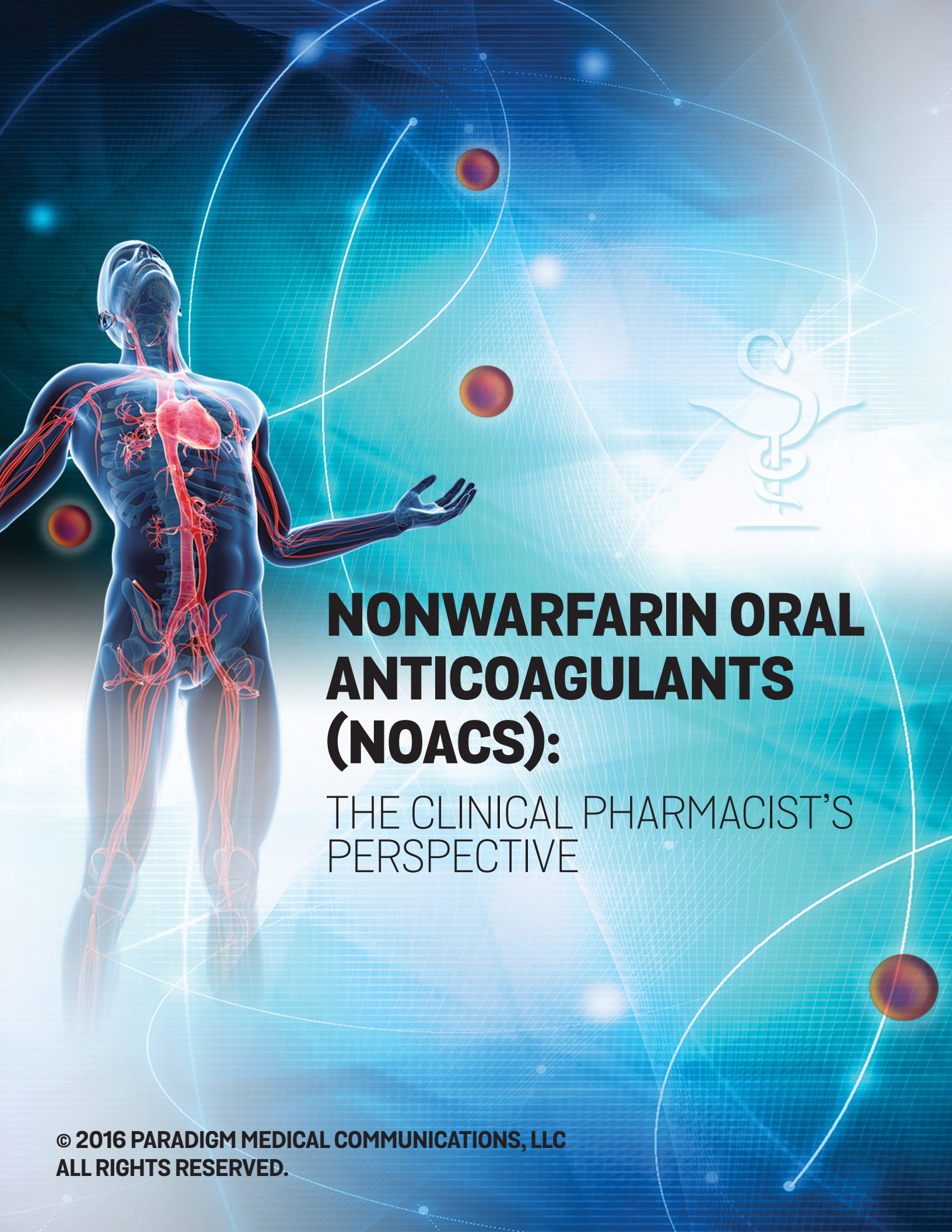

NONWARFARIN ORAL ANTICOAGULANTS (NOACS):

THE CLINICAL PHARMACIST'S PERSPECTIVE

NONWARFARIN ORAL ANTICOAGULANTS (NOACS): THE CLINICAL PHARMACIST'S PERSPECTIVE

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LEARNING OBJECTIVES

Upon proper completion of this activity, participants should be better able to:

- Outline evidence-based strategies for assessing thrombosis and bleeding risk to identify appropriate candidates for oral anticoagulation.
- Apply current clinical evidence to select the most appropriate oral anticoagulant for individual patients considering comorbidities and patient preferences.
- Describe evidence-based strategies for ensuring the safe use of nonwarfarin oral anticoagulants.
- Identify ways pharmacists can be actively involved in ensuring adherence to oral anticoagulation therapy.

CHAPTER 1.
CALL TO ACTION: OPPORTUNITIES TO IMPROVE ORAL ANTICOAGULANT (OAC) THERAPY

Pharmacists play a major role in educating clinicians and patients about anticoagulation. Hospital-based pharmacists are often consulted on a broad array of anticoagulation issues, and their interventions improve anticoagulation therapy use.

"As hospital pharmacists, we get questions about laboratory testing, how to switch between anticoagulants, switching from heparin to the NOACs, dose adjustments. Pharmacists participate in making these decisions."

—Dr Spinler

For example, a study found that 49% of nonwarfarin oral anticoagulant (NOAC) prescriptions made at a teaching hospital for at-risk patients with nonvalvular atrial fibrillation (NVAF) were inappropriate, including suboptimal choice of agent, wrong dosage, and impractical modalities of administration. **[Larock 2014]** At this institution, pharmacists intervened to address issues with coagulation assays, how to switch patients from one anticoagulant to another, dose adjustment of warfarin or the NOACs, identifying or eliminating drug-drug interactions, and improving administration of warfarin or the NOACs, as well as patient education. In a systematic review of more than 11,000 patients taking an anticoagulant, pharmacist-managed warfarin therapy resulted in significantly improved rates of time in therapeutic range (TTR; P=.013), major bleeding events (P<.001), thromboembolic events (P<.001), hospitalization (P<.001), and emergency department (ED) visits (P<.0001), **[Entezari-Maleki 2016]** which suggests that pharmacist-directed anticoagulation services can improve delivery of care and patient outcomes. Furthermore, data indicate that both patients and physicians are satisfied with pharmacist-managed anticoagulation services. **[Bishop 2015]**

For pharmacists to provide evidence-based information for both physicians and patients, they must be knowledgeable on the intricacies of anticoagulation for the prevention and treatment of thrombosis.

Thrombosis due to atrial fibrillation (AF) or venous thromboembolism (VTE) is a growing problem. In 2010, the incidence of AF was estimated at 1.2 million cases, and the prevalence was estimated at 5.2 million, with an expected increase to 12.1 million cases by 2030. **[Colilla 2013]** Similarly, the prevalence of VTE is currently estimated at about 450 cases per 100,000 patients, which is expected to increase to about 570 cases by 2050. [Deitelzweig 2011] Of note, both AF and VTE are associated with substantial morbidity, and in some cases, mortality.

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Atrial Fibrillation

AF confers about a 5-fold increased risk of stroke, **[Mozaffarian 2015]** and about 15% of strokes that occur each year in the United States are attributable to NVAF. **[Reiffel 2014]** However, these numbers likely underestimate the true incidence of stroke in patients with AF because AF is often asymptomatic, and is undetected in some patients. **[Mozaffarian 2015]** Furthermore, patients with NVAF who develop stroke are more likely to experience substantial morbidity—up to 30% of survivors experience permanent disability and 20% require long-term institutional care. **[Lloyd-Jones 2010]** In addition, the mortality rate of patients with NVAF who develop stroke is 20%. **[Reiffel 2014]** Patients with AF are also more likely to experience other poor outcomes such as dementia, physical disability, heart failure, and myocardial infarction (MI). **[Mozaffarian 2015]**

For most patients with NVAF, anticoagulation is necessary to reduce the risk of developing stroke or systemic embolism (SSE). Over the past 50 years, this was effectively achieved by administering vitamin K antagonists (VKAs) such as warfarin, albeit with drug-related challenges such as the need for frequent monitoring, dose adjustments, and potential drug-drug and diet-drug interactions. **[Tran 2011]** However, since 2010, NOACs have been available as an alternative to warfarin for the reduction of SSE risk in patients with NVAF.

Venous Thromboembolism

VTE can result in substantial morbidity, as up to 50% of patients who experience deep vein thrombosis (DVT) develop long-term complications such as post-thrombotic syndrome and chronic venous insufficiency and recurrent VTE. **[Beckman 2010]** When a portion of a DVT is dislodged and travels to the lungs, pulmonary embolism (PE) develops. PE is the leading preventable cause of death in hospitalized patients. **[Walter 2014]** Without appropriate treatment, about 30% of patients with PE will die—a rate that is reduced to 8% with adequate treatment. **[Bělohlávek 2013]** In addition, about 25% of patients with PE present as sudden death. **[Beckman 2010]**

DVT and PE have historically been treated with unfractionated heparin or low-molecular-weight heparin (LMWH) that is typically transitioned to a VKA for longer-term treatment. However, a newer option for treatment is the NOACs, which are also indicated for the treatment and prevention of recurrent DVT or PE.

