SYMPOSIUM PROCEEDINGS

Effective AC Management:

Focus on Promoting and Simplifying Adherence

May 8, 2013
Phoenix, Arizona

National Blood Clot Alliance
Stop The Clot®

The National Blood Clot Alliance extends its appreciation to the sponsors of this program.

This meeting was made possible through sponsorship support from:

Boehringer Ingelheim • Platinum Sponsor

Janssen Pharmaceuticals, Inc. • Gold Sponsor

Introduction

In May 2013, the National Blood Clot Alliance (NBCA) convened a multidisciplinary group of physicians, nurses, patients, pharmacists and other stakeholders in anticoagulation management to focus their expertise on an agenda covering the use of oral anticoagulation (OAC) therapy and adherence. This NBCA symposium — *Effective AC Management: Focus on Promoting and Simplifying Adherence* — was held in Phoenix, AZ, as an official affiliate meeting of the Anticoagulation Forum's 12th National Conference on Anticoagulation Therapy.

Many complex factors that contribute to nonadherence among patients taking OACs were reviewed. With the introduction of new OACs to prevent blood clots related to atrial fibrillation (AF) and venous thromboembolism (VTE), new challenges involving adherence emerge.

Nonadherence is both a common and complex issue. According to a survey conducted in 2006 by the National Community Pharmacists Association and Pharmacists for the Protection of Patient Care, nearly three out of four Americans do not always take their medication as prescribed. The reasons for nonadherence can range from something as simple as forgetting to take medication or as complicated as the onset of troublesome side effects or the inability to pay for a prescription. In anticoagulation therapy, studies have shown that 22% to 32% of patients affected by AF do not take warfarin therapy as prescribed, which generally corresponds with results of a survey conducted by NBCA, in which 26% of 259 AF patients taking warfarin reported nonadherence.

As reviewed during this symposium, several factors combine to make this a subject of growing importance, including the aging of America, the growing incidence of AF, the emergence of new OACs that no longer require monitoring, and the costs of medications and healthcare.

NBCA was honored to have such a dynamic group gathered to contribute to this program, and also to have the direction and input of our distinguished faculty for this symposium.

A summary of the proceedings of this meeting are reported here, and video presentations from each symposium speaker can be viewed on NBCA's website at www.stoptheclot.org.

Symposium Co-Chairs

Gary Raskob, PhD
Dean, College of Public Health, and Professor, Epidemiology and Medicine,
University of Oklahoma Sciences Center
Incoming Chair, NBCA's Medical and Scientific Advisory Board

Jack Ansell, MD
Professor of Medicine,
New York University School of Medicine
Chair, NBCA's Medical & Scientific Advisory Board

Faculty

Randy Fenninger
NBCA President

Mellanie True Hills
Founder and CEO, StopAfib.org

Jack Ansell, MD
Professor of Medicine,
New York University School of Medicine
Chair, NBCA's Medical & Scientific Advisory Board (MASAB)

Meera Viswanathan, PhD
Director, RTI-UNC Evidence-based Practice Center
RTI International

Julie Kuhle, BS, Pharm
Senior Director of Performance Measurement.
Pharmacy Quality Alliance

Margaret Fang, MD, MPH
Associate Professor of Medicine, Division of Hospital Medicine, UCSF
Medical Director, UCSF Anticoagulation Clinic

Scott Kaatz, DO, MSc
Chief Quality Officer, Director, Hospitalist Program
Hurley Medical Center

Gary Raskob, PhD
Dean, College of Public Health, and Professor, Epidemiology and Medicine,
University of Oklahoma Sciences Center
Incoming Chair, NBCA's MASAB

Participants

Arthur Allen, PharmD, CACP
VA Sierra Nevada Health Care System
Reno, NV

Jack Ansell, MD
New York Univ School of Medicine
New York, NY

Thomas Berger, PhD
Veterans Health Council
Vietnam Veterans of America
Silver Spring, MD

Alan Brownstein, MPH
National Blood Clot Alliance
Tarrytown, NY

Allison Burnett, PharmD, PhC
Univ of New Mexico Hospital
Albuquerque, NM

Henry Bussey, PharmD
ClotCare.org and ClotFree Texas
San Antonio, TX

Susan Conway, PharmD
Univ of Oklahoma College of
Pharmacy & INTEGRIS Baptist Clinic
Oklahoma City, OK

Diane DeTour, RN
Anticoagulation Mgmt Service
Massachusetts General Hospital
Boston, MA

James Douketis, MD
St. Joseph's Healthcare Hamilton
Hamilton, ON

Stacy Ellsworth
Henry Ford Health System
Detroit, Michigan

Margaret Fang, MD, MPH
Univ of California San Francisco
Anticoagulation Clinic
San Francisco, CA

Randy Fenninger, JD
National Blood Clot Alliance
Vienna, VA

Greg Flaker, MD
University of Missouri
Columbia, MO

Lisa Fullam
LFA, Inc.
Scottsdale, AZ

Candice Garwood, PharmD, BCPS
Wayne State Univ &
Harper Univ Hospital
Detroit Medical Center
Detroit, MI

