

Content Contact: Steve L, PharmD

Avera's Patient Education

Avera's custom patient education brochure on Warfarin that is available to order in print from the Marketing Reorder Library. Click here to preview (21-PHAR-26219-ML).

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Information presented were developed to assist in the delivery of care and are not intended to define the standard of care.

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Direct-Acting Oral Anticoagulants (DOACs)

Author: Annette Johnson, Pharm.D

Executive Summary:

- Direct-acting oral anticoagulants (DOACs) have several advantages over conventional warfarin, including faster onset and offset. There are four DOACs, apixaban, dabigatran, edoxaban and rivaroxaban. Each DOAC differs in their approved indications, dosing and recommendations in special populations. Thus, the selection of DOAC should be based off of individual patient characteristics.
- Stopping DOAC therapy before a procedure is based off of two factors, a patient's pre-procedural renal function and their bleed risk for the procedure.
- Resuming DOACs following a procedure should be based off the bleed risk of the procedure and procedural site hemostasis.

	PREVENTION					TREATMENT
Drug	Stroke in NVAF	Recurrent DVT and PE	VTE after TKA or THA	VTE in hospitalized patients	Major CV in Chronic CAD/PAD	DVT and PE
Dabigatran (Pradaxa®)	X	X	X			X
Rivaroxaban (Xarelto®)	X	X	X	X	X	X
Apixaban (Eliquis®)	X	X	X			X
Edoxaban (Savaysa®)	X					X

Clinical Pearls

For All DOACs Agents -

- Dosing adjusted with renal impairment
- DOACs are preferred anticoagulation for most patients with atrial fibrillation.
    - Studies have shown benefit for each of the DOACs vs. warfarin in the endpoints of death, stroke or systemic embolic event, hemorrhagic stroke and major bleeding.
- Non-cancer patients - DOAC therapy over warfarin as long-term anticoagulation for VTE treatment, per CHEST Guideline recommendations.

See next page for clinical pearls on each DOAC agent.

Direct-Acting Oral Anticoagulants (DOACs) – 4 Available Agents

Dabigatran (Pradaxa®)

- Requires twice daily dosing
- DVT/PE treatment: Start dabigatran after ≥ 5 days of initial therapy with a parenteral anticoagulant
- Causes gastrointestinal symptoms in > 10% of patients
- Must be kept in original packaging. Once opened, must be used within 4 months
- Patients ≥ 75 years: Use extreme caution or consider other treatment options due to increased risk of GI bleeding (per Beers list)

➔ SWITCHING AGENTS

Warfarin → Dabigatran

- Stop warfarin and then start agent when INR < 2

Dabigatran → Warfarin

- If CrCl > 50 mL/min, start warfarin 3 days prior to discontinuing dabigatran
- If CrCl 30 to < 50 mL/min, start warfarin 2 days prior to discontinuing dabigatran
- If CrCl 15 to 30 mL/min, start warfarin 1 day prior to discontinuing dabigatran
- Agent not recommended when CrCl <15 mL/min
- Agent can increase INR, thus will better reflect warfarin's effect after agent has been stopped for at least 2 days

Apixaban (Eliquis®)

- Requires twice daily dosing.
- NVAF: If patient has any of the following: Age ≥ 80 years, weighs ≤ 60 kg or a serum creatinine ≥ 1.5 mg/dL → Reduce dose to 2.5 mg twice daily.
- Use not recommended with severe hepatic impairment.
- Patients at increased risk of recurrent VTE after 6 months of therapeutic anticoagulation, recommended dose is 2.5 mg twice daily.

➔ SWITCHING AGENTS

Warfarin → Apixaban

- Stop warfarin and then start agent when INR < 2

Apixaban → Warfarin

- Apixaban increases INR, check the INR near the end of apixaban dosing interval
- Some experts suggest overlapping apixaban with warfarin for ≥ 2 days until INR is therapeutic OR start a parenteral anticoagulant + warfarin when the next dose of apixaban is due. Discontinue parenteral agent when INR reaches desired range.

Rivaroxaban (Xarelto®)

- Avoid with moderate to severe liver impairment or liver disease with coagulopathy.
- Take doses ≥ 15 mg with food
  - Bioavailability of 15 mg and 20 mg doses is reduced in a fasting state
  - Taking agent with food increases bioavailability of the 15 mg and 20 mg doses
  - Bioavailability for 2.5 to 10 mg dose range is 80-100% and not affected by food
- Patients at increased risk of recurrent VTE after 6 months of therapeutic anticoagulation → recommended dose is 10 mg once daily
- Patients ≥ 75 years: Use extreme caution or consider other treatment options due to increased risk of GI bleeding in this age category (per Beers list)

