

# Attending Physician Attitudes Toward Choice of Oral Anticoagulant for the Treatment of Venous Thromboembolism

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## ABSTRACT

Until recently, warfarin has been the primary treatment of venous thromboembolism (VTE). Limited data are available regarding physician attitudes toward anticoagulant choice in the setting of novel oral anticoagulant (NOAC) availability. This study sought to evaluate attending physician attitudes toward NOACs. A survey was sent to attending physicians from internal medicine (primary care and hospitalist medicine), family medicine, cardiology, and hematology-oncology asking about their preference and reasoning for choice of oral anticoagulant for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). Warfarin was the most common choice of initial treatment of both DVT (85.6%) and PE (89%). Among the specialties surveyed, cardiologists were more likely to use rivaroxaban as initial treatment of VTE as compared to other specialties including internal medicine or hematology ( $p=0.011$  for DVT and  $0.004$  for PE). Cost-effectiveness and lack of a reversal agent were cited as the major disadvantages for NOAC use.

**KEYWORDS:** Venous thromboembolism, Dabigatran etexilate, Warfarin, Rivaroxaban, Physician practice patterns

## INTRODUCTION

For over five decades, the vitamin K antagonist warfarin has been the standard of care for outpatient treatment of acute venous thromboembolic disease (VTE). However, warfarin is not without its limitations as it has a narrow therapeutic window requiring frequent laboratory monitoring, many drug-drug and drug-food interactions, and requires individual dosing based on the international normalized ratio (INR).<sup>1</sup>

It has now been over 3 years since the novel oral anticoagulants (NOAC) were approved by the United States Food and Drug Administration (FDA).<sup>2</sup> Initially dabigatran etexilate gained approval for atrial fibrillation based on the RE-LY trial, followed by the approval for both rivaroxaban and apixaban for this purpose based on the ROCKET-AF and ARISTOTLE trials respectively.<sup>3,4</sup> These agents have also been approved for thromboprophylaxis after total hip and knee replacement.<sup>5</sup>

On Nov. 2, 2012, rivaroxaban was the first NOAC approved in the United States for the treatment and secondary prevention of DVT/PE. The NOACs have a broad therapeutic

window allowing for fixed dosing and no requirement for laboratory monitoring or adjustments based on body weight. As a result, novel anticoagulants have been rapidly adopted for anticoagulation in patients with atrial fibrillation.<sup>6</sup> This is in contrast to their adoption for patients with venous thromboembolic disease, which has been lower than expected.<sup>7,8</sup> Some have suggested that the possible reasons for its low uptake are cost, inability to readily measure the level of anticoagulation, and the lack of an immediate antidote in the event of life-threatening bleeding. Furthermore, the level of comfort for prescribing rivaroxaban may be different depending on one's specialty, level of training, and experience in treating patients with thromboembolic disease.<sup>7</sup>

By surveying a large group of both community and academic physicians affiliated with a tertiary care center, we sought to identify the factors that influence physicians' decisions in prescribing NOACs for the treatment of thromboembolic disease in clinical practice, and to compare these factors between specialties and across experience levels. These data reveal the current attitudes toward prescribing NOACs for thromboembolic disease and may elucidate the reasons for the slow uptake of rivaroxaban for the treatment DVT/PE.

## METHODS

### Survey methods

The study is a cross-sectional questionnaire based survey of attending physicians in the State of Rhode Island who would be likely to have prescribed therapy for venous thromboembolism (VTE) within the previous 6 months. After review and approval by the Rhode Island Hospital Institutional Review Board (IRB), an investigator-authored survey was sent electronically to 365 attending physicians from internal medicine and family medicine. Physicians were identified in one of three ways: 1. All physicians within the Lifespan Health System (Rhode Island) provider directory with a primary specialty listing of internal medicine, primary care, general internal medicine, hospitalist medicine, hematology, cardiology, or family medicine; 2. Physicians from these specialties on the distribution list for Medical Grand Rounds at the Alpert Medical School of Brown University (Providence, Rhode Island); and 3. Physicians from these specialties with publicly available contact information on practice websites within the region. Details of the survey content are shown in the Appendix. Both academic and community practitioners were surveyed and among the physicians from

internal medicine, this group included cardiology, hematology, primary care, and hospital medicine. The online survey was active from Dec. 5, 2013 until Feb. 1, 2014.