Mary George, MD, MPH, FACS
Division for Heart Disease &
Stroke Prevention, CDC
Atlanta, GA

Kristen Holgerson
National Blood Clot Alliance
Tarrytown, NY

Scott Kaatz, DO, MSc
Hurley Medical Center
Flint, MI

Julie Kuhle, BS Pharm
Pharmacy Quality Alliance
Indianola, Iowa

Rob Lavender, MD
Univ of Arkansas for Medical Sciences
Little Rock, AR

Debra McCall
StopAfib.org
Greenwood, TX

Mary Ellen McCann, RN, MA
National Blood Clot Alliance
Tarrytown, NY

Laura McDermott, RN, BSN, CACP, SNP
Univ Hospitals AC Services
Coumadin Clinic
Albuquerque, NM

Edith Nutescu, PharmD
Univ of Illinois at Chicago,
College of Pharmacy and
Hospital & Health Sciences System
Chicago, IL

Leslie Raffini, MD, MSCE
Children's Hospital of Philadelphia
Philadelphia, PA

Gary Raskob, PhD
Univ of Oklahoma
Health Sciences Center
Oklahoma City, OK

Lisa Richardson, MD, MPH
Division of Blood Disorders, CDC
Atlanta, GA

Erin Robinson, PharmD
Univ of Wisconsin Health
Anticoagulation Clinic
Madison, WI

Shawna Russo
National Blood Clot Alliance
Streetsboro, OH

Paul and Susan Scribner
Washington, MI

Nancy Shapiro, PharmD, FCCP, BCPS
Univ of Illinois at Chicago
Hospital Health Sciences System
Antithrombosis Clinic, & Univ of Illinois
at Chicago College of Pharmacy
Chicago, IL

Michael Streiff, MD
Johns Hopkins
Baltimore, MD

Jennifer Taylor, PharmD
Providence Anticoagulation
Pharmacotherapy Clinic
Spokane, WA

JoAnn Thierry, PhD
Division of Blood Disorders, CDC
Atlanta, GA

Darren Triller, PharmD
IPRO
Albany, NY

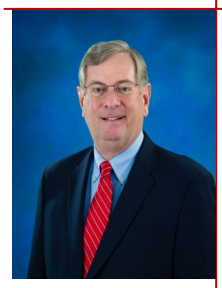
Mellanie True Hills
StopAfib.org
Greenwood, TX

Meera Viswanathan, PhD
RTI International
Research Triangle Park, NC

Welcome

Randy Fenninger, JD

NBCA President



Utilizing Patient Advocacy Teams to Reach Patients & Enhance Adherence

As a survivor of bilateral pulmonary embolisms, I know first-hand the impact of venous thromboembolism (VTE) and the importance of adherence to proper anticoagulation therapy. My commitment to adherence is firmly rooted in the fact that I never want to go back to the ER and experience what I experienced when I suffered with blood clots in both lungs. Also, I don't want to experience any strange or undue side effects because I'm not adherent or didn't take my medication properly. Most importantly, I want to be here for my family and for my children.

As healthcare professionals — doctors, nurses, patients, pharmacists, policy makers and other stakeholders — we know that adherence is a complex issue and that a number of factors need to be addressed to help us improve our understanding of adherence as it pertains to oral anticoagulation (OAC) management.

Our symposium objectives include:

- Recognize and document the need for effective OAC/adherence in patients affected by AF and VTE.
- Differentiate AC options for the treatment of patients, for both warfarin and newer OACs
- Evaluate potential screening and assessment options for adherence
- Discuss strategies for patients and healthcare professionals to overcome common obstacles to effective OAC management/adherence.

Adherence. Thankfully, we are moving into a new era characterized by new options or newer anticoagulation therapies. These newer therapies are expected to provide important benefits, such as eliminating the need to monitor INRs, but they may also provide new challenges for us to consider, such as adherence. Therefore, it is important to evaluate, among other things, potential screening and assessment options for adherence issues, and for us to discuss strategies for patients and healthcare professionals to overcome these obstacles.

Advocacy. Advocacy organizations and lay educators build the framework for the exchange of a spectrum of information that can impact adherence, which has a dramatic impact on improving public health. As such, they pave pathways for information sharing and interventions that may foster improved understanding of, and adherence to, lifesaving anticoagulation therapies.

Affordable Care Act. The advent of the Affordable Care Act perhaps makes these issues more important than ever before, as the law challenges providers and patients to do things differently, with improved results and reduced cost. Multiple opportunities exist in this regard for public-private partnerships to help benefit patient care, quality of life, and health outcomes, while respecting the finite resources that we can apply to healthcare or any other endeavor. These matters are important, as they involve an effort to change the way we think about the delivery of medical care. We want to get to a point through this law where the patient is engaged. Whether care is administered via a doctor's office or anticoagulation clinic, we are paying for value and that value is defined by quality of care and outcomes. Increased adherence will contribute to improved treatment outcomes. OAC therapy is intended to promote quality and to promote value for patients. As someone who has worked in DC for many years, and also served as NBCA's president for several years, I know that our efforts relative to adherence can be critical to making the Affordable Care Act work in our favor by moving healthcare to a better place where we can, for example, reduce clotting, reduce disability and death, and make a difference using the framework of this law and the new opportunities it brings to us.