➔ SWITCHING AGENTS

Warfarin → Rivaroxaban

- Stop warfarin and then start agent when INR < 3

Rivaroxaban → Warfarin

- Rivaroxaban increases INR. Check INR near the end of rivaroxaban dosing interval
- Some experts suggest overlapping agent with warfarin ≥ 2 days until INR is therapeutic OR start a parenteral anticoagulant + warfarin when the next dose of rivaroxaban is due
- Discontinue parenteral agent when INR reaches desired range

Edoxaban (Savaysa®)

- DVT/PE Treatment: Start after ≥ 5 days of initial therapy with a parenteral anticoagulant; dose is weight based
- If CrCL > 95 mL/min: use not recommended for non-valvular atrial fibrillation due to increased risk of ischemic stroke
- Not recommended with moderate to severe hepatic impairment

➔ SWITCHING AGENTS

Warfarin → Edoxaban

- Stop warfarin and start edoxaban when INR ≤ 2.5

Edoxaban → Warfarin

- Decrease edoxaban dose by 50% and then start warfarin
- Stop edoxaban when INR is ≥ 2 and stable OR stop and use parenteral anticoagulant with warfarin until INR is ≥ 2 and stable

Content Contact: Annette Johnson, PharmD

Perioperative Management

If anticoagulation (DOAC) has to be stopped for a procedure, hold DOAC based on chart below:

(View Avera's preoperative guideline for full details).

DOAC	Pre-procedural renal function	Low procedural bleed risk	Uncertain, intermediate, or high procedural bleed risk
Dabigatran	CrCl ≥ 80 mg/dL CrCl 50 - 79 mg/dL CrCl 30 - 49 mg/dL CrCl 15 - 29 mg/dL CrCl < 15 mg/dL	Stop 24 hours before Stop 36 hours before Stop 48 hours before Stop 72 hours before Stop 96 hours before[a]	Stop 48 hours before Stop 72 hours before Stop 96 hours before Stop 120 hours before Consider dTT*
Factor Xa Inhibitors (apixaban, edoxaban, rivaroxaban)	CrCl ≥ 30 mL/min CrCl < 30 mL/min	Stop 24 hours before Stop 48 hours before[b]	Stop 48 hours before Stop 72 hours before [c]

*dilute thrombin time assay
[a]Consider dTT
[b]For CrCl <15 ml/min, consider anti Xa level
[c]Consider anti Xa level

After surgery/procedure is performed, resume DOAC based on bleed risk:

- Ensure procedural site hemostasis. Consider procedure-specific bleeding complications, evaluate patient-specific bleeding factors and collaborate with proceduralist and care team.
- Following procedures with low post-procedural bleed risk, resume DOAC therapy at full dose on the day after the procedure.
- Following high post-procedural bleed risk procedures. Wait 48 to 72 hours before resuming DOAC therapy.
- DOAC dosing should reflect post-procedural renal function

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Obesity and Anticoagulation

Author: Samantha Trumm, PharmD

Executive Summary:

- Obesity defined in this issue are patients who have a 35 or greater BMI and/or weigh 120 kg or more.
- Oral anticoagulant options for treatment and primary prevention of VTE in obese patients include 3 options: warfarin, apixaban and rivaroxaban[1].
- Anticoagulation in obese patients with atrial fibrillation based on available literature suggests that warfarin, apixaban, and rivaroxaban have similar efficacy and safety outcomes[2]
- When enoxaparin is preferred or required for bridging, suggested dosing should be based on actual body weight versus capped dosing[3].
- Anticoagulant selection should take into account patient specific factors, including affordability, renal function, compliance, etc.

Acronyms:

ACC	American College of Cardiology
AHA	American Heart Association
ASH	American Society of Hematology
BMI	Body Mass Index
DOACs	Direct-acting Oral Anticoagulants
HRS	Heart Rhythm Society
ISTH	International Society on Thrombosis and Haemostasis
JAHA	Journal of the American Heart Association
VTE	Venous Thromboembolism

Direct Oral Anticoagulants (DOACs)

Venous Thromboembolism (VTE)

A majority of study patients in apixaban (Eliquis®) and rivaroxaban (Xarelto®) phase 3 trials weighed less than 100 kg.[2] Even though the subgroup analysis of obese patients suggested DOACs were efficacious and safe, data was still limited to include in ISTH 2016 Guidelines. Since then, more research is available (see Table 1). Limited data exists for dabigatran and edoxaban and currently not recommended for use in obese patients[1].