Limitations of VKAs

Warfarin is highly effective at preventing thrombosis, as it reduces the risk of SSE in patients with NVAF by about 60%. **[Weitz 2012]** However, the use of warfarin is challenging owing to its narrow therapeutic window, as well as multiple drug-drug and diet-drug interactions. **[Kneeland 2010]**

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"Warfarin had been the traditional anticoagulant available for over 50 years. And we are keenly aware it has numerous limitations: frequent blood testing, diet-drug interactions, and numerous drug-drug interactions. Despite over 50 years of management experience, there is still some suboptimal care in terms of selection of patients, especially in AF, as far as the percentage of patients that meets definitions for anticoagulation but are not receiving anticoagulation and don't have documented contraindications, as well as low time in the therapeutic range."

—Dr Spinler

There is also a problem with persistence to warfarin therapy. Although many patients will begin treatment with warfarin, more than 70% will discontinue it within the first year. **[Gallagher 2008]** The reasons for this are not well understood, but the frequent monitoring and dose adjustments likely play a role in this lack of persistence.

In addition, anticoagulation carries an increased risk of bleeding, and some cases can be life-threatening. Therefore, development of NOACs was pursued, with the goal of improving upon the limitations of warfarin. During Paradigm's symposium at the American Society of Health-System Pharmacists 2015 Annual Meeting in November 2015, Sarah A. Spinler, PharmD, FCCP, FCPP, FAHA, FASHP, AACC, BCPS-AQ Cardiology, a professor of clinical pharmacy at the Philadelphia College of Pharmacy, stated, "Within the last 5 years, we've really had a growth of options available for these patients, with dabigatran approved in 2010 and then the fourth of these new agents approved in January 2015."

Currently, there are 4 NOACs that target specific points in the coagulation cascade. Dabigatran is a direct thrombin inhibitor, while apixaban, edoxaban, and rivaroxaban are factor Xa inhibitors. As a drug class, the NOACs have been demonstrated to be noninferior to the standard of care for the treatment of VTE **[van Es 2014]** and the prevention of DVT/PE recurrence. **[Schulman 2013]**

In addition, the NOACs decreased the risk of SSE by 19% compared with warfarin in patients with NVAF. **[Ruff 2014]** Furthermore, the NOACs as a class reduced the risk of major bleeding and intracranial hemorrhage (ICH) compared with warfarin. **[Ruff 2014]** The NOACs offer several advantages over warfarin, including fixed dosing, no laboratory monitoring requirement to assess coagulation, and fewer drug-drug and no diet-drug interactions.

"We've grown in our experience and our ability to manage patients taking NOACs, but there are still a lot of questions remaining," Dr Spinler commented.

CHAPTER 2. INDIVIDUALIZED USE OF NOACS FOR SPAF

Risk Assessment

When a patient presents with AF, the first step in terms of reducing risk of SSE is to determine his or her stroke risk and if he or she needs to be on an anticoagulant.

According to the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guideline for the management of AF, stroke risk assessment should be conducted using the CHA_2DS_2-VASc score in order to determine if a patient with NVAF should be treated with anticoagulation. [January 2014]

CHA_2DS_2-VASc estimates stroke risk based on the presence of the following risk factors: **C**ongestive heart failure, **H**ypertension, **A**ge 65 to 74 or 75 and older, **D**iabetes mellitus, previous **S**troke, transient ischemic attack (TIA), or thromboembolism, **VA**scular disease (MI, peripheral artery disease, or aortic plaque), and female **S**ex (**Table 1**). Each risk factor is assigned 1 to 2 points, and increasing number of points corresponds to an increasing risk of stroke. The AHA/ACC/HRS guideline recommends that patients with a CHA_2DS_2-VASc score of 0 not receive anticoagulation, but that patients with a score of 2 or higher should receive anticoagulation with warfarin or a NOAC. A CHA_2DS_2-VASc score of 1 is considered somewhat of a gray area and patient preference is important to determine whether a patient should receive anticoagulation, aspirin, or no therapy at all. However, a score of 0 or 1 indicates a patient has a low risk of developing stroke and generally indicates that the potential benefit of anticoagulation does not outweigh the risks. [January 2014] **"The scoring system, I think, helps us figure out who truly does not need anticoagulation, and separate out those few patients who are at low risk of stroke,"** said Dr Dobesh.

Table 1. CHA_2DS_2-VASc Stroke Risk Assessment Score and Corresponding Risk of Stroke [January 2014]

Variable	Points
Congestive heart failure	1
Hypertension	1
Age ≥75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65-74 y	1
Sex category (ie, female)	1
Maximum score	9

CHA_2DS_2-VASc Score	Adjusted Stroke rate (%/y)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

PAD, peripheral artery disease; TE, thromboembolism; TIA, transient ischemic attack

Reprinted from January CT et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *J Am Coll Cardiol.* 2014;64(21):e1-e76, with permission from Elsevier.

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"What we have to ask ourselves right from diagnosis is, does my patient who now has AF need to be on anticoagulation? And what is their risk of having a stroke?"

—Dr Dobesh

Of note, prior to the 2014 update of the AHA/ACC/HRS guideline, the recommendation was to use the $CHADS_2$ score. Therefore, the pivotal trials of the NOACs used the $CHADS_2$ score instead of the CHA_2DS_2-VASc score as an inclusion criterion. **[January 2014]** Dr Dobesh said, **"With a $CHADS_2$ score of 0 or 1, you still had some risk. The really nice thing about the CHA_2DS_2-VASc score is that it helps us differentiate who is truly at low risk."** The change in recommendation to the CHA_2DS_2-VASc score was because the additional variables of vascular disease, sex, and separating age into 2 risk categories caused the score to be more sensitive to stroke risk, particularly for patients who scored 0 or 1 with the $CHADS_2$ score. **[January 2014]**

Risk assessment tools are also available to help determine bleeding risk; however, none of these tools are well validated or well utilized in clinical practice. The AHA/ACC/HRS guideline recommends against the use of these tools to disqualify a patient with NVAF for anticoagulation. **[January 2014]** Probably the most commonly used bleeding risk assessment tool is HAS-BLED, which assigns a score based on the presence of the following variables: **H**ypertension (defined as systolic blood pressure >160 mm Hg), **A**bnormal renal or liver function, **S**troke, **B**leeding tendency or predisposition, **L**abile international normalized ratio (INR; if patient is taking warfarin), ag**E** older than 65 years, and **D**rug or alcohol use. **[January 2014; Lane 2012]** Dr Dobesh emphasized that the bleeding risk scores should not be used to eliminate the use of anticoagulation, but instead to identify risk factors for bleeding. **[Lane 2012; January 2014]**

"The HAS-BLED gives you a sense of balance between what is the risk of bleeding and what is the risk of developing a thrombotic event. It does not say that you don't anticoagulate those patients who have higher scores."

—Dr Dobesh

Clinical Trial Data of the NOACs in AF

Head-to-head comparative studies of the NOACs have not been conducted, so direct comparisons between the NOACs cannot be made. For all agents, the phase 3 pivotal trials were designed to establish noninferiority to warfarin in from more than 14,000 to 21,000 patients with NVAF; however, there were also differences in the design among the trials, as discussed below. Investigators analyzed the primary outcome based on a modified intention-to-treat population, meaning that only patients who received treatment were included in the analysis. **[Granger 2011; Connolly 2009; Giugliano 2013; Patel 2011]** The trials were ARISTOTLE for apixaban, RE-LY for dabigatran, ENGAGE AF-TIMI 48 for edoxaban, and ROCKET-AF for rivaroxaban. The primary efficacy endpoint for the trials was SSE, and all of the NOACs were found to be noninferior to warfarin, **[Granger 2011; Connolly 2009; Giugliano 2013; Patel 2011]** with apixaban and dabigatran found to be superior to warfarin. **[Granger 2011; Connolly 2009]**

NONWARFARIN ORAL ANTICOAGULANTS (NOACS): THE CLINICAL PHARMACIST'S PERSPECTIVE

> "Hemorrhagic stroke—this is a critical event. You want to know how these drugs benefit patients? The benefit is that all 4 of them provide a significant reduction in hemorrhagic stroke."
>
> **—Dr Dobesh**

However, only dabigatran demonstrated an improved rate of ischemic stroke. **[Connolly 2009]** There was no difference in major bleeding between patients treated with warfarin compared with dabigatran or rivaroxaban; **[Connolly 2009; Patel 2011]** however, treatment with apixaban or edoxaban resulted in improved major bleeding rates compared with warfarin. **[Granger 2011; Giugliano 2013]** In the ARISTOTLE trial, all-cause mortality was lower in the apixaban arm compared with the warfarin arm; **[Granger 2011]** no difference vs warfarin in all-cause mortality was seen with dabigatran, edoxaban, or rivaroxaban, **[Connolly 2009; Giugliano 2013; Patel 2011]** but all of the NOACs provided a 10% to 11% decrease in all-cause mortality.