### Statistical methods

General descriptive statistics were calculated while responses from various specialties were compared using Chi-square analysis. Given the hypothesis that number of years in independent practice may affect choice, a Mantel-Haenszel Chi-Square trend test was used to compare responses among categories based on years since completion of residency or fellowship. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

Of the 365 physicians who were sent the survey invitation, 89 (24.4%) completed all or some of the questionnaire. Self-reported characteristics of the respondents are shown in **Table 1**. Most attending physicians (81%) reported starting a patient on an oral anticoagulant for treatment of DVT or PE in the previous six months. Warfarin was the most commonly reported oral medication for treatment of VTE with 85.6% of physicians choosing it as initial treatment of DVT and 89% of physicians choosing it as initial treatment of PE. The distribution of results is shown in **Table 2**.

Among those choosing warfarin as initial treatment of DVT, most (52.2%) felt that the cost of the newer anticoagulants was the most important factor in their decision. Only 42% reported cost as the major factor in choosing warfarin for PE with 30% stating they felt comfortable with warfarin and found no reason to change. Additionally, 26% reported the lack of an effective reversal agent with the newer anticoagulants to be the major factor in their decision to choose warfarin as initial agent for PE therapy. Among those who chose rivaroxaban as initial treatment of DVT, most (75%) said the most important factor was that no lab monitoring was required. For those choosing rivaroxaban to treat PE, 100% of the respondents said the lack of required lab monitoring was the major deciding factor. Physician responses as to the items they considered advantages and disadvantages of rivaroxaban as compared to warfarin are shown in **Table 3**.

Differences were seen by specialty in regards to treatment of DVT (Chi-Square 21.3, DF=9; p=0.011) and PE (Chi-Square 24.2, DF=9; p=0.004) as shown in **Table 4**. The number of years since completing residency/fellowship did not significantly affect choice of oral anticoagulant for treatment of PE (Mantel-Haenszel Chi-Square 2.46, DF=1; p=0.12) or for treatment of DVT (Mantel-Haenszel Chi-Square 2.13, DF=1; p=0.15).

## DISCUSSION

With the addition of NOACs, the treatment landscape of thromboembolic disease has undergone a major change. These newer agents have clear advantages over the traditional vitamin K antagonist warfarin. There are also some disadvantages to therapy with NOACs, however. To our

**Table 1.** Self-reported characteristics of the survey respondents

Primary Specialty	N=85
Internal Medicine	84 (98.8%)
Cardiology	11 (12.9%)
Hematology	16 (18.8%)
Hospital Medicine	18 (21.2%)
Primary Care	39 (45.9%)
Family Medicine	1 (1.2%)
Years since finishing residency/fellowship	N=86
<5 years	23 (26.7%)
5–9 years	10 (11.6%)
10–19 years	25 (29.1%)
20 years or more	28 (32.6%)

**Table 2.** Attending physician responses for initial choice of anticoagulant in patients with normal renal function and VTE.

Deep Vein Thrombosis (DVT)	N=84
Apixaban	1 (1.2%)
Dabigatran	2 (2.4%)
Rivaroxaban	9 (10.8%)
Warfarin	71 (85.6%)
Pulmonary Embolism	N=83
Apixaban	1 (1.2%)
Dabigatran	3 (3.7%)
Rivaroxaban	5 (6.1%)
Warfarin	73 (89%)

**Table 3.** Physician responses regarding advantages and disadvantages of rivaroxaban as compared to warfarin

Advantages	N=88
Cost-effectiveness balance	5
Superiority of rivaroxaban in preventing recurrent DVT/PE	12
Less drug-food interactions	38
Reduced clinic/lab visits	71
Disadvantages	N=88
Cost-effectiveness balance	47
Limited personal clinical experience with rivaroxaban	49
Lack of reversal agent	57
Inability to monitor degree of anticoagulation	23
Risk of intracranial hemorrhage	10
Risk of gastrointestinal bleeding	16

knowledge, this is the first attempt at understanding factors that influence physician attitudes towards NOAC treatment in an acute setting such as thromboembolic disease. Based on this survey, cardiologists felt the most comfortable in the use of NOAC for therapy for thromboembolic disease, more

**Table 4.** Percentage of internal medicine respondents in each specialty choosing a particular oral anticoagulant for treatment of VTE.