Effective AC Management:

Focus on Promoting and Simplifying Adherence

Mellanie True Hills

StopAfib.org Founder and CEO

Anticoagulation Management and Adherence: Putting Patients First

In 2007, I founded StopAfib.org, a non-profit patient advocacy organization, to help those living with atrial fibrillation (AF). I am an AF survivor. Nearly eight years ago, I had a surgical procedure that stopped my AF, but I am always looking over my shoulder to make sure that the afib beast doesn't strike again. I'm here today to share insights I've received from afib patients on the topic of adherence.

AF turns a patient's life upside down. In my case, it was the most frightening thing that had ever happened to me. I was nervous, scared, and lost. The dizziness, light headedness, and racing heart were overwhelming. The most terrifying aspect of AF is the risk of stroke, with the threat of disability or death.

Since its founding, StopAfib.org has been active in advocating for people affected by AF. Shortly after our founding, we started Atrial Fibrillation Awareness Month, and then worked with the Heart Rhythm Society, the American College of Cardiology, and the American Heart Association to gain official recognition, by the US Senate, of September as National Atrial Fibrillation Awareness Month.

Through my work with healthcare professionals, I have come to understand that doctors are frustrated by AF due to the complexity of treating it. Because of this complexity, when a patient's INR level is too high or too low, the doctor may perceive that the patient is being nonadherent when that may not be the case at all.

Through our work at StopAfib.org, we have had the opportunity to work with thousands of AF patients, including through our online discussion forums and other AF forums. Through these interactions, we have been able to capture their perspectives about why patients are not adherent with their medications and treatments. If we can begin to understand nonadherence from a patient's perspective, then we can begin to take steps toward addressing this crucial problem.

There appear to be two different groups of AF patients. The elderly patients, who are aged 75 years and older, can be forgetful and sometimes cannot afford their medications. Those are the problems we typically try to deal with to increase adherence, and certain tools and techniques used to address these problems may work well with this older group. But, for younger AF patients, or those under the age of 75, adherence seems to revolve around a different set of issues. It is the perspective of this younger group that I am going to share with you.

We reached out to the afib patient community and received anecdotal information from hundreds and hundreds of afib patients. This information is not intended to place blame, but rather to provide another perspective about why afib patients may not be adherent with their medications and treatment. The following themes emerged when patients explained why they didn't take their medication, or didn't take it as prescribed.

- Didn't accurately hear what their doctor had said
- Didn't understand the medical jargon, or what their doctors told them
- Didn't understand why anticoagulants were being prescribed, or why they were important
- Didn't trust the doctor's decision, because they had no input into the decision-making process, or felt that their opinions and concerns were dismissed or not heard
- Didn't feel that their doctor had considered, or even asked about, their lifestyle or their concerns
- Didn't like the option their doctor had chosen, and preferred other medications or other options such as procedures or a natural approach
- Had heard "horror" stories from other patients about anticoagulant medications and were afraid to take their medication

These patient experiences and perspectives point to one critical issue: Communication. There clearly is a failure to communicate effectively between the patient and the doctor. I believe that adherence must be viewed as a two-way street, and that communication between the patient and their doctor is a central issue that must be addressed as we explore the topic of anticoagulation management and adherence. It's important to note that these are not "bad" or "dumb" patients. These are smart patients who feel that their voice is not being heard.

After collecting this information, we then explored the different ways that doctors could address this situation. The responses from patients fell into five categories:

Respect Patients want to be taken seriously and have their concerns heard. It's important for doctors to listen, engage, and focus on the patient. Regardless of the potential time crunch or the nature of the question, it's important for doctors to be respectful and respond promptly to patient inquiries and issues.

Communication A key obstacle that patients report is communication, which is, I believe, central to adherence. Avoiding medical jargon, and presenting information at an appropriate pace, are important things to consider, especially for patients who are experiencing "brain fog" from being on beta blockers for their afib. Doctors need to explain terms in simple, clear language, without medical jargon, because patients are often too scared or intimidated to tell the doctor that they don't understand what he or she is saying. Patients also stress that they need their doctors to slow down and take time to address their questions or concerns, or to make sure that they provide or direct patients toward helpful resources.

Education and Support Despite the digital age we now live in, a good number of patients report that their doctors still tell them to "stay off the Internet," preferring that the patient view the doctor as their sole information source. Clearly, patients need education and support beyond what their doctors have time to provide, particularly about stroke risk and how to prevent strokes. Patients want their doctors to help them identify high-quality resources, including those that offer direct support to AF patients. We encourage doctors to suggest that patients look for the HON code seal, from the Health on the Net Foundation, to determine if a website is credible and trustworthy. Patients want their healthcare providers to recognize that they have emotional needs, too, and that resources such as AF patient support groups can help meet these needs.

