New Oral Anticoagulants: Topic Brief

June 9, 2015

High-Level Research Question

In patients with nonvalvular atrial fibrillation (AF) or venous thromboembolic disease, or who have undergone surgery for knee and hip replacement, what are the comparative benefits and harms between warfarin and the new oral anticoagulants (NOACs) for anticoagulation, or among the NOACs? What is the impact of renal dysfunction, other co-morbidities, and age on the decision of which anticoagulant to use?

Assignment for Workgroup Participants

- Based on your perspective (patient, clinician, payer, etc.), what are two to three of the most relevant comparative effectiveness research questions related to use of NOACs?
- Submitted questions will be used to generate the agenda for the workgroup meeting.

Opportunity Snapshot

As part of PCORI's efforts to fund high-impact and useful research on critical patient-centered health and healthcare issues, PCORI is hosting a multistakeholder workgroup to discuss high-priority topics that focus on the comparative effectiveness of NOACs. PCORI intends to use feedback from the workgroup to conduct further gap analyses and to develop a funding announcement in this area. The objective of the workgroup is to create a set of comparative research questions whose findings could improve patient-centered outcomes.

1. Introduction

Oral anticoagulants are used in several serious health conditions, the most common of which are AF (to prevent stroke), deep vein thrombosis (DVT; to prevent further thrombosis and pulmonary embolism [PE]), and postoperative prevention of DVT (particularly after hip and knee surgery).[1] Until 2010, virtually the only oral anticoagulant available was the vitamin K antagonist, warfarin. However, since 2010, NOACs (also called direct thrombin inhibitors [DTIs] or director factor Xa inhibitors) now account for 62 percent of new prescriptions and 98 percent of anticoagulant-related drug costs.[2] The four NOACs are dabigatran, rivaroxaban, apixaban, and edoxaban.[3] (Dabigatran is a DTI; rivaroxaban, apixaban, and edoxaban are factor Xa inhibitors.) These widely advertised[4] medications are gaining popularity over warfarin due to several advantages:

- Their fixed, once- or twice-a-day dosing is more straightforward and convenient.
- They do not require monitoring, compared with an international normalized ratio (INR, a test for adequacy of warfarin anticoagulation)) every four weeks after a stable dose is achieved for warfarin.
- Compared with warfarin, they are associated with up to a 50-percent reduction in intracranial hemorrhage, 19-percent reduction in stroke or embolic events, and 10-percent reduction in all-cause mortality in the setting of AF.[5]
- Their effectiveness is not sensitive to dietary changes, such as in vitamin K–containing vegetables.

However, the NOACs do have some firm and some arguable drawbacks:

- NOACs are significantly more expensive than warfarin.[6] Relative 30-day costs are:
    - $16 for generic warfarin 2 or 5 mg once daily
    - $383 for rivaroxaban 20 mg once daily
    - $400 for apixaban 5 mg twice daily
    - $373 for dabigatran 150 mg twice daily
    - Not yet available for edoxaban (30 mg or 60 mg once daily)
- Not all NOACs are covered by insurance.[6]

- While bleeding associated with use of NOACs is reversible using an infusion of prothrombin complex concentrate, and specific antidotes are expected to be marketed soon,[6] the reversibility is not as well recognized as using vitamin K as an antidote for bleeding on excessive doses of warfarin.
- Recent concerns about excess bleeding risk prompted a high-profile lawsuit against Boehringer Ingelheim, the maker of Pradaxa.[7]
- Dosage must be adjusted in the setting of renal dysfunction.
- Creatinine clearance must be determined before prescribing edoxaban.[8]

2. Patient-Centeredness

The choice between warfarin and one of the NOACs, and among the NOACs, is a common and important one, because of the tradeoffs between cost, convenience, bleeding risk, and other noted factors.

3. Impact (Burden) of the Condition on the Health of Individuals and Populations

AF

Prevalence: 2.3 million Americans have AF, including 9 percent among the elderly;[9] the risk of stroke with AF is 5 percent per year without anticoagulation.
Mortality: There is an 8-to-15-percent fatality rate 30 days after an ischemic stroke.[10]
Burden of taking anticoagulants: Patients with AF must remain on anticoagulants *for the rest of their lives*. The NOACs are associated with significant out-of-pocket costs, and all anticoagulants carry an increased risk of bleeding.

DVT and PE

Prevalence: The conditions occur in 300,000 to 600,000 people every year in the United States.
Mortality: Of those with DVT or PE, 10 percent to 30 percent will die within one month of diagnosis.[11]
Burden of taking anticoagulants: After initial intravenous heparin treatment for DVT or PE, patients must remain on oral anticoagulants *for three to six months*. The NOACs are associated with significant out-of-pocket costs, and all anticoagulants carry an increased risk of bleeding.