	Cardiology	Hematology	Hospital Medicine	Primary Care
<b>PE</b>	<b>N=11</b>	<b>N=14</b>	<b>N=18</b>	<b>N=38</b>
Apixaban	0	0	0	1 (2.6%)
Dabigatran	1 (9%)	0	1 (5.6%)	1 (2.6%)
Rivaroxaban	4 (36.4%)	1 (7.1%)	0	0
Warfarin	6 (54.6%)	13 (92.9%)	17 (94.4%)	36 (94.7%)
<b>DVT</b>	<b>n=11</b>	<b>N=15</b>	<b>N=18</b>	<b>N=38</b>
Apixaban	0	0	0	1 (2.6%)
Dabigatran	1 (9%)	0	1 (5.6%)	0
Rivaroxaban	5 (45.5%)	1 (6.7%)	1 (5.6%)	2 (5.3%)
Warfarin	5 (45.5%)	14 (93.3%)	16 (88.9%)	35 (92.1%)

so than primary care physicians and hospitalists.

There were four major conclusions of this study. First, treatment with NOACs still do not have widespread acceptance as first-line outpatient therapy for VTE as the vast majority of physicians surveyed still are using warfarin for first-line therapy. Secondly, the most common reasons reported for not using therapy with NOAC were cost and lack of reversibility with NOACs. Thirdly, the vast majority of physicians who reported using a NOAC for VTE therapy felt that not having blood level monitoring was the major reason for their choice. Interestingly, cardiologists were more likely to use therapy with NOACs for treatment of DVT/PE than internists, and years since completion of training did not seem to matter in the use of NOACs.

Lee et al, in a Markov model using a United States payer/Medicare perspective and a lifetime time horizon, concluded rivaroxaban was cost-effective in patients with atrial fibrillation in comparison to warfarin.<sup>9</sup> Despite these data, however, cost has been described as the major reason for not using NOAC therapy in a paper by Huang et al, analyzing the use of NOAC therapy in stroke prevention in patients in atrial fibrillation.<sup>10</sup> Our study shows similar findings.

The cost of rivaroxaban is approximately \$300–\$350 in US dollars per month. One limitation to our study is that it did not specifically look at what factors involved in the cost of NOACs ultimately led to NOAC nonuse; however, it is possible that the direct cost to patients who may have high insurance copays for newer medications may be a deterrent for its widespread use.

Of no surprise, the major reason cited for use of NOAC therapy in patients with DVT/PE was lack of required laboratory blood monitoring. This has been cited before and is the major patient motivator in requesting a switch from warfarin to a NOAC in many patients.

Doctors' personal experience with prescribing newer drugs has been recognized as a major influential factor in a doctor's willingness to prescribe a drug.<sup>11</sup> Interestingly, our study showed that cardiologists were more likely to

prescribe a NOAC for treatment of DVT/PE than other specialties. This is likely on the basis of the U.S. Food and Drug Administration (FDA) having approved dabigatran on Oct. 19, 2010 for stroke prevention in atrial fibrillation, allowing for cardiologists to have more experience with the NOACs as they are the predominant specialty for treatment of this condition. In fact, it has been suggested that physicians who have prescribed dabigatran for atrial fibrillation more than 10 times are more comfortable in prescribing the drug than those who have not.<sup>10</sup> It is likely that the cardiologists who have had a positive experience with

NOAC therapy in atrial fibrillation are more comfortable in prescribing NOACs in VTE therapy. Hence, with more time and more experience of other specialties in the use of NOACs, it is likely that use of NOACs in the treatment of DVT/PE will rise.

In our study, one factor that did not influence the decision to use NOACs was the physician's number of years out of residency/fellowship. Although one might assume that physicians who have been recently trained may be more likely to invoke a newer drug therapy, interestingly, that was not the case in our study. Similar findings, however, were also seen in a collection of physicians surveyed for dabigatran use in atrial fibrillation, and in a survey amongst general practitioners prescribing new drugs.<sup>10,12</sup>

Limitations of this study include its survey of a limited geographic region as well as the low response rate (24.4%). There are data, however, that surveys of physicians are less sensitive to issues with response rates and that even surveys with low response rates are still indicative of the larger physician population.<sup>13</sup>

At the time this survey was conducted, only warfarin and rivaroxaban held active FDA approvals for the treatment of VTE. Efficacy data were available, however, in the form of published trials for rivaroxaban (EINSTEIN-DVT and EINSTEIN-PE), dabigatran (RECOVER and RECOVER II), and apixaban (AMPLIFY).<sup>14-18</sup>

Novel oral anticoagulants are a major advance in the treatment of VTE and many physicians in this survey cited lack of blood laboratory monitoring as the major reason for their use. One year after the approval for NOACs for the treatment of DVT/PE, however, warfarin was still the overwhelming first choice for anticoagulation for the treatment of VTE. Cost and lack of reversibility were cited as the major reasons for NOAC nonuse. Based on the higher acceptance of NOAC use among cardiologists surveyed who treat DVT/PE, we feel that with more experience in prescribing NOAC therapy, we will likely see a significant increase in prescriber usage of NOAC therapy.