Personalized Care The personalization of care is of great importance to patients. They want to be seen as individuals and have their specific lifestyles and concerns taken into account. In my experience, each patient can be viewed as an experiment of one: There may be similarities between patients, but AF is experienced differently by each individual patient. The doctor needs to understand who the patient is. Is this patient a vegetarian? Do they work? Do they live alone or have a support system in place? Gender also affects care. More and more, patients want to be involved in their care. The mantra of these empowered patients, or ePatients, is "Nothing about me without me." Understanding and addressing the needs of individual patients, and providing personalized care to meet those needs, will help with adherence.

Coordinating Care It is not uncommon for an AF patient to be under the care of multiple physicians. When this happens, patients may become "stuck in the middle." In fact, one patient told of being pressed to choose between her cardiologist and her electrophysiologist. When patients are left to fend for themselves, they are more likely to become nonadherent. Therefore, effective coordination of care is crucial to anticoagulation management among AF patients.

StopAfib.org is committed to the AF patient community and we work to help doctors better understand the needs of these patients. In addition, we provide doctors with patient cards to give to their patients to help them locate high quality atrial fibrillation resources.

Lastly, teamwork is the preferred approach among patients. As evidenced by the diverse number of experts contributing to this symposium, teamwork will be a key to improving adherence among patients for whom the proper use of anticoagulant medications can mean the difference between life and death.

Effective AC Management:

Focus on Promoting and Simplifying Adherence

Jack Ansell, MD

Professor of Medicine, New York University School of Medicine
Chair, NBCA's Medical & Scientific Advisory Board

Anticoagulation Management: New Challenges in a New Era of Anticoagulation Therapy

As we enter a new era of anticoagulation therapy, given the recent introduction of new oral anticoagulants (OACs) that do not require INR monitoring, we also find ourselves entering a new era of examination. I believe we have much to learn. This symposium brings together experts in anticoagulation and experts in adherence to explore several questions, including:

- What is the importance of good medication adherence in OAC management?
- What is different about standard OAC (warfarin) versus the new OACs?
- Will adherence be an issue with the new OACs?

In addressing these questions, I want to stress that it is the existence now of the newer OACs that provides the impetus for this meeting, and that with their availability we will likely see adherence become an increasingly important issue. We need to look no further than the incidence of AF and VTE in the U.S. to realize the importance of this symposium:

- AF — More the 2.5 Americans are affected by AF. The incidence of all-cause stroke in patients with AF is 5% per year. AF increases the risk of stroke about five-fold and about 15% of strokes in the U.S. are caused by AF.
- VTE — Every year, up to 600,000 Americans will develop a blood clot — such as a deep vein thrombosis or pulmonary embolism — and about 100,000 of these cases will result in death.

Factors That Influence Medication Adherence

Looking at the literature, we see many references to nonadherence in different patient populations. One review conducted by John Garner, MD (Am J Cardi 2010;105:1495-1501), looks at nonadherence in cardiology in general, and indicates that at least one in seven cardiology patients report nonadherence for a variety of reasons, including: communication difficulties, polypharmacy, different objective and perceived side effects, drug costs, and depression.

Looking more systematically at the factors that influence nonadherence, the literature reflects several key drivers, including:

- Therapeutic complexity Several studies show that therapeutic complexity is a key driver in nonadherence. For example, one study published by Dr. Choudry and others (Arch Intern Med 2011; 171:814) shows that subjects filled 11.4 prescription, for 6.3 different medications, written by two prescribers and made five visits to a pharmacy over a three-month period, resulting in 67% adherence or 33% nonadherence.

- Dose regimens Fortunately, the OACs are dosed either once or twice daily. However, it's important to note that a systematic review of the associations between dose regimens and medication compliance (Claxton et. al. Clin Ther 2001 23L 1296) showed a 10% decline in adherence going from a once daily to twice daily medication.

- Nuisance side effects Another study (Garner, *Problems of nonadherence in cardiology and proposal to improve outcomes.* Am J Cardio 2010;105:1495) shows that nuisance side effects can also contribute to nonadherence. Mild bleeding, for example, can occur with OAC use, but also is commonly seen in the elderly and may not be related to OAC therapy. When nuisance side effects like these occur, a patient may decide to discontinue their medication.

- **Absence of symptoms**. Asymptomatic disease, as we see with AF and also frequently see with VTE prior to the presentation of a potentially critical event such as a pulmonary embolism, is also of concern. Numerous studies have shown that asymptomatic patients are more likely to be nonadherent to prescribed drug therapy and treatment plans. (Sloma et al. *Knowledge of stroke risk factors among primary care patients with previous stroke or TIA: a questionnaire study. BMC Family Practice. 2010; 11*:47–57.)