> "The patients in these trials and some of the endpoints that were evaluated were drastically different. Each one of these studies has a gold nugget, that you could say, 'Wow, that is an awesome reason to use that drug.'"
>
> **—Dr Dobesh**

There were some notable differences among the NOAC trials, specifically among the study populations (**Table 2**). A major difference in trial design was that the RE-LY trial with dabigatran was the only NOAC trial that was not blinded. **[Connolly 2009]** In addition, the ARISTOTLE and ENGAGE AF-TIMI 48 trials only evaluated bleeding endpoints for a short period of time after treatment initiation. **[Granger 2011; Giugliano 2013]** Interestingly, these 2 blinded trials were the only ones to demonstrate a significant reduction in major bleeding compared with warfarin.

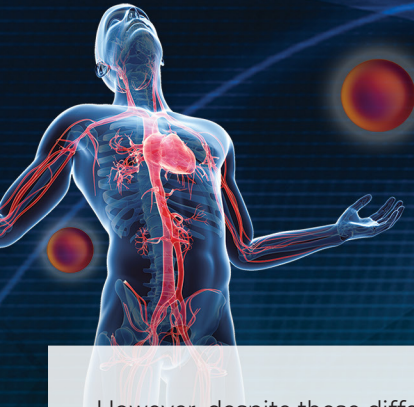
Table 2. Differences Between Pivotal NOAC Trials [Connolly 2009; Patel 2011; Granger 2011; Giugliano 2013]

Variable	RE-LY (dabigatran)	ROCKET-AF (rivaroxaban)	ARISTOTLE (apixaban)	ENGAGE AF-TIMI 48 (edoxaban)
Blinding	NO	YES	YES	YES
VKA naïve, %	50	38	43	4b
TTR	Mean, 64% Median, NR	Mean, 55% Median, 58%	Mean, 62% Median, 66%	Mean, NR Median, 68%
Protocol to manage INR	Yes	No	Yes	Yes
Censoring of bleeding endpoints	Throughout study	Throughout study	Only for 2 d	Only for 3 d
Mean $CHADS_2$ score	2.1	3.5	2.1	2.8
$CHADS_2$ score ≥3, %	32	87	30	77
Mean age, y	71	73	70	72
Heart failure, %	32	63	36	57
Diabetes mellitus, %	23	40	25	36
Prior stroke/TIA, %	20	55	19	28
Prior MI, %	17	17	14	NR

NR, not reported

There are multiple differences among the study populations. TTR was highest in the ENGAGE AF-TIMI 48 trial (median, 68%) and the RE-LY trial (mean, 64%; median not reported), followed by ARISTOTLE (median, 66%), and finally, ROCKET-AF (median, 58%). **[Granger 2011; Connolly 2009; Giugliano 2013; Patel 2011]** In an attempt to replicate real-world practice, ROCKET-AF was the only trial to not have a protocol in place to manage INR in patients receiving warfarin. **[Patel 2011]**

The mean $CHADS_2$ score differed among the study populations as well, with patients in the ROCKET-AF trial having the highest score at 3.5, **[Patel 2011]** suggesting that patients enrolled in the ROCKET-AF trial had more risk factors for SSE, and thus patients were "higher risk," according to Dr Dobesh. Consistent with this notion is that more participants in ROCKET-AF had a $CHADS_2$ score of 3 or higher, heart failure, diabetes mellitus, and a history of stroke or TIA. **[Granger 2011; Connolly 2009; Giugliano 2013; Patel 2011]**



However, despite these differences in trial design and study populations, a consistent theme across the NOAC pivotal trials was that the drug class improved rates of hemorrhagic stroke, and were at least noninferior to warfarin for rates of ischemic stroke (**Table 3**).

Table 3. Outcomes of the Efficacy and Safety Endpoints Compared With Warfarin in the Pivotal NOAC Trials [Connolly 2009; Patel 2011; Granger 2011; Giugliano 2013; Sherwood 2015]

Outcome (RR ±95% CI)	RE-LY[1] Dabigatran 150 mg BID	ROCKET-AF[2] Rivaroxaban 20 mg QD	ARISTOTLE[4] Apixaban 5 mg BID	ENGAGE TIMI-AF 48[5] Edoxaban[a] 60 mg QD
SSE	**0.66 (0.53-0.82)**	0.88 (0.74-1.03)	**0.79 (0.66-0.95)**	**0.87 (0.73-1.04)[a]**
Ischemic stroke	**0.76 (0.60-0.98)**	0.94 (0.75-1.17)	0.92 (0.74-1.13)	1.00 (0.83-1.19)
Hemorrhagic stroke	**0.26 (0.14-0.49)**	**0.59 (0.37-0.93)**	**0.51 (0.35-0.75)**	**0.54 (0.38-0.77)**
Major bleeding	0.93 (0.81-1.07)	1.04 (0.90-1.20)	**0.69 (0.60-0.80)**	**0.80 (0.71-0.91)**
ICH	**0.40 (0.27-0.60)**	**0.67 (0.47-0.93)**	**0.42 (0.30-0.58)**	**0.47 (0.34 -0.63)**
GI	**1.50 (1.19-1.89)**	**1.66 (1.34-2.05)**	0.89 (0.70-1.15)	**1.23 (1.02-1.50)**
CV mortality	**0.85 (0.72-0.99)**	0.89 (0.73-1.10)	0.89 (0.76-1.04)	**0.86 (0.77-0.97)**
All-cause mortality	0.88 (0.77-1.00)	0.85 (0.70-1.02)	**0.89 (0.80-0.998)**	0.92 (0.83-1.01)

BID, twice daily; CI, confidence interval; CV, cardiovascular; GI, gastrointestinal; QD, once daily; RR, relative risk

[a]For the primary endpoint of SSE in the ENGAGE AF-TIMI 48 trial, the CI was 97.5%.

Bolded type indicates statistically significant difference from warfarin.

Dosing of the NOACs in AF

Unlike warfarin, the NOACs offer fixed dosing with limited monitoring and fewer drug-drug and no diet-drug interactions.

> "Across different indications, realize that it's not the same dose for every patient. They all have some level of renal clearance and dose adjustment. They all have bleeding risk associated with them. So it's not the same dose for everybody or even the same drug. We want to make sure when we're using our medications and trying to optimize our patient outcomes, that we do it in the safest and best proven way possible."
>
> **—Dr Dobesh**

The dosing of the NOACs in NVAF is summarized in **Table 4**. Of note, rivaroxaban and edoxaban are administered once daily for the prevention of SSE in AF, whereas apixaban and dabigatran are administered twice daily. Rivaroxaban should be administered with the evening meal, while the other NOACs can be administered without regard to meals.

Table 4. Dosing of the NOACs in Patients With NVAF [Pradaxa 2014; Xarelto 2014; Eliquis 2014; Savaysa 2015]

Drug	Dose[a]
Dabigatran	• For patients with CrCl >30 mL/min: 150 mg orally, BID • For patients with CrCl 15-30 mL/min: 75 mg orally, BID • CrCl <15 mL/min or on dialysis: dosing recommendations cannot be provided
Rivaroxaban	• For patients with CrCl >50 mL/min: 20 mg orally, QD with evening meal • For patients with CrCl 15-50 mL/min: 15 mg orally QD with evening meal • Avoid the use of rivaroxaban in patients with CrCl <15 mL/min as drug exposure is increased
Apixaban	• Recommended dose 5 mg orally BID • In patients with ≥2 of the following characteristics: age ≥80 y, body weight ≤60 kg or serum creatinine ≥1.5 mg/dL, recommended dose is 2.5 mg orally BID • No dose adjustment recommended for renal impairment alone, including those with ESRD maintained on hemodialysis, except NVAF patients who meet criteria for dose adjustment
Edoxaban	• Recommended dose 60 mg QD in patients with CrCl >50 to ≤95 mL/min • Do not use in patients with CrCl >95 mL/min • Reduce dose to 30 mg QD in patients with CrCl 15–50 mL/min

ESRD, end-stage renal disease; CrCl, creatinine clearance

[a]Patients with CrCl <30 mL/min for rivaroxaban, edoxaban, and dabigatran and <25 mL/min for apixaban excluded from clinical trials

CHAPTER 3. INDIVIDUALIZED USE OF NOACS FOR VTE

Clinical Trial Data of the NOACs for the Acute Treatment of VTE

Similar to the setting of NVAF, there are no head-to-head trials between the NOACs in the acute treatment of patients with DVT and/or PE, or the prevention of VTE recurrence. For the acute treatment of DVT and PE, the phase 3 pivotal trials were designed to establish noninferiority in the primary outcome. **[Dobesh 2014]** The trials were AMPLIFY for apixaban, RE-COVER I and II for dabigatran, Hokusai-VTE for edoxaban, and EINSTEIN-DVT and -PE for rivaroxaban. **[Agnelli 2013; Schulman 2009; Schulman 2013; Hokusai-VTE Investigators 2013; EINSTEIN Investigators 2010; EINSTEIN-PE Investigators 2012]** The primary efficacy endpoint for the trials was recurrent symptomatic VTE or death related to VTE for the RE-COVER and AMPLIFY trials, and recurrent symptomatic VTE for the EINSTEIN and Hokusai-VTE trials. All of the NOACs were found to be noninferior to the standard of care (unfractionated heparin, LMWH, and/or warfarin) for the primary efficacy endpoint (**Table 5**).