## APPENDIX

### Physician Survey Regarding Novel Oral Anticoagulant (NOAC) Use for the Treatment of Venous Thromboembolism

#### DEMOGRAPHICS

- What is your primary specialty?
- Internal Medicine/Primary Care
- Internal Medicine/Hospital Medicine
- Internal Medicine/Hematology
- Internal Medicine/Cardiology
- Family Medicine

Approximately how many years since you finished residency/fellowship?

- <5 years
- 5 - 9 years
- 10-19 years
- 20 years or more

#### ATTITUDE QUESTIONS

Have you started a patient on an oral anticoagulant for treatment of DVT or PE in the last 6 months?

- Yes
- No

For patients with normal renal function, my initial choice for an oral anticoagulant is

	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Deep vein thrombosis (DVT)				
Pulmonary Embolism (PE)				

*Display This Question:*

*If Deep vein thrombosis (DVT) - Apixaban Is Selected*

The most important factor in my choice of apixaban as initial treatment for DVT is:

- No lab monitoring required for my patients
- It has less of a chance for intracranial hemorrhage than warfarin
- No food restrictions for my patients
- Less medication interactions

*Display This Question:*

*If Deep vein thrombosis (DVT) - Dabigatran Is Selected*

The most important factor in my choice of dabigatran as initial treatment for DVT is:

- No lab monitoring required for my patients
- It has less of a chance for intracranial hemorrhage than warfarin
- No food restrictions for my patients
- Less medication interactions

*Display This Question:*

*If Deep vein thrombosis (DVT) - Rivaroxaban Is Selected*

The most important factor in my choice of rivaroxaban as initial treatment for DVT is:

- No lab monitoring required for my patients
- It has less of a chance for intracranial hemorrhage than warfarin
- No food restrictions for my patients
- Less medication interactions

*Display This Question:*

*If Deep vein thrombosis (DVT) - Warfarin Is Selected*

The most important factor in my choice of warfarin as initial treatment for DVT is:

- Cost of newer anticoagulants
- I am comfortable with using warfarin and find no reason to change
- I am concerned about the risk of gastrointestinal bleeding with newer anticoagulants
- Lack of an effective reversal agent with the newer anticoagulants

*Display This Question:*

*If Pulmonary Embolism (PE) - Apixaban Is Selected*

The most important factor in my choice of apixaban as initial treatment for PE is:

- No lab monitoring required for my patients
- It has less of a chance for intracranial hemorrhage than warfarin
- No food restrictions for my patients
- Less medication interactions

*Display This Question:*

*If Pulmonary Embolism (PE) - Dabigatran Is Selected*

The most important factor in my choice of dabigatran as initial treatment for PE is:

- No lab monitoring required for my patients
- It has less of a chance for intracranial hemorrhage than warfarin
- No food restrictions for my patients
- Less medication interactions

*Display This Question:*

*If Pulmonary Embolism (PE) - Rivaroxaban Is Selected*

The most important factor in my choice of rivaroxaban as initial treatment for PE is:

- No lab monitoring required for my patients
- It has less of a chance for intracranial hemorrhage than warfarin
- No food restrictions for my patients
- Less medication interactions

*Display This Question:*

*If Pulmonary Embolism (PE) - Warfarin Is Selected*

The most important factor in my choice of warfarin as initial treatment for PE is:

- Cost of newer anticoagulants
- I am comfortable with using warfarin and find no reason to change
- I am concerned about the risk of gastrointestinal bleeding with newer anticoagulants
- Lack of an effective reversal agent with the newer anticoagulants

Please check any of the items that you consider as *ADVANTAGES* of RIVAROXABAN as compared to WARFARIN for the treatment of DVT and PE:

- Cost-effectiveness balance
- Superiority of rivaroxaban in preventing recurrent DVT/PE
- Less drug/food interactions
- Reduced clinic/lab visits

Please check any of the items that you consider as *DISADVANTAGES* of RIVAROXABAN as compared to WARFARIN for the treatment of DVT and PE:

- Cost-effectiveness balance
- Limited personal clinical experience with rivaroxaban
- Lack of reversal agent
- Inability to monitor degree of anticoagulation
- Risk of intracranial hemorrhage
- Risk of gastrointestinal bleeding



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## Disclosure

The authors have no conflicts of interest in relation to this work.

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