- **Costs** Studies also have demonstrated that the cost of care, particularly out-of-pocket costs, will impact adherence. Newer OACs may be cost effective on a societal basis, but their potentially higher co-pays could be challenging for patients, particularly those taking other therapies. (Cutler et al. Thinking *outside the pillbox: medication adherence as a priority for health care reform.* N Engl J Med 2010; 362;1553. Fox et al. *Cash strapped US patients may be skipping drugs.* Reuters, Feb 10, 2009.)

What is Different About Standard OAC (warfarin) Versus New OACs

For decades, warfarin was the sole OAC available. Today, we have new therapies available to us, and new choices to make. The differences between these choices is crucial to the consideration of adherence issues.

	Warfarin	Dabigatran etexilate	Rivaroxaban	Apixaban
T (max)	72-96 h	2 h	2.5-4 h	3 h
Half-life	40 h	14-17 h	9-13 h	8-15 h
Monitoring	INR-adjusted	None	None	None
Dosing	Once daily	Twice daily	Once daily	Twice daily
Metabolism / Elimination	Cytochrome P450	80% renal 20% biliary	33% renal, 66% biliary, liver	25% renal 75% biliary
Assay	PT/INR	aPTT / TT / dilute TT	? PT / Anti-factor Xa	Anti-factor Xa
Drug Interactions	CYP 2C9	Potent P-gp inhibitors/ inducers;	Potent P-gp inhibitors/ inducers; CYP3A4 inhibitors/ inducers	Potent P-gp inhibitors/ inducers; CYP3A4 inhibitors/ inducers

If we look at pharmacokinetic data, we know that warfarin has a long half-life and can take days to wear off. With warfarin, you have AC therapy in the blood for three or four days, and you will generally still be anticoagulated, even if you miss a dose or two. If a dose is missed with a new OAC, drug effects will wear off much more quickly and could potentially have a deleterious impact. Therein rests the challenge of this new landscape.

With the newer therapies we do have both once and twice daily dosing, and as has been pointed out, we could see diminishing adherence with a twice daily OAC.

With warfarin, it's crucial for monitoring to take place. As clinicians, we don't like it, and it can be an inconvenience for patients as well, particularly for those who may not drive, who work full time, or who may be house bound. Nonetheless, this routine monitoring does bring the patient back and forth to the doctor's office or AC clinic, and the INR levels can perhaps tell us something about adherence too. With the newer therapies, monitoring is not required, and currently we don't know how often these patients should be seeing see their doctors.

While there are some drug assays available to give us a small bit of information about these newer therapies, the tests themselves are largely inadequate, because they are imprecise, difficult to perform, or slow in delivering results.

Lastly, in comparing the old and newer AC therapies, it's important to note that warfarin can take a week or more to get a patient's INR up to therapeutic range, with the goal being to keep the INR in therapeutic range consistently. You can maintain therapeutic range and monitor it with prothrombin time. Conversely, with the newer OACs, the peak drug effect will occur in the morning or evening, depending on whether it's a once or twice daily dose. We will have a peak and then a trough, and then another peak and another trough. If we try to monitor these newer therapies to detect adherence, we face the question of when to monitor. Do we monitor in the peak or in the trough or in the middle of the day? You cannot monitor the newer AC therapies in the same way as warfarin, because the many variables you will encounter in doing so will yield nonsensical results.

	Warfarin	New Agents
Onset	Slow	Rapid
Half-Life	Long	Short
Dosing	Variable	Fixed
Dietary Interaction	Yes	Minimal
Drug Interaction	Yes	Less
Monitoring	Yes	No
Antidote	Yes	No

Is adherence a problem with warfarin?

INR testing with warfarin, however, does not provide a panacea. Warfarin is no stranger to nonadherence, as demonstrated by several important studies, including:

- 36% of out-of-range INRs were due to non adherence in a cohort of 347 patients over a year (Waterman et al. *Effect of warfarin nonadherence on control of the INR.* Am J Health Syst Pharm 2004; 61:1258)
- Nonadherence occurred in 21% of patient days observed in a cohort of 111 patients initiating warfarin therapy; 92% of patients missed at least one bottle opening and 36% missed > 20% of their bottle openings (Platt et al. *Risk factors for nonadherence to warfarin: results from the IN-RANGE study.* Pharmacoepidemiol Drug Saf 2008; 17:853)
- Poor compliance with INR monitoring appointments was associated with a decreased percentage of INRs-in-range and a moderate increase in thromboembolic events (HR 1.51) but no increase in bleeding events. (Witt et al. *Nonadherence with INR monitoring and anticoagulant complications*, submitted)

Advantages and Disadvantages of New Anticoagulants

The advantages and disadvantages of these new anticoagulants can be summarized as follows.

- Rapid onset of action, eliminates 2 drug regimen when patients present with a thromboembolic event. Patients can be started on drug therapy and sent home when stabilized, offsetting the need for hospital admission.
- Rapid offset of action, advantageous if you have bleeding problems, and also offsets the need for bridging if other procedures are needed. It does, however raises concern about adherence.
- Predictable therapeutic effect, fixed dosing, limited drug interactions, and no need for monitoring, eliminates burden on patient and physicians related to routine testing, but reduces visits to foster adherence.
- More convenient, eliminates 2 drug regimen and no monitoring.
- Possible superior efficacy and safety, better outcomes; more therapy.
- Potentially more cost effective, but out-of-pocket expense may impact adherence.