"The story here is not really on the efficacy side. The story is really on the safety side. That is where we pick up some benefits. I think the biggest benefit falls on the side of convenience for our patients."

—John Fanikos, RPh, MBA

Rates of major bleeding were similar in the RE-COVER I and II, Hokusai-VTE, and EINSTEIN-DVT trials, but were significantly reduced with NOAC treatment in the AMPLIFY and EINSTEIN-PE trials. **[Dobesh 2014]** These data are consistent with a meta-analysis that demonstrated that all of the NOACs were noninferior to LMWH followed by VKA for the treatment of acute VTE. **[van der Hulle 2014; van Es 2014]** In addition, treatment of acute VTE with the NOACs resulted in a decreased risk of major bleeding, nonfatal bleeding at a critical site, major GI bleeding, and fatal bleeding compared with LMWH and VKA.

Table 5. Outcomes of Efficacy and Safety Endpoints Compared With Standard of Care in Pivotal NOAC Trials in Acute VTE [Dobesh 2014]

	Dabigatran		Rivaroxaban		Apixaban	Edoxaban
	RE-COVER I	RE-COVER II	EINSTEIN-DVT	EINSTEIN-PE	AMPLIFY	Hokusai-VTE
Primary efficacy endpoint, %	2.4 vs 2.1	2.3 vs 2.2	2.1 vs 3.0	2.1 vs 1.8	2.3 vs 2.7	3.2 vs 3.5
Major bleeding, %	1.6 vs 1.9	1.2 vs 1.7	0.8 vs 1.2	**1.1[a] vs 2.2**	**0.6[a] vs 1.8**	1.4 vs 1.6
CRNM bleeding, %	4.0 vs 6.9	3.8 vs 6.2	7.3 vs 7.0	9.5 vs 9.8	**3.8[a] vs 8.0**	**7.2[a] vs 8.9**
Major and CRNM bleeding, %	**5.6[a] vs 8.8**	**5.0[a] vs 7.9**	8.1 vs 8.1	10.3 vs 11.4	**4.3[a] vs 9.7**	**8.5[a] vs 10.3**

CRNM, clinically relevant nonmajor

[a]Represents statistically significant reduction (**bold** type)

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There were some notable differences in trial design (**Table 6**). The EINSTEIN-DVT and -PE trials were the only NOAC trials that were open-label. **[Dobesh 2014]** In addition, the AMPLIFY and EINSTEIN-DVT and -PE and trials used an escalated initial dose for 7 days (apixaban) or 3 weeks (rivaroxaban), followed by a lower dose for long-term therapy. Initial parenteral anticoagulation was used for a minimum of 5 days and a median of 9 days in the RE-COVER I and II and Hokusai-VTE trials, but was limited to 2 days in the AMPLIFY and EINSTEIN-DVT and -PE trials.

> "A thought process for this was that the risk of recurrence, the risk of propagation of the clot, and the risk for embolization of that thrombus, is highest in the early treatment period. Studies using the drug melagatran demonstrated a high risk of recurrence in the early period. So, to take away that confounding factor, these studies were designed with a parenteral run-in period. With rivaroxaban and apixaban, the studies were a little bit more aggressive and went directly to the oral agent."
>
> **—John Fanikos, RPh, MBA**

Finally, trial duration differed, as both AMPLIFY and EINSTEIN-DVT and -PE had extension trials that were conducted beyond the initial 3- and 6-month trials. The RE-COVER I and II trials were conducted for 6 months, and the Hokusai-VTE trial lasted for 12 months.

Table 6. Differences in NOAC Trial Design for Acute VTE [Dobesh 2014][a]

	Dabigatran		Rivaroxaban		Apixaban	Edoxaban
	RE-COVER I	RE-COVER II	EINSTEIN-DVT	EINSTEIN-PE	AMPLIFY	Hokusai-VTE
Study design	Randomized, double-blind, noninferiority, parallel group		Randomized, open-label, event-driven, noninferiority, parallel group		Randomized, double-blind, parallel group	Randomized, double-blind, noninferiority parallel group
Intervention	150 mg BID	150 mg BID	15 mg BID x 3 wk → 20 mg QD		10 mg BID x 7 d → 5 mg BID	60 mg QD or 30 mg QD[b]
Comparator	Warfarin		Enoxaparin/VKA		Enoxaparin/ Warfarin	Warfarin
Parenteral anticoagulation[c]	≥5 d		Optional, maximum 48 h		Optional, maximum 36 h	≥5 d

[a]Patients excluded from studies if CrCl<30 mL/min except AMPLIFY where exclusion was CrCl <25 mL/min.

[b]In patients with CrCl of 30-50 mL/min, body weight ≤60 kg, or receiving strong P-glycoprotein inhibitors

[c]Unfrationated heparin, LMWH, fondaparinux

Based on the data from these pivotal trials, the 2016 Antithrombotic Therapy for VTE Disease: CHEST guideline recommends the use of one of the NOACs over warfarin for the treatment of provoked or unprovoked proximal DVT or PE for 3 months. **[Kearon 2016]**

Risk Factors for VTE Recurrence and Bleeding

Unlike for NVAF, there are no validated risk assessment tools to determine risk of VTE recurrence; thus, there is no clear strategy to identify which patients should receive long-term anticoagulation to prevent VTE recurrence. However, there are several known risk factors that are associated with recurrence, which include some comorbidities, biomarkers, and the etiology of the first DVT (**Table 7**). **[Fahrni 2015]**

Table 7. Risk Factors for VTE Recurrence [Fahrni 2015]

Risk Factor	RR/HR (95% CI)
Unprovoked proximal DVT	2.3 (1.8-2.9)
Obesity	1.6 (1.1-2.4)
Male sex	2.8 (1.4-5.7)
Positive D-dimer testing	2.6 (1.9-3.5)
Residual thrombosis	1.5 (1.1-2.0)
Hereditary thrombophilia	1.5 (1.1-1.9)
Inflammatory bowel disease	2.5 (1.4-4.2)
Antiphospholipid antibody	2.4 (1.3-4.1)
Asian, Pacific Islander ethnicity	0.7 (0.5-0.9)

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"Unlike AF, the major bleeding episodes in the setting of VTE are actually quite low; they hover around 1%. So long-term therapy in the global population for secondary prevention is a better strategy than providing patients with no therapy."

—John Fanikos, RPh, MBA

Risk factors for bleeding in patients with VTE include: **[Kearon 2016]**

- Age >65 y or >75 y
- History of bleeding
- Presence of cancer
- Renal or liver failure
- Thrombocytopenia
- Antiplatelet therapy use
- Previous stroke
- Diabetes
- Anemia
- Poor anticoagulant control
- Recent surgery
- Alcohol abuse
- History of frequent falls
- Nonsteroidal anti-inflammatory use

The American College of Chest Physicians (ACCP) recommends the classification of bleeding risk according to the number of risk factors, such that low risk is defined as 0 risk factors, moderate risk as 1 risk factor, and high risk as 2 or more risk factors. **[Kearon 2016]** The increase in bleeding associated with a risk factor will vary with the severity of the risk factor, temporal relationships (eg, interval from surgery or a previous bleeding episode), and how effectively a previous cause of bleeding was corrected. Although this scheme has not been validated, patients with moderate risk of bleeding have an approximate 2-fold increased risk of major bleeding, and high-risk patients have about an 8-fold increased risk. For patients with unprovoked VTE, the guidance document by the Anticoagulation Forum recommends long-term anticoagulation because their risk of recurrence is high. **[Streiff 2016]** The guideline acknowledges that there are few data about the risks and benefits of long-term anticoagulation in this population; therefore, clinicians should reassess the patient yearly to determine if anticoagulation should be continued.

The 2016 ACCP Guidelines on Antithrombotic Therapy for VTE Disease recommend NOACs over VKAs in patients without cancer for both acute treatment and secondary prevention. The guidelines recommend 3 months of treatment for provoked VTE and more than 3 months of treatment for unprovoked VTE with a continued risk-benefit assessment of ongoing anticoagulant treatment.

Clinical Trial Data of the NOACs for the Long-Term Secondary Prevention of VTE

Patients enrolled in the EINSTEIN or AMPLIFY trials had the option of participating in extension trials to assess the safety and efficacy of long-term secondary prevention of VTE. **[Dobesh 2014]** For dabigatran, new trials were conducted, called RE-MEDY and RE-SONATE. There was no long-term study conducted for edoxaban; therefore, edoxaban is not currently indicated for the secondary prevention of VTE. All of the trials for secondary prevention evaluated the study drug compared with placebo, except the RE-MEDY trial, which compared dabigatran with warfarin.

