



Prioritizing Comparative Effectiveness Research Questions around the Use of New Oral Anticoagulants

A Stakeholder Workshop

Overview

On June 9, 2015, PCORI hosted a one-day multi-stakeholder workshop to discuss whether clinical comparative effectiveness research (CER) can help to answer questions about the use of newer oral anticoagulants (blood thinners). Oral anticoagulants are used to prevent stroke in people with atrial fibrillation (AF), to treat deep vein thrombosis (DVT), and in the postoperative setting after hip and knee replacement to prevent DVT ([Topic Brief](#)). The meeting, which was chaired by Geno Merli, MD, chief medical officer and director of the Jefferson Center for Vascular Diseases, was [audio recorded](#) and open to the public via webinar. Representatives from a wide range of stakeholder groups, including patients, caregivers, clinicians, industry, payers, and researchers, were tasked with identifying, refining, and prioritizing two to three clinical CER questions on the use of new oral anticoagulants (NOACs).

Introduction

PCORI's Program Director of Clinical Effectiveness Research, Dr. David Hickam, opened the session by providing a general overview of PCORI and the goals of the workshop. Then Dr. Merli reviewed the meeting agenda and participants introduced themselves.

Discussion

Prior to the meeting, [attendees](#) were asked to identify relevant CER questions. Stakeholders submitted approximately 50 questions, which were compiled and refined by PCORI staff. Those questions were reviewed for CER pertinence and a total of 11 key questions were used to provoke discussions centered on three major themes:

1. Comparative benefits and harms among the NOACs
2. Comparative benefits and harms of NOACs versus warfarin
3. Special clinical settings

Workgroup participants provided input on each topic area. They then discussed specific topics and/or research questions within each of the topic areas. To determine the most critical

research gaps, the workgroup considered patient-centeredness, potential for impact, other ongoing research, feasibility, and durability of information. During lunch, stakeholders were given a revised set of questions based on the morning discussion. Stakeholders commented on the feasibility and implications of each research question, and the research question language evolved accordingly. The revised prioritized questions with their associated PICOTS (Population, Intervention, Comparator, Outcome, Timing, and Setting) -focused discussions are presented below.

Atrial Fibrillation—NOAC versus NOAC or NOACs versus warfarin:

Most of the evidence comparing different NOACs is indirect. Meta-analyses suggest that few differences exist between NOACs in terms of effectiveness. The evidence base could be strengthened through direct comparisons between NOACs in specific patient populations. Other themes that emerged during this discussion are as follows:

- Special populations
 - Research on the appropriate use of NOACs in older populations
- Primary care physicians (PCPs) underuse NOACs due to fall risks and associated bleeds.
- PCPs lack a complete understanding of NOACs.
 - Selection of NOAC for patients with renal insufficiency or renal failure
 - Minority populations—evaluating different NOAC risks and uses
 - Women—evaluating different NOAC risks and uses
 - Obese patients
- Adherence to treatment
 - Evaluate patient concerns about risk of stroke versus risk of bleeding complications and include this information in shared decision making.
 - Fear of bleeding hinders adherence to medication.
 - Patient-doctor interaction affects adherence.
- Therapy should be optimized through dosing adjustments based on anticoagulant blood levels and renal function to improve outcomes.
- PCORI should decide whether to compare a NOAC to itself (in different doses and contexts) or to compare different NOACs.
- How could all four NOACs be included in a study?
 - The panel was concerned that there would be enough data on bleeding but not enough power to detect differences in rates of ischemic stroke.
- Investigators should take into account the already approved doses for each NOAC.

- Physicians prescribe anticoagulants to their patients when indicated; however, they are under-dosing patients due to bleeding risk.

Orthopedics and Risk of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE):

After discussing basic information on this topic—1 million hip and knee surgeries are performed in the United States per year; different drugs are used for orthopedic risks; and guidelines exist for the prevention of venous thromboembolism (VTE)—the group questioned whether PCORI should focus on this area given that treatment occurs over a short period of time and all therapies other than aspirin seem to be effective. The following themes emerged during the discussion:

- Bridging therapy
 - When should patients stop taking anticoagulants before orthopedic surgery?
 - Are patients stratified by level of risk to determine if bridging therapy is necessary?
 - NOACs and low molecular weight heparin (LMWH) have the same half-life. Bridging around a NOAC with LMWH is not necessary, yet the misperception persists.
 - Communicating the correct information to patients who switch agents.
- Special populations
 - Different populations have different risks (e.g., cancer patients, pregnant women, geriatric patients, younger patients).
- Risk of major bleeding associated with NOACs
 - Different populations have different levels of risk.
- There is a risk of late recurrence in provoked and unprovoked venous thrombosis.
- Does dose adjustment (using blood levels or measures of renal function) improve effectiveness and bleeding rates for patients prescribed NOACs?
- Recurrence
 - Can biomarkers, like a D-dimer, indicate continued risk for a blood clot? A negative D-dimer is not reassuring in certain populations—the risk for recurrence can still be high.
- Adherence
 - After one year, 60 percent of patients who were followed by an anticoagulant clinic had stopped taking warfarin.
 - Adherence is not evaluated as diligently in DVT and PE as compared with AF due to shorter treatment periods.
 - In general, if no bleeding occurs during the treatment period, then adherence will be higher.
 - Adherence is important to reduce the risk of recurrence.

- Based on the type of patient and his or her previous adherence history, adherence rates can be estimated by predictive analytics.
- Research addressing adherence will need buy-in from the caregiver for a strong patient support system.
- Adherence is based on the outcome perceived:
 - A patient's understanding of why he or she needs to take an anticoagulant
 - Other factors of which patients should be aware
 - When a patient should report back to his or her physician
- Dosing
 - If there is minor bleeding with a NOAC, is there a marker that can be used to adjust therapy to the right dose?
- There is poor initiation of these medications, not just poor adherence.
- Predictive modeling is not always useful due to variability in the U.S. population.
- Ecosystem
 - There are many options to choose from to educate patients. A systems approach as opposed to a specific-question approach should be kept in mind. A systems approach moves faster than a traditional study.
- Consider asking patients why they are not adherent.
 - Physician and clinician education must be considered here—patients feel that some clinicians do not explain well the reasons for taking a NOAC or warfarin.
 - A patient's low understanding leads to low adherence.
- The methods used to increase adherence to anticoagulant therapy could be used as a model to improve adherence for other types of medications.

How do three strategies (continuing treatment at the same dose, reducing the dose, or stopping treatment) compare for patients who have been on an anticoagulant for at least six months after an episode of DVT or PE?

What are the comparative safety and effectiveness of standardized perioperative strategies (stopping warfarin and bridging with enoxaparin, switching to a NOAC temporarily, or stopping and restarting a NOAC) for anticoagulation in patients with nonvalvular AF who are undergoing invasive procedures?

- This question represents an unmet area of need.
- This area of research is being actively pursued by other groups (pharma).
- This area is already being studied from a patient perspective.

- The group agreed that this question does not address a priority area.

What are the comparative benefits and harms of NOACs compared with LMWHs for extended treatment in patients with VTE and active cancer?

- Pharma has already conducted clinical trials in this area with several NOACs, although there may be other areas for PCORI to evaluate.
- This question presents a challenging research area:
 - Some chemotherapy agents contribute to VTE.
 - Cancer patients experience nausea and vomiting that might make taking anticoagulant medication difficult.
- Consider the added component of injectable versus oral anticoagulants.

Is the initial use of a NOAC as effective as initial treatment with heparin for the acute treatment of DVT or PE?

- There is a subset of patients who present to the hospital with DVT or PE who might benefit from this study.
- Data already exist in this area (via previous meta-analysis). Pharma is also looking into this area.
- Consider that patients are not given oral anticoagulants for an emergent PE. They are given heparin followed by an oral regimen a few days later. Follow-up is difficult because patients often do not stay in the hospital longer than five days.
- Sending patients home on NOACs
 - AF—Sending a patient home is acceptable as long as there is consistent follow-up.
 - DVT—There have been discussions with American College of Emergency Physicians about the standard of care regarding sending patients home. There is an expectation that sending patients home on a NOAC may eventually be the standard of care.
- Treatment is mostly individualized, not standardized.
- The timing of follow-up would be very important for this question.
- The group did not reach consensus on whether this question should be a priority.

Other: important topics

- Sex differences
- Underutilization of these agents (under-treatment or no treatment)
- Population of switchers (patients who switch from warfarin to a NOAC)



- NOACs for reduction of stroke risk in heart failure patients

Moving Forward

The workshop provided an opportunity for key questions to be discussed and refined by a diverse range of stakeholders. The PCORI Board of Governors will decide whether to pursue the development of a targeted research priority on the use of newer oral anticoagulants.