Important Questions to Consider

In moving forward, there are a number of questions that need to be considered:

- Which patients are candidates for new OACs? Prevention and/or management among patients with AF, VTE, acute coronary syndrome, mechanical heart valves, and for patients needing VTE prophylaxis.
- What factors will play a role in the decision to use a new OAC? At the onset of a new disorder the newer therapies will be considered. In switching a warfarin patient to a newer therapy, it will be important to evaluate adherence. If patients are unstable on warfarin, they may be a good candidate, unless they are unstable due to nonadherence.
- What factors might discourage new OAC use? Patients deemed unreliable with drug use/monitoring.
- Where and by whom will AC services be provided in the future? Primary care physicians, cardiologists, neurologists, family practitioners, vascular surgeons, emergency medicine physicians, orthopedists. This matter, however, also points to the issue of AC management clinics, which have been built up over the years to manage a drug, not necessarily a disease, and now OAC drug monitoring is not needed.
- What role will pricing of new OACs play in their use? We will need to evaluate over time the cost effectiveness of these new therapies to determine how price points and co-pays impact our patients?

Meera Viswanathan, PhD

Director, RTI-UNC Evidence-based Practice Center, RTI International

Anticoagulation Management: New Challenges in a New Era of Anticoagulation Therapy

Despite advances in medicine, numerous published studies and reports demonstrate the gap between expected and achieved outcomes from pharmacotherapy. Non-adherence to treatment is one explanation for this gap. A comparative effectiveness review prepared for the Agency for Healthcare Research & Quality (AHRQ) suggests that numerous pathways provide opportunities to improve medication adherence across a spectrum of clinical conditions.

Our team assessed the effectiveness and comparative effectiveness of interventions set in the United States that are:

- Seeking to improve medication adherence for adults with chronic health conditions
- Directed at intervening with patient, provider, systems, or policy to improve medication adherence for this same population

This systematic review of published studies and reports was supported by AHRQ Contract 290-2007-10056, with the involvement of several authors.

A copy of this report is available at the following link:
http://www.effectivehealthcare.ahrq.gov/ehc/products/296/1248/EvidenceReport208_CQGMedAdherence_FinalReport_20120905.pdf

A description of the report and its findings, as reported in the Annals of Internal Medicine, is found at the following link: http://annals.org/article.aspx?articleid=1357338

What we do know today is that suboptimal medication adherence is common and costly. Research has shown that 20-30% of prescriptions are never filled, and 50% of medications are not taken as prescribed.[1,2] Also, non-adherence leads to 10% of hospitalizations and 125,000 deaths annually.[1] Further, nonadherence contributes to $100-289 billion in healthcare costs annually.[1, 3-5] (1. Peterson, AM et al., 2003, 2. Haynes, RB et al., 2008. 3. Mahoney JJA, Fleming WK, Butterworth SW, 2008, 4. New England Healthcare Institute, 2009, 5. Showalter, A, 2006)

What is unclear is the expected rate of nonadherence with newer anticoagulation therapies. In sharing the results of our extensive review, we hope to inform the anticoagulation community about how to focus on this important issue.

Adherence and Persistence

In our work, we looked at both adherence and persistence. We define these two factors as follows:

- Adherence: Pertaining to the timing, dose and frequency prescribed
- Persistence: Pertaining to the duration therapy was prescribed, which may be over a life time for many chronic conditions

It's important to note that we looked specifically at interventions focused on medication adherence and/or persistence. We did not look at the efficacy of a drug that might happen to look at adherence as a secondary outcome, which may explain why we didn't come across many warfarin studies. Also, we only looked at adults, and therefore our findings are not applicable to children. Further, we looked only at chronic health conditions, as opposed to drug use and mental health for which studies into cognitive processes might be different and influence adherence.

Study Eligibility

The inclusion and exclusion criteria involved with this assessment are outlined in the table below:

PICOTS	Inclusion	Exclusion
Population	Adults prescribed medication for secondary or tertiary prevention of chronic diseases	Adults on over-the-counter medication Primary prevention medication Infectious diseases: (HIV/AIDS) Mental illness (psychosis, bipolar) Substance abuse medications
Interventions	Prescribed, self-administered medications	Primary prevention measures (screening, diet, lifestyle changes)
Outcomes	Medication Adherence Health-related outcomes	All other outcomes when interventions did not result in improved medication adherence
Time Period	January 1, 1994 – June 4, 2012	Earlier than 1994
Settings	Outpatient, community, or home-based care	Institutional settings (skilled nursing facilities, inpatient)
Geography	United States	All others

We examined five key questions, namely:

KEY QUESTION 1
Among patients with chronic disease with self-administered medication prescribed by a provider, what is the comparative effectiveness of interventions aimed at patients, providers, and/or systems in improving medication adherence? And, is improved medication adherence associated with improved health related outcomes?