As a class, the NOACs resulted in a significant reduction in the rate of recurrent VTE in the AMPLIFY-EXT, RE-SONATE, and EINSTEIN-EXT trials, with noninferiority established in the RE-MEDY trial with dabigatran (**Table 8**). **[Agnelli 2013; Schulman 2013; The EINSTEIN-DVT Investigators 2010]** In addition, there was no significant difference in rates of major hemorrhage or fatal bleeding events between the NOACs and their comparator (placebo or warfarin).

Table 8. Outcomes of Efficacy and Safety Endpoints in NOAC Trials in Secondary VTE Prevention [Dobesh 2014]

	Dabigatran		Rivaroxaban	Apixaban	Edoxaban
	RE-MEDY 150 mg BID[a]	RE-SONATE 150 mg BID	EINSTEIN-Extension 20 mg QD	AMPLIFY-EXT 2.5 mg BID	AMPLIFY-EXT 5 mg BID
Primary efficacy endpoint, %	1.8 vs 1.3	**0.4[b] vs 5.6**	**1.3[b] vs 7.1**	**3.8[b] vs 11.6**	**4.2[b] vs 11.6**
Major bleeding, %	0.9 vs 1.8	0.3 vs 0.0	0.7 vs 0.0	0.2 vs 0.5	0.1 vs 0.5
CRNM bleeding, %	4.7 vs 8.4	5.0 vs 1.8	5.4 vs 1.2	3.0 vs 2.3	**4.2[c] vs 2.3**
Major and CRNM bleeding, %	**5.6[b] vs 10.2**	**5.3[b] vs 1.8**	**6.0[c] vs 1.2**	3.2 vs 2.7	4.3 vs 2.7

[a]Compared with warfarin. All others compared with placebo.

[b]Represents a statistically significant reduction with the use of the new oral anticoagulant.

[c]Represents a statistically significant increase with the use of the new oral anticoagulant.

Dosing of the NOACs in VTE

"Unlike in AF, the dosing is a little bit different and I think you should recognize that," Mr Fanikos said.

The initial treatment of acute DVT or PE with the NOACs differs somewhat from the secondary prevention of recurrent VTE (**Table 9**). For initial therapy, it is important to note that a lead-in with a parenteral anticoagulant for at least 5 days is required with dabigatran and edoxaban. A dose reduction is indicated with edoxaban in patients with a CrCl of 15 to 50 mL/min, body weight 60 kg or less, or who use certain P-glycoprotein inhibitors such as ketoconazole, itraconazole, ritonavir, or clarithromycin.

Table 9. Dosing of the NOACs for Acute Treatment and Secondary Prevention of VTE [Pradaxa 2014; Xarelto 2014; Eliquis 2014; Savaysa 2015]

Dabigatran[1]	Rivaroxaban[2]	Apixaban[3]	Edoxaban[4]
Initial treatment			
For treatment of DVT, PE in patients who have been treated with parenteral anticoagulant for 5-10 d	Treatment of DVT, PE Take tablets with food	For treatment of DVT, PE	Treatment of DVT, PE following 5-10 d initial therapy with parenteral anticoagulant
Reduction in risk of recurrence			
To reduce risk of recurrence of DVT, PE in patients who have been previously treated	For reduction in risk of recurrence of DVT, PE		
Take tablets with food	For reduction in risk of recurrent DVT, PE following initial therapy	Not indicated	

P-gp; P-glycoprotein

CHAPTER 4. SPECIAL CONSIDERATIONS AND CHALLENGES WITH NOAC USE

Although the NOACs tend to make the management of AF and VTE somewhat easier compared with warfarin, there are some factors that must be considered.

Health-system pharmacists are in a strong position to help address these concerns by helping to provide long-term surveillance of patients.

In addition to appropriate follow-up, questions remain about how to measure the anticoagulant effect of the NOACs, how to best switch between anticoagulant agents, dealing with dosing errors, management of complications, how to manage patients undergoing planned surgical interventions or ablation, how to treat patients who have an indication for both anticoagulation and antiplatelet therapy, the role of NOACs in patients with cancer, and how to improve adherence rates among patients taking anticoagulation.

"It's easy to give patients a prescription for an oral agent, but we still need to have some sort of follow-up; in the early initiation period, the follow-up is important."

—John Fanikos, RPh, MBA

Case 1: Renal Impairment

A 78-year-old white woman with newly diagnosed NVAF who is to begin treatment with an oral anticoagulant (OAC) to reduce the risk of SSE.

- Current medications:
  - 50 mg of metoprolol succinate once daily for rate control
  - Angiotensin converting enzyme (ACE) inhibitor for hypertension
  - Diuretic for chronic kidney disease (CKD)
  - Statin for hyperlipidemia
- Vitals:
  - Weight, 65 kg
  - Blood pressure, 140/90 mm Hg
  - Heart rate, 110 bpm
  - CrCl, 40 mL/min
  - Serum creatinine, 1.2 mg/dL

The CHA_2DS_2-VASc score for this patient is 4, because she has hypertension (1 point), is older than 75 years (2 points), and is female (1 point). Therefore, according to the AHA/ACCP/HRS guideline, she should receive oral anticoagulation to reduce her risk of SSE. **[January 2014]**

NONWARFARIN ORAL ANTICOAGULANTS (NOACS): THE CLINICAL PHARMACIST'S PERSPECTIVE

One of the variables that is evaluated in the CHA_2DS_2-VASc score is hypertension. However, there is a question of whether a patient with hypertension that is well controlled should be assigned 1 point, or if this point is reserved for patients with untreated or uncontrolled hypertension.

"Look at how the scoring for stroke and bleed risk [CHA_2DS_2-VASc score and HAS-BLED score] were developed. It was uncontrolled hypertension. So we can improve stroke and bleeding risk reduction by paying careful attention to blood pressure control."

—Dr Spinler

"I would have scored the patient 1 point. A considerable proportion of treated hypertensive patients do not achieve target blood pressure levels. Furthermore, tight blood pressure control does not always translate into a reduction of cardiovascular events."

—John Fanikos, RPh, MBA

When determining the dosing of a NOAC, it is important to assess CrCl or serum creatinine levels. In this patient, her CrCl and serum creatinine levels indicate a need for dose reduction with edoxaban (30 mg instead of 60 mg) and rivaroxaban (15 mg instead of 20 mg), **[Savaysa 2015; Xarelto 2014]** but not apixaban or dabigatran, which should be administered at full dose. **[Eliquis 2014; Pradaxa 2014]** Neither her age of 78 years, nor her weight of 65 kg are considered factors for dose adjustment. ACE inhibitors and diuretics have no known interactions with the NOACs.

This patient has several characteristics that warrant follow-up. The patient currently has a CrCl of 40 mL/min, but in the setting of CKD, her renal clearance is likely to continue to decline. It is important to continue surveillance of her CrCl so that a dose reduction can be prescribed when appropriate. **[January 2014]** If it falls below 15 mL/min, NOACs should be discontinued and warfarin should be initiated. **[January 2015]**

"They don't need to come back every month like they would with warfarin, but patients still need to be seen multiple times a year, and that partially depends on their renal function. For me, their renal function dictates how often I'm going to see them."

—Dr Dobesh

In addition, it is important that the patient continues rivaroxaban as directed to prevent her from becoming vulnerable to stroke due to a missed dose. Finally, although the patient has not stated that she is taking antiplatelet therapy, in the setting of her hypertension and dyslipidemia, albeit controlled, it is possible that she may take aspirin for a risk reduction of cardiovascular disease. Some patients do not report over-the-counter medications such as aspirin. An anticoagulant combined with antiplatelet therapy unnecessarily increases the risk of bleeding in patients with NVAF without ischemic heart disease. This is an important area in which health-system pharmacists can intervene to improve patient outcomes.

> "I think that's a limitation in many of the registries where they don't capture over-the-counter medications."
>
> **—John Fanikos, RPh, MBA**

> "I think there's a big area for pharmacists to intervene in patients taking antiplatelet therapy for primary prevention of vascular disease, who then develop AF. They don't necessarily need to continue antiplatelet therapy combined with anticoagulation because the risks of bleeding outweigh the benefits. We know anticoagulation alone has evidence of benefit for primary prevention of vascular disease events."
>
> **—Dr Spinler**

Case 2: **Managing NOACs in the Perioperative Setting**

A 66-year-old woman with NVAF with a history of hypertension is scheduled to undergo elective abdominal surgery.

Current medications:

- 60 mg edoxaban once daily
- Calcium channel blocker
- Beta blocker

Vitals

- CrCl, 80 mL/min

Invasive surgeries, such as abdominal surgery, are associated with a high risk of bleeding. **[Heidbuchel 2015]** Therefore, edoxaban should be interrupted for at least 48 hours from the time of surgery (**Table 10**). **[Savaysa 2015]** In addition, the prescribing information for edoxaban recommends that it be discontinued 24 hours prior to an invasive procedure to minimize the risk of bleeding. Apixaban and rivaroxaban follow a similar schedule with dose interruption for at least 48 hours for invasive procedures. **[Eliquis 2015; Xarelto 2015]** For dabigatran, the time of dose interruption is dependent on CrCl. **[Pradaxa 2015]** Before reinitiating anticoagulation, it is important to know that the patient had a noncomplicated surgery and that their hemoglobin levels are stable.