Postoperative DVT from Knee or Hip Surgery

Prevalence: In the United States in 2010, there were 719,000 total knee replacements (TKR) and 332,000 total hip replacements.[12]

Mortality: In the absence of thromboprophylaxis, the incidence of DVT and PE are reportedly 41 percent to 85 percent, and 1.5 percent to 10 percent, respectively, after TKR[13]; symptomatic PE is rapidly fatal in approximately 10 percent of patients.[14]

Burden of taking anticoagulants: Patients may remain on anticoagulants *for two weeks to one month* after surgery.[15] The NOACs are associated with significant out-of-pocket costs, and all anticoagulants carry an increased risk of bleeding.

4. Ongoing Evidence Gaps

Given the recent introduction of NOACs, heavy marketing, and several ongoing trials, this is a fairly rapidly evolving area.

Treatment of Nonvalvular AF

Clinical Guidelines: The American Academy of Neurology recommends that clinicians choose among warfarin or the NOACs, but recommends NOACs if there is a high risk of intracranial hemorrhage or if the patient is unable to monitor INR frequently (Level B).[a16]

The American College of Chest Physicians (ACCP) recommends dabigatran (the first NOAC) over warfarin (Grade 2B[b]).[17] The search that resulted in these guidelines included studies published between 2005 and 2009, and no other NOACs are mentioned. The guidelines note: "Antithrombotic therapy for AF is evolving rapidly because of the development of new oral anticoagulants that directly target different parts of the coagulation pathway, have a more predictable anticoagulant effect, and do not require INR monitoring. . . . Results of large phase 3 clinical trials of these agents in patients with AF have been recently published or will be reported soon."

Recent Reviews: A Cochrane review, which included eight studies of "adequate" quality that reported on more than 27,000 participants, noted that NOACs were as efficacious as vitamin K antagonists for the composite outcome of vascular death and ischemic events, and only the dose of dabigatran 150 mg twice daily was found to be superior to warfarin in the treatment of patients with nonvalvular AF. NOACs were associated with fewer major hemorrhagic events, including hemorrhagic strokes. Adverse events that led to discontinuation of treatment occurred more frequently with the DTIs (dabigatran). There was no difference in death from all causes.[18]

Treatment of DVT and PE

[a] B denotes a guideline that "should" be followed, based on the strength of the evidence.

[b] Grade 2B indicates that benefits closely balanced with risks and burden—evidence from randomized controlled trials (RCTs) with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.

Clinical Guidelines: The ACCP suggests, after treatment of the acute phase in patients with DVT of the leg and no cancer, warfarin over low-molecular-weight heparin (LMWH)—which is given subcutaneously—for long-term therapy (Grade 2C[c]), and it recommends LMWH over dabigatran or rivaroxaban for long-term therapy (Grade 2C).[19] However, recent studies have directly compared warfarin with NOACs in this setting,[20, 21] so the guidelines may need to be updated.

In patients with DVT of the leg and cancer, the AACP suggests LMWH over warfarin (Grade 2B). In patients with DVT and cancer who are not treated with LMWH, the expert panel suggests warfarin over dabigatran or rivaroxaban for long-term therapy (Grade 2B).

Note that only rivaroxaban and apixaban are approved for (venous thromboembolism) VTE prevention; this clinical indication was not further considered in this brief, which only considered treatment.

Recent Reviews: A 2014 Cochrane review on treatment of DVT in patients with cancer[22] identified one study using ximelagatran and one using dabigatran, suggesting that NOACs are being considered for treatment of DVT and PE in this setting; however, the review did not comment on their use and focused instead on use of LMWH and vitamin K antagonists (VKA). In other reviews, dabigatran and rivaroxaban were found to be as effective as conventional therapy (heparin/vitamin K antagonists), and there were no safety concerns.[23] Compared with VKAs, NOACs were deemed not only effective in treating VTE but also safer in terms of bleeding, thereby conferring net clinical benefit. Their safety and efficacy was confirmed further in secondary prevention trials.[24]

Post-op from Knee and Hip Surgery

Clinical Guidelines: The American Academy of Orthopedic Surgeons suggests that, for patients with average bleeding risk, pharmacologic agents or mechanical compressive devices should be used (Grade of Recommendation: Moderate[d]), but notes that current evidence is unclear about which treatment strategies are optimal, and does not recommend for or against specific prophylaxis in these patients (Grade of Recommendation: Inconclusive[e]).[25] The ACCP recommends that patients of average bleeding risk receive LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH), adjusted-dose VKA, aspirin (all Grade 1B, or "strong" with moderate-quality evidence[f]), or an