KEY QUESTION 2
Among patients with chronic disease with self-administered medication prescribed by a provider, what is the comparative effectiveness of policy interventions for improving medication adherence? And, is improved medication adherence associated with improved health-related outcomes?

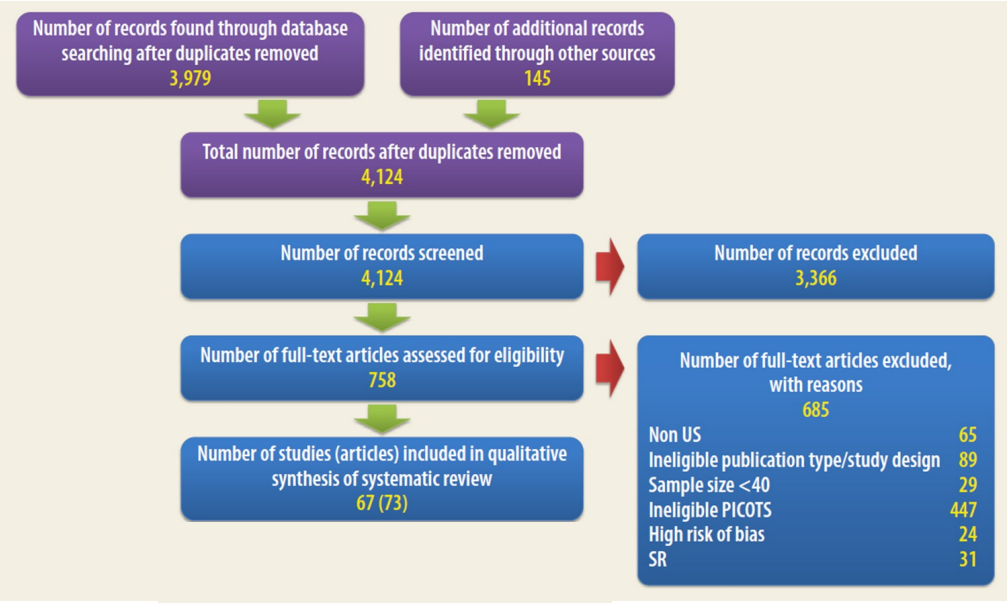
KEY QUESTION 3
How do medication-adherence intervention characteristics (e.g., mode of delivery, intervention, target, intensity) vary? To what extent do the effects of adherence inventions vary based upon their characteristics?

KEY QUESTION 4
To what extent do the effects of adherence interventions vary based on differences in vulnerable populations?

KEY QUESTION 5
What unintended consequences are associated with interventions to improve medication adherence?

Flow of study

We started with a pool of 4,124 records, and found 67 relevant studies published in 73 articles. Of these, 62 involved patient provider systems interventions and five involved policy interventions.



FINDINGS

KEY QUESTION 1 RESULTS

Patient provider or systems interventions, medication adherence outcomes

In 33 of 62 randomized controlled trials, we saw statistically significant improvements in medication adherence. This body of evidence showed tremendous heterogeneity, so we were unable to do a meta analysis.

Clinical Condition	RCTs[a] (improved adherence[b]); patients	Intervention Types	Number of RCTs by Intervention Type (improved adherence[b]); patients	Strength of Evidence
Hypertension	18 (8); 9,691	Blister packaging	1 (1); 93	Low for benefit
		Case management	3 (2); 516	Low for benefit
		Collaborative care	3 (0); 1,194	Low for *no* benefit
		Education (pharmacist, in person)	3 (2); 348	Low for benefit
		Education (& behavioral support)	6 (3); 7,252	Low for benefit
		Education (& social support)	1 (0); 199	Insufficient
		Risk communication	1 (0); 89	Insufficient
Depression	13 (8); 11,445	Case management	4 (4); 690	Moderate for benefit
		Collaborative care (telephone + in person)	5 (3); 921	Moderate for benefit
		Telephone counseling and monitoring	2 (0); 270	Insufficient
		Reminders (to nonadherent patients)	1 (1); 9,564	Low for benefit
Hyperlipidemia	9 (4); 19,228	Collaborative care	1 (0); 329	Insufficient
		Decision aids	2 (1); 248	Insufficient
		Education (& behavioral support)	5 (2); 18,492	Low for benefit
		Multicomponent (face-to-face education & blister packaging)	1 (1); 159	Insufficient

Although numerous approaches may improve adherence, we were not able to say which interventions work best under which conditions.

Some interventions may work only in some specific clinical areas. For example, collaborative care works well in depression, when care may be optimized when primary care physician talks to the psychiatrist, but it remains unclear what role collaborative care might play in hyperlipidemia.

Self-management was shown to work for asthma, but we saw no evidence that it worked or was even tried in other areas.