"The pharmacist is called in to manage these patients. The pharmacist will get called for consultations relating to these drugs, as many people don't know how to transition them during the perioperative period."

—Dr Spinler

Table 10. Dose Interruption of the NOACs for Perioperative Management [Heidbuchel 2015]

	Dabigatran		Apixaban, Edoxaban,[a] Rivaroxaban	
Clearance, mL/min	**Low risk**	**High risk**	**Low risk**	**High risk**
≥80	≥24 h	≥48 h	≥24 h	≥48 h
50-80	≥36 h	≥72 h	≥24 h	≥48 h
30-50	≥48 h	≥96 h	≥24 h	≥48 h
15-30	Not indicated		≥36 h	≥48 h

[a]Edoxaban prescribing information suggests discontinuation at least 24 h before invasive surgical procedures because of risk of bleeding. [Savaysa 2015]

Heidbuchel H et al. *Europace*. 2015. [epub ahead of print]. doi: http://dx.doi.org/10.1093/europace/euv309. By permission of Oxford University Press and the European Society of Cardiology.

Case 3: Management of Bleeding in a Patient Treated With a NOAC

A 70-year-old man with NVAF presents to the ED with deep lacerations following a car accident. His bleeding is severe and he is currently being prepped for surgery.

Current medications:

- 150 mg dabigatran twice daily; last dose was taken 4 hours prior

Vitals:

- Blood pressure, 100/60 mm Hg
- Heart rate, 120 bpm
- Hemoglobin, 8 g/dL
- CrCl, 60 mL/min

Patients taking anticoagulants are commonly seen in the ED for a variety of reasons: unrelated medical reasons, periprocedural, trauma, and anticoagulation-related adverse events. **[Pollack 2015a]** In this case, the patient presents with bleeding as a result of trauma sustained in a car accident; however, possibly as a result of taking dabigatran, his bleeding is serious and, despite supportive measures, his hemoglobin level is dropping. Because the patient is going to surgery, he should be given blood products, fresh frozen plasma (FFP) to replace blood volume, and idarucizumab to reverse the dabigatran anticoagulation.

An important consideration of patients taking a NOAC is the timing of their last dose, as the NOACs have a rapid onset and offset of action, unlike warfarin (Table 11). In some cases, dose interruption may be sufficient.

Table 11. Onset and Offset of Anticoagulation Effect of the NOACs [Pradaxa 2014; Xarelto 2014; Eliquis 2014; Savaysa 2015; Coumadin 2015]

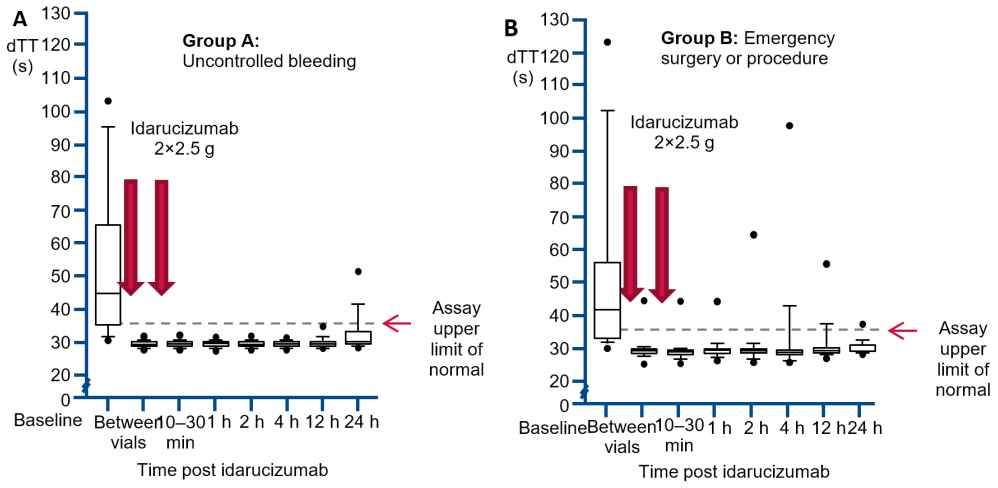
Parameter	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
Time to C_{max}	1 h	2-4 h	3-4 h	1-2 h	72-96 h
Half-life	12-17 h (healthy pts)	5-9 h (healthy pts)	≈12 h	10-14 h	20-60 h
Renal excretion (unchanged drug)	80% of absorbed dose	66% of total dose; 36% of absorbed dose	27%	50%	Very little

C_{max}, maximal concentration; pts, patients

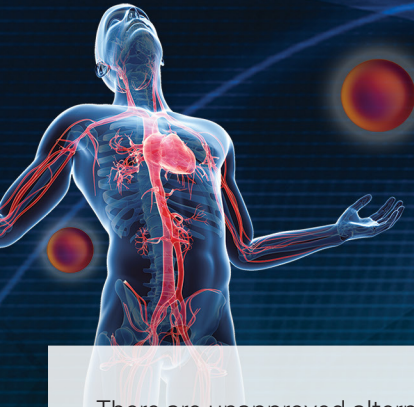
The half-life of dabigatran is between 12 and 17 hours in healthy patients. **[Pradaxa 2015]** It is likely that the patient is experiencing enough of an anticoagulant effect from his last dose of dabigatran to warrant intervention. Currently, there are no approved strategies to specifically reverse anticoagulation in patients taking a NOAC, except dabigatran.

In October 2015, the FDA approved idarucizumab, a humanized fab fragment, for the reversal of anticoagulation by dabigatran during emergent situations. **[FDA 2015]** Idarucizumab specifically binds to dabigatran with about 350-fold greater affinity than thrombin. **[Pollack 2015b; Pollack 2015c]** The pivotal trial that led to the approval of idarucizumab was the ongoing, multicenter, single-arm, open-label RE-VERSE AD trial. **[Pollack 2015b]** In this trial, there were 2 cohorts of patients taking dabigatran: Group A, in which patients presented to the ED with uncontrolled bleeding; and Group B, in which patients presented to the ED for emergency surgery or procedure. Upon presentation to the ED, patients were administered an initial dose of idarucizumab, and within 15 minutes given a second dose. Patients were followed for 90 days, and the primary endpoint of dabigatran reversal as measured by diluted thrombin time (dTT) or ecarin clotting time (ECT) was assessed at 4 hours after the second dose. Interim results demonstrated that, in Group A, idarucizumab normalized dTT in 98% and ECT in 89% of patients before the second dose was administered, which continued over 24 hours (**Figure 1A**). For Group B, dTT was normalized in 93% and ECT in 88% of patients before the second dose of idarucizumab was administered and maintained over 24 hours, and also led to normal intraoperative hemostasis as judged by the treating physician in 33 out of 36 patients (**Figure 1B**).

Figure 1. Interim Results From the REVERSE AD Trial [Pollack 2015b]



From *New Engl J Med*, Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal, 2015;373(6):511-520. ©2015. Massachusetts Medical Society.



There are unapproved alternatives to idarucizumab that may be effective for reversal of dabigatran, as well as other NOACs, though the data are sparse.

> "I tell my students: If you're working at the pharmacy at 3 AM and the ED calls and says, 'We've got a patient here on dabigatran and they're bleeding,' you can't say, 'Sorry, there's no randomized controlled trials' and hang up the phone."
>
> **—Dr Dobesh**

> "A bleeding event is a global term without having a precipitating factor, and my advice is we consider this a failure of dabigatran. I would look for an alternative agent."
>
> **—John Fanikos, RPh, MBA**

These alternatives include activated prothrombin complex concentrate (aPCC), 3-factor PCC (PCC3), 4-factor PCC (PCC4), FFP, dialysis, and recombinant factor VIIa (rVIIa). Although PCC4 is only approved for warfarin reversal, it may be considered for rivaroxaban, apixaban, and edoxaban reversal as well; however, the data that support its efficacy in reversing NOAC-induced anticoagulation are based on healthy volunteers. In 2 studies in which healthy volunteers received rivaroxaban for 2.5 or 4 days, prothrombin time prolongation was corrected by the infusion of PCC4 and/or PCC3. **[Erenberg 2011; Levi 2013]** Based on these data, PCC4 appears to be more effective for rivaroxaban than for dabigatran. **[Erenberg 2011]** Another potential option is FFP; however, it is limited by several factors, including its much lower concentration of clotting factors compared with PCCs, storage requirements, and required volume for treatment. PCCs do not need to be thawed, whereas FFP is stored frozen and requires about 30 to 45 min to thaw. Furthermore, because there are fewer clotting factors per unit of FFP, a large volume is required, whereas a single unit of PCC is effective. The recommended dosing of concentrated clotting factor products is summarized in **Table 12**. Although a feasible alternative, dialysis is impractical and not necessary when there is an antidote, idarucizumab, available.