[c] Grade 2C indicates uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced—evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence.
[d] Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention.
[e] Evidence is insufficient or conflicting, and does not allow a recommendation for or against the intervention.
[f] "B" means evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies.

intermittent pneumatic compression device (Grade 1C, or strong with low-quality evidence[g]).[26] The ACCP recommends the use of LMWH in preference to NOACs or LDUH (all Grade 2B[h]). This recommendation was due in part to concerns over lack of long-term safety data for apixaban, dabigatran, and rivaroxaban. The Scottish Intercollegiate Guidelines Network recommends that patients with average bleeding risk receive any one of LMWH, fondaparinux, rivaroxaban, or dabigatran (Grade A[i]). Preference between these treatments is not stated and is recommended to be combined with mechanical prophylaxis.[27]

Recent Reviews: A recent Cochrane review of 14 studies concluded that DTIs, a subgroup of NOACs, are as effective in the prevention of major venous thromboembolism in total hip replacement and total knee replacement as LMWH and VKAs. However, they show higher mortality and cause more bleeding than LMWH. Use of ximelagatran is not recommended for VTE prevention in patients who have undergone orthopedic surgery. It was concluded that more studies regarding dabigatran are necessary.[28] The quality of the evidence comparing DTIs with LMWH was deemed low for major VTE events and total bleeding events, and moderate for all-cause mortality.

Another review stated that, although some guidelines provide recommendations for the use of rivaroxaban, dabigatran, and apixaban in clinical practice, there are still questions regarding the optimal practical management of patients receiving these agents.[29]

5. Ongoing Research

A search was performed in clinicaltrials.gov, using the terms "anticoagulant" and either "total knee," "atrial fibrillation," or "deep vein thrombosis." No date range was specified.

Condition	Number of trials/observational studies	Head-to-head	NOAC vs. warfarin	NOAC vs. NOAC	Sample size range (mean)
AF	77/33	58	37	22	10–100,000 (3,568)
DVT	34/2	20	6	6	25–8,292 (1,504)
Total knee	18/1	9	0	8	56–2,615 (1,011)

Notes: "Head-to-head" means a comparator was listed that was not a placebo. Studies were deleted if they did not appear to include a NOAC. A NOAC may include an investigational drug. NOAC versus

[g] "C" means evidence for at least one critical outcome from observational studies or case series, or from RCTs with serious flaws or indirect evidence.
[h] "B" means evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.
[i] "A" means at least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.

warfarin and NOAC versus NOAC are not mutually exclusive. Specific searches for total hip replacement and PE were not performed.

6. Likelihood of Implementation in Practice

Some of the recommendations described above indicate that research to strengthen these guideline recommendations is likely to affect clinical practice.

7. Durability of Information

Three NOACs are currently marketed, one was recently approved by the FDA, and several more are under development.[30] There are three antidotes currently in development,[31] which will reduce one of the listed drawbacks of the NOACs. Thus, this is likely to be an area with changing clinical options for several years.

8. Potential Research Questions

The major research questions revolve around comparisons between warfarin and NOACs, or among the NOACs for patients with conditions that require anticoagulation, and in specific subgroups of patients, particularly those with varying levels of renal function.

Thus, the following questions may be germane:

- What are the comparative benefits and harms among the NOACs?
    - In patients with AF
    - In patients with VTE
    - In patients who have undergone surgery for knee and hip replacement
- What are the comparative benefits and harms of warfarin versus the NOACs?
    - In patients with AF
    - In patients with VTE
    - In patients who have undergone surgery for knee and hip replacement
- What are the comparative benefits and harms among the NOACs?
    - In patients with AF and with co-morbidity, such as renal dysfunction, or in the elderly
    - In patients with VTE and with co-morbidity, such as renal dysfunction, or in the elderly
    - In patients who have undergone surgery for knee and hip replacement and with co-morbidity, such as renal dysfunction, or in the elderly
- What are the comparative benefits and harms of warfarin versus the NOACs?
    - In patients with AF and with co-morbidity, such as renal dysfunction, or in the elderly
    - In patients with VTE and with co-morbidity, such as renal dysfunction, or in the elderly
    - In patients who have undergone surgery for knee and hip replacement and with co-morbidity, such as renal dysfunction, or in the elderly

9. Conclusion

Although the decision to use warfarin versus the NOACs in AF, to treat DVT or PE, and in the postoperative setting for total hip and knee replacement is commonly faced and lacks evidence in some circumstances, the field is rapidly evolving such that many believe that NOACs are likely to prevail in the near future, replacing warfarin, particularly in the setting of AF. Out-of-pocket drug costs or selective insurance reimbursement often play a key role in the choice of therapy. Deciding among the NOACs may be important, given limited available information on differences in benefits and harms among these drugs.

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