One factor that did seem to work more generally, or may be applicable across a broader spectrum of clinical categories, is educational and behavioral support. We saw evidence that it worked in multiple clinical areas. Interventions like education and counseling and behavioral support like a telephone call or video or other types of reminders do seem to work.

Clinical Condition	RCTs[a] (improved adherence[b]); patients	Intervention Types	Number of RCTs by Intervention Type (improved adherence[b]); patients	Strength of Evidence
Diabetes	6 (1); 1,056	Case management/collaborative care	3 (1); 569	Low for benefit
		Education (& social support)	1 (0); 199	Insufficient
		Health coaching	1 (0); 56	Insufficient
		Telephone counseling by pharmacist	1 (0); 232	Insufficient
Heart failure	5 (4); 719	Access to electronic medical records	1 (0); 107	Insufficient
		Case management	1 (1); 156	Low for benefit
		Education (& behavioral support)	1 (1); 82	Low for benefit
		Multicomponent pharmacist-led	1 (1); 314	Low for benefit
		Reminder video and telephone calls	1 (1); 60	Low for benefit
Myocardial infarction	1 (1); 907	Education (& behavioral support)	1 (1); 907	Low for benefit

Another factor the literature showed to be useful or working across multiple clinical areas is case management in diseases like hypertension, depression, diabetes, heart failure. Among the 33 studies with improved medication adherence, 26 of them also evaluated clinical outcomes and 18 of these 26 (69%) found improvements in clinical outcomes.

KEY QUESTION 2 RESULTS

Policy intervention

Some of the most promising findings were seen in the area of policy intervention. We saw one trial and four cohorts in which the potential impact of reducing out-of-pocket expenses, by improving coverage or reducing co-pays, was evaluated. All five of these efforts evaluated adherence to cardiovascular medication.

Three also evaluated adherence to diabetes medications, and one also evaluated adherence to respiratory medications.

Clinical Condition	Number of Studies[a] (improved adherence); patients	Intervention Types	Strength of Evidence
Cardiovascular disease	5 (5); >70,000	Improved prescription drug coverage[b]	Moderate for benefit
Diabetes	3 (3); ~20,000	Improved prescription drug coverage[b]	Moderate for benefit
Respiratory Conditions	1 (0); Not reported	Reduced medication copay	Insufficient

Unlike Question 1, where hundreds of patients were evaluated, in Question 2 we are looking at tens of thousands of patients. For example, the number of patients for cardiology in Question 2 is greater than 70,000 and more than 20,000 for diabetes.

In both cardiovascular disease and diabetes, the evidence of these studies show that intervention involving improved prescription drug coverage as being moderate for benefit.

One of these studies also looked at clinical outcomes and found:

- A 14% reduction in first vascular events
- A 26% reduction in total patient spending (pharmaceutical and non pharmaceutical)
- No change in total insurer payments (pharmaceutical and non pharmaceutical)

KEY QUESTION 3 RESULTS

Medication adherence intervention characteristics

In terms of the agenda for this meeting, Question 3 speaks most directly to our interests, as it looks at some of the most effective interventions and potential ways they can be scaled up. In these studies, researchers looked at several factors and several intervention characteristics were recorded, including:

- Intervention target
- Intervention agent (who delivers the intervention)
- Mode of delivery
- Intensity of intervention
- Duration of intervention
- Components of intervention

In evaluating these studies, the results show how difficult adherence can be to address, and the level of time and resources required to address it effectively or successfully. Clearly, there are complexities to be seen in those things that do work. In terms of the characteristics of interventions, we found:

- Intervention target:
  - Nearly 60% addressed systems or policy change, or addressed multiple sources of change
  - 40% directed at patients alone

- Agent of intervention delivery
  - Pharmacist, physician, or nurse delivered about half of interventions.
  - Remainder delivered by automated systems, multidisciplinary teams, care managers, medical assistant, health coach, and so on
- Mode of delivery
  - About half of interventions involved at least some face-to-face delivery
- Intensity of intervention
  - Range for number of contacts: 1 to 30
  - Range for frequency: daily to once in 3 months
  - Range for total contact time: 6 minutes to 12 hours
  - 58% of 26 trials reporting information had less than 2 hours total contact time
- Duration
  - Duration ranges from 4 weeks to 2 years (N=38 interventions)
  - Mode: 6 months
- Number of components
  - Range: 1-9
  - Mode: 3

Common Intervention Components

In terms of common intervention components, the following occurred in more than 10% of interventions:

- Knowledge (77% of interventions)
  - Enhanced memory and understanding, information about consequences of health behavior
- Awareness
  - Risk communication, reflective listening, behavioral feedback
- Facilitation techniques
  - Ongoing professional support, dealing with adverse effects, individualizing/simplifying regimen, reducing environmental barriers
- Self-efficacy
  - Modeling, practice, verbal persuasion, coping responses, graded tasks, reattribution of success/failure
- Intention formation activities
  - General intention, medication schedule, goals, behavioral contract
- Action control
  - Cues/reminders, self-persuasion, social support
- Addressing attitudes
  - Targets attitudes toward