> "We say you can remove dabigatran by dialysis and that sounds like a nice safety net. But you do not snap your fingers and get dialysis. It takes 6 hours or more sometimes."
>
> **—Dr Dobesh**

> "The FFP dose in life threatening bleeding is 15 mL/kg, so you're giving large volume in terms of replacement."
>
> **—John Fanikos, RPh, MBA**

Table 12. Recommended Dosing of Concentrated Clotting Factor Products for Repletion[a] [Nutescu 2013; Babilonia 2014; Zahir 2015]

Repletion Agent	Clotting Factors Replaced	Dose(s) for Repletion of Specific Anticoagulant[b]		
		Warfarin[1]	Rivaroxaban1/ Apixaban[2d]	Edoxaban[3]
PCC3	II, IX, and X (inactivated)	25-50 units/kg	50 units/kg	
PCC4	II, VII, IX, and X (inactivated)	25-50 units/kg	25-50 units/kg	50 units/kg
aPCC	II, IX, X (inactivated), and VII (activated)	500 units for INR <5; 1000 units for INR ≥5	Up to 25 units/ kg initially; no data available in patients with active bleeding; 80 units/kg	
rFVIIa	VII (activated)	17.7-53.4 µg/kg	20-120 µg/kg	

rFVIIa, recombinant Factor VIIa

[a]None of the PCCs are indicated for the urgent reversal of anticoagulation of the NOACs.

[b]Experience with doses listed in this table is limited; consult current references and product label for most current information.

[c]If premade PCC4 is not available, an alternative option to using PCC3 alone is building a PCC4 by using low-dose rFVIIa in combination with PCC3.

[d]Limited data are available for apixaban reversal; however, it may be rational to apply information from rivaroxaban because of their similar mechanisms of action. [Babilonia 2014]

[1]Nutescu EA et al. *Am J Health Syst Pharm*. 2013;70(21):1914-1929. Reproduced with permission of the American Society of Health-System Pharmacists.
[2]Babilonia K et al. *Thromb J*. 2014;12:8.
[3]Zahir H et al. *Circulation*. 2015;131:82-90.

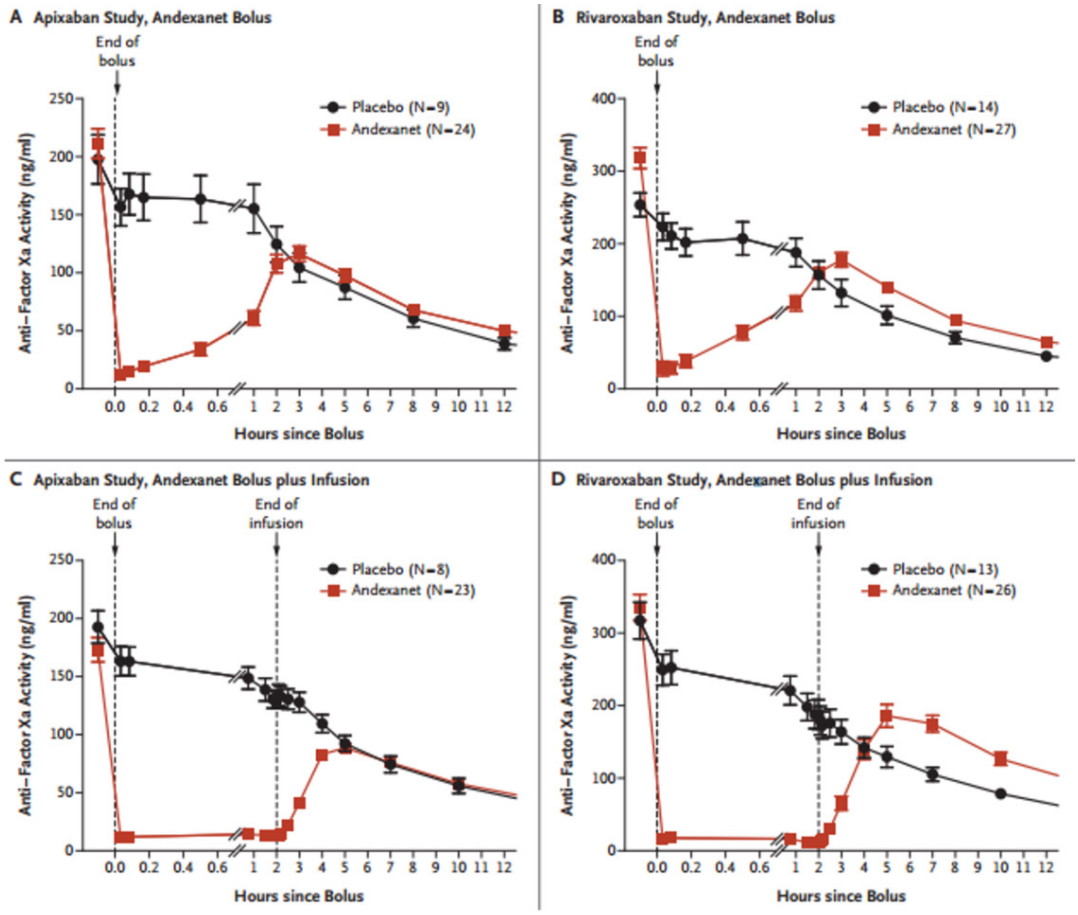
When administering reversal or repletion agents, it is important to consider the risk of thrombosis.

> "One of the things to always remember is that the patient is on anticoagulation for a reason. We walk a little bit of a fine line here, so this is not a 'more is better' thing. We have to be fairly judicious in the way we do this."
>
> **—Dr Spinler**

Additional specific agents are currently in development for the reversal of the NOACs and other anticoagulants. Andexanet alfa targets all factor Xa inhibitors (NOACs, LMWH, and fondaparinux) through a decoy, or sponge, effect; factor Xa inhibitors bind to andexanet alfa instead of factor Xa. The FDA has granted andexanet alfa breakthrough therapy status, and granted it an orphan drug designation. **[(a)Portola 2015]** The efficacy and safety of andexanet alfa were also evaluated in 2 phase 3 trials, ANNEXA-A with apixaban and ANNEXA-R with rivaroxaban. **[Siegel 2015]** Each trial was conducted in healthy older volunteers age 50 to 75 years and at a single center. In part 1 of each study, andexanet alfa was administered as an intravenous (IV) bolus alone, and the second part evaluated andexanet alfa as an IV bolus followed by a continuous 120-minute infusion. Safety outcomes were observed over 43 days. In ANNEXA-A, volunteers received 5 mg of apixaban twice daily for 3.5 days, and were randomly assigned 3:1 to receive a 400-mg bolus of andexanet alfa (followed by continuous infusion of 4 mg per min for 120 min in Part 2) or placebo 3 hours after the final dose of apixaban. In ANNEXA-R, volunteers received 20 mg of rivaroxaban once daily for 4 days and then were randomly assigned 3:1 to receive an 800-mg bolus of andexanet alfa

(followed by a 30-mg per min continuous infusion in Part 2) or placebo 4 hours after the final dose of rivaroxaban. The difference in andexanet alfa dosage is due to the fact that it was found in phase 2 trials that a higher dose is needed to reverse rivaroxaban than apixaban due to the higher peak levels and larger volume of distribution of rivaroxaban. Andexanet alfa bolus resulted in an anti-factor Xa activity reduction of 94% and 92% for apixaban and rivaroxaban, respectively, compared with 21% and 18% for placebo (P<.001 for apixaban and rivaroxaban; **Figures 2A** and **2B**). Anti-factor Xa activity rebounded within 2 hours with just bolus administration of andexanet; however, continuous infusion prolonged the suppressed anti-factor Xa activity for an additional 2 to 3 hours (**Figures 2C** and **2D**). There were no serious adverse or thrombotic events, but D-dimer and prothrombin fragments 1 and 2 elevation occurred for up to 72 hours. Phase 4 confirmatory trials are currently underway. **[(b)Portola 2015]**

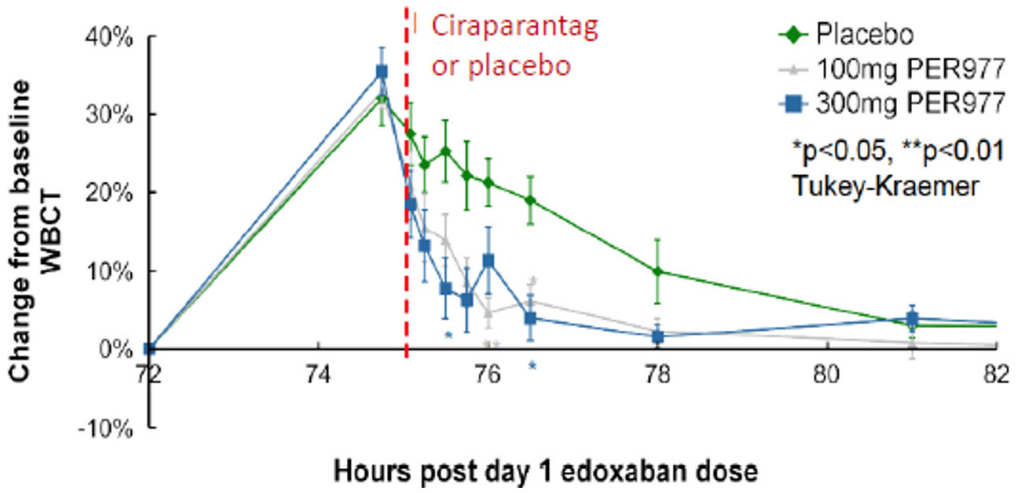
Figure 2. Reversal of Apixaban and Rivaroxaban by Andexanet Alfa [Siegal 2015]



From *New Engl J Med,* Siegal et al, Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity, 2015 Nov. 11. ©2015. Massachusetts Medical Society.