Table 1 - Efficacy and Safety Outcomes: DOACs & Vitamin K Antagonists (VKA) Comparison in VTE Treatment

	Phase 3 DOACs with VKA in VTE		**Phase 4** DOAC with VKA in VTE (Including retrospective & prospective studies & meta-analyses)	
	BMI > 35 or Weight >120 kg	BMI > 40	BMI > 35 or Weight >120 kg	BMI > 40
Apixaban (Eliquis®)	X	X	Similar outcomes	Similar outcomes
Dabigatran (Pradaxa®)	X	X	X	X
Edoxaban (Savaysa®)	X	X	X	X
Rivaroxaban (Xarelto®)	Similar outcomes*	X	Similar outcomes*	Similar outcomes*
Pooled DOAC	Similar outcomes*	X	Similar outcomes*	Similar outcomes*

*Similar outcome = DOAC compared with LWMH/VKA; X = N/A Data

Atrial Fibrillation (AF)

The AHA/ACC/HRS Guideline (2019) for atrial fibrillation does not address obesity when choosing anticoagulation for qualifying patients. However, analyzing literature on obese patients with atrial fibrillation may give guidance on utilizing anticoagulants for this population.
While renal dose adjustments are provided, warfarin may be a better option for obese patients (e.g. BMI ≥ 35 or weighs over 120 kg) with severe renal impairment.

Table 2 - Dosing of Apixaban (Eliquis®) and Rivaroxaban (Xarelto®)

	Apixaban (Eliquis)[6]	Rivaroxaban (Xarelto)[7]
Atrial Fibrillation	5 mg BID	20 mg Daily
Dose Adjustments	**At least 2 to qualify:** ☐ SCr > 1.5mg/dL ☐ Age > 80 ☐ Weight < 60 kg • 2.5 mg BID	**CrCl 15 to 50 ml/min** • 15 mg daily **CrCl <15 ml/min** • Avoid - Not Dialyzable
Venous Thromboembolism (VTE)	**Treatment** • 10 mg BID for 7 days; then 5 mg BID **Prophylaxis** • 2.5 mg BID	**Treatment** • 15 mg BID for 21 days; then 20 mg daily **Prophylaxis** • 10 mg daily
Dose Adjustments	**No dose adjustments recommended**	**CrCl < 30 ml/min** • Avoid - Not Dialyzable

AF Supporting Literature

A study on Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation (ROCKET-AF Trial) noted a statistically significant[5] lower incidence of stroke and systemic embolism in overweight and obese patients. Moreover, a study published in JAHA, indicated patients with atrial fibrillation on DOACs, concluded similar efficacy and safety across all BMI groups[2] with a majority on either apixaban or rivaroxaban. The AHA/ACC/HRS Guideline expressed Serum Xa levels may be considered[4]. However, there is no established therapeutic range of Xa inhibition and ISTH Guidelines recommends against this[1].

For DOACs, keep in mind patient specific characteristics, including compliance (once versus twice daily dosing) and renal function. Costs of DOACs may be prohibitive. Patients should check with their insurance provider for coverage. See Table 2 for dosing recommendations.

Warfarin (Coumadin)

Even though updated guidelines support apixaban and rivaroxaban for obese patients— *warfarin should still be considered*. Especially higher costs of DOACs for patients and those with underlying renal impairment, where DOAC dosing may be less reliable. INR goals remain the same based on indication. However, obese patients have found to require higher total weekly doses of warfarin to achieve same goal INR compared to those with normal bodyweight.[8,9] Therefore, this should be taken into account along with patient specific factors when their dose (e.g. diet, interacting medications, acute illness, genetic polymorphisms, etc.).

Parenteral Anticoagulation: Enoxaparin (Lovenox) – Low Molecular Weight Heparin (LMWH)

VTE/Bridging:
Avera's Enoxaparin Rounding Policy recommends individualized dosing for obese patients based on indication, renal function and bleeding risk. See Table 3 and Table 4 for weight-based dosing recommendations. For patients weighing 150 kg or more, low quality of evidence exists regarding the use of initial LMWH doses based on actual body weight compared with capped dosing. Due to concerns for potentially under dosing obese patients and the potentially serious consequence of therapeutic failure and lack of correlation between supratherapeutic anti–factor Xa concentrations and bleeding, in most situations, LMWH doses based on actual body weight should be deliberated over capped dosing.[3,10] Monitoring of anti-Xa levels may be considered, but are not supported by 2018 ASH Guidelines.[3]

- For example, a 180 kg stable patient on warfarin for atrial fibrillation will undergo surgery in a week. Patient's CHA2DS2-VASc score is 7 and has a relatively low bleeding risk. Avera's Preoperative Guideline indicates to bridge this patient with enoxaparin. Capped dosing suggests a max dose of 150 mg twice daily while a dose based on actual body weight would be 180 mg twice daily. For this patient, benefits likely outweigh the risk for enoxaparin 180 mg twice daily dose.