Ciraparantag (PER977) is a synthetic small molecule that binds to the NOACs, heparin, and fondaparinux, and is being developed as a universal antidote for anticoagulants. A phase 1 trial conducted in healthy volunteers anticoagulated with edoxaban found that whole-blood clotting time fell to 10% above baseline within 10 minutes of ciraparantag administration compared with 12 to 15 hours in patients who received placebo (**Figure 3**). **[Ansell 2014]**

Figure 3. Reversal of Edoxaban by Ciraparantag [Perosphere 2015]



PER977, ciraparantag; WBCT, whole-blood clotting time

Although the patient experienced bleeding that was unrelated to dabigatran, there are several factors to consider when determining which agent to reinitiate anticoagulation with.

CHAPTER 5.
ENSURING ADHERENCE TO THERAPY: THE IMPORTANCE OF PATIENT EDUCATION AND MONITORING ACROSS CARE TRANSITIONS

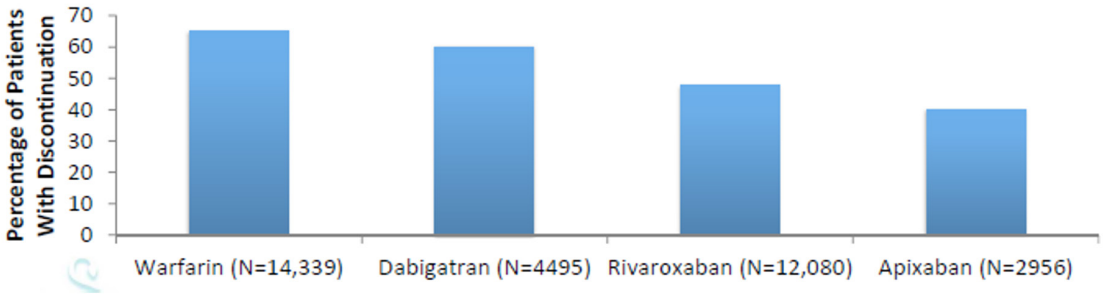
Adherence and Persistence

Two concerns of anticoagulation therapy are patient adherence to treatment (defined as the patient taking most of their doses) and persistence to therapy (defined as 30 days without missed therapies or missed prescription refills). However, a study presented at the 2015 European Society of Cardiology (ESC) Congress suggests that adherence rates are good among patients taking the NOACs, with rates highest with apixaban, followed by rivaroxaban, then dabigatran (**Figure 4**). **[Lip 2015a]** Rates of adherence were lowest among patients taking warfarin. Results from the Assessment of an Education and Guidance Program for Eliquis Adherence in Nonvalvular AF (AEGEAN) study were also presented at the 2015 ESC Congress and demonstrated an overall adherence of 88% and persistence of 90.8% among patients taking apixaban, with no additional improvement with an education program versus the standard of care. **[Lip 2015b]** However, the standard of care in this trial was likely very good.

"Adherence is linked to patient educational levels, so in a patient population with low health literacy, more effort will be needed to have high persistence rates."

—Dr Spinler

Figure 4. Adherence Rates for OAC [Lip 2015a]



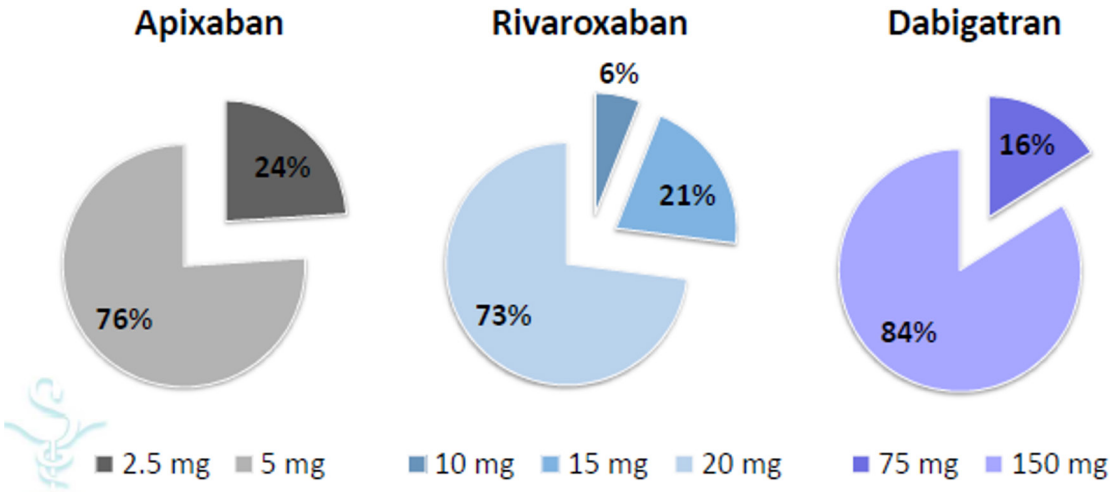
Underdosing of the NOACs

Another concern is underdosing of the NOACs. In some patients, a dose reduction is indicated; however, a study presented at the 2015 ESC Congress indicated that an unexpectedly large number of prescriptions for apixaban, dabigatran, and rivaroxaban were for lower doses than should have been prescribed based upon product labeling (edoxaban was not included in the study because it was not yet approved; **Figure 5**). **[Alexander 2015]** Interestingly, the NOAC with the greatest percentage of dose reductions was with apixaban, which is the NOAC that is least dependent on renal function. Some clinicians may prescribe a reduced dose of apixaban based on the ESC guideline, which recommends a one-half dose in patients taking triple therapy—combined antiplatelet therapy with a $P2Y_{12}$ inhibitor, aspirin, and an anticoagulant for patients with an indication for dual antiplatelet therapy (such as acute coronary syndromes) and anticoagulation. **[ESC guideline]** However, this recommendation is not based on clinical trial data, as no studies have been conducted using the NOACs in this setting.

"I see it with all of the NOACs. About one-third of patients have a dose reduction that is correct based on renal function. We see about one-third of patients have a dose reduction based on prior history of bleeding or not meeting one of the 3 parameters for apixaban dose reduction. Finally, there is a percentage of prescribers that are unfamiliar with the dose recommendations."

—John Fanikos, RPh, MBA

Figure 5. Rate of Underdosing of the NOACs[a] [Alexander 2015]



[a]Edoxaban was not included in the study because it was not yet approved.

NONWARFARIN ORAL ANTICOAGULANTS (NOACS): THE CLINICAL PHARMACIST'S PERSPECTIVE

Patient Management Tools

Pharmacists can help patients manage their care regarding anticoagulation therapy. For example, patients can carry a "NOAC anticoagulation card" that outlines details of the NOAC they are taking, as well as information about planned or unplanned visits, instructions, concomitant medications, and emergency information. **[Heidbuchel 2015]** In addition, pharmacists can ensure that structured follow-up care is initiated with the patient's primary care provider or cardiologist for when the patient is discharged from the hospital. This requires communication between healthcare providers and should include documentation, all of which the pharmacist can facilitate.

> "There is a long list of items that have a role for pharmacists to play in terms of patients' long-term management. We have a role in providing long-term surveillance to make sure these patients do what they need to do."
>
> **—John Fanikos, RPh, MBA**

> "We ensure that the clinician that is going to be in charge of anticoagulation is identified before the patient is discharged, whether that be an anticoagulation clinic, cardiologist, or a primary care provider."
>
> **—Dr Spinler**

Patient Preferences

The AHA/ACC/HRS guideline for the management of AF recommends that patient preferences be considered when determining whether or not to prescribe an anticoagulant and which agent to use. According to Dr Spinler, this includes "considerations in terms of efficacy, safety, patients maintaining persistence, patients taking the actual prescribed medication and taking the correct doses." Health-system pharmacists should consider these factors not only during the initiation of an anticoagulant, but also during follow-up.

Health-system pharmacists are critical members of the team who care for patients with NVAF or VTE who are receiving oral anticoagulation. Therefore, in-depth, evidence-based knowledge of the NOACs in terms of their use and their reversal is important in order to appropriately address the concerns of clinicians and provide them with a meaningful consultation, as well as to properly educate patients about their therapy.

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