Table 3 - 1 mg/kg Enoxaparin Dosing

Actual Bodyweight	Dose
36 to 49 kg	40 mg
50 to 69 kg	60 mg
70 to 89 kg	80 mg
90 to 109 kg	100 mg
110 to 136 kg	120 mg
137 to 159 kg	150 mg
≥160 kg	Individualize dosing

Table 4 - 1 mg/kg Enoxaparin Dosing - (Patients with Impaired Renal Function)

Actual Bodyweight	Dose
36 to 46 kg	60 mg
47 to 59 kg	80 mg
60 to 73 kg	100 mg
74 to 89 kg	120 mg
90 to 100 kg	150 mg
>100 kg	Not Recommended

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Key Words: atrial fibrillation; obesity; stroke prevention; DOACs; anticoagulants; obesity

Considerations for Generic Dabigatran

Author: Don Bladt, PharmD

Executive Summary

In the second quarter of 2022, dabigatran (Pradaxa®) is expected to be the first direct-acting oral anticoagulant (DOAC) to face generic competition. Currently, at least eight generic drug manufacturers have received FDA approval to launch their versions of dabigatran. The likely result of the high level of competition in the space is rapid price erosion, with cost savings of $250 or more per prescription when compared to brand names, Pradaxa, Eliquis, Savaysa and Xarelto. Preferred generic tiering on insurance plans is also expected. Avera Health Plans (AHP) expects to add generic dabigatran to its preferred generic tier.

Dabigatran currently has FDA approved indications for stroke prevention in nonvalvular atrial fibrillation (NVAF), treatment of DVT and PE following parenteral therapy, prevention of recurrent DVT and PE and prevention of VTE after hip replacement.

Dabigatran hasn't been compared directly to competitors, such as apixaban (Eliquis) or rivaroxaban (Xarelto), but has shown to be superior to warfarin in a randomized clinical trial at preventing stroke and systemic embolism with similar bleeding risk in patients with atrial fibrillation.[1]

Observational studies have shown inconsistent results when comparing the safety and efficacy of DOACs, and the 2019 AHA/ACC/HRS Focused Update of the 2014 Guideline for Management of Patients with Atrial Fibrillation does not recommend any DOAC over another.[2-5] Overall, generic dabigatran may be a more affordable alternative to branded DOACs in select patients.

Table 1 – Drug Costs of DOACs (As of March 2022)

Drug Name	Approx. Cost - 30 Day Supply (Atrial Fibrillation Dose)	Insurance Tier at AHP
Pradaxa® (dabigatran)	$600	Not Covered
Xarelto® (rivaroxaban)	$590	*Preferred Brand*
Eliquis® (apixaban)	$630	*Preferred Brand*
Savaysa® (edoxaban)	$470	Not Covered

FDA Approved Indications for DOACs

	PREVENTION					TREATMENT
Drug	Stroke in NVAF	Recurrent DVT and PE	VTE after TKA or THA	VTE in hospitalized patients	Major CV in Chronic CAD/PAD	DVT and PE
Dabigatran (Pradaxa®)	X	X	X			X
Rivaroxaban (Xarelto®)	X	X	X	X	X	X
Apixaban (Eliquis®)	X	X	X			X
Edoxaban (Savaysa®)	X					X

Current National Market Share and Generic Pipeline

The table below provides the current DOACs on the market with an estimated timeline on when a generic version will be available. Moreover, the table also shows the date when the FDA approved each drug and the percent of the total direct-acting oral anticoagulant market each drug holds (e.g. 3% of all patients on a DOAC are on Pradaxa).

Brand Name	FDA Approval for Brand Name Drug	Generic Name	Estimated Loss of Exclusivity (i.e. Availability of a Generic)	National Market Share
Pradaxa®	October 19, 2010	dabigatran	Q2 2022	3%
Savaysa®	January 8, 2015	edoxaban	Q2 2027	0.1%
Eliquis®	December 28, 2012	apixaban	2027 to 2030	64%
Xarelto®	July 1, 2011	rivaroxaban	2030 to 2031	33%

Considerations for Generic Dabigatran

- 2019 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation does not differentiate among DOACs.
- Dabigatran will likely be the only generically available DOAC for 5 or more years.
  - Copay differences between brand and generic tiers may lead to thousands of dollars in out-of-pocket savings for patients.
  - Cost of generic dabigatran will not be available until the product reaches the market. It is anticipated to cost between $20 and $150 per month after 12 months.
- No head-to-head data comparing DOACs is available. Observational studies suggest no or minor differences in safety and efficacy among DOACs[2,3,5]
- Dabigatran may not be appropriate in patients with obesity[6].
- Dabigatran has not been studied in patients with a CrCl less than 30 mL/min[1].
- Dabigatran requires at least 5 days of initial therapy with a parenteral anticoagulant for treatment of DVT/PE.
- Dabigatran must be kept in original container/packaging – should not be used in patients requiring pill packs or utilizing pill organizers for adherence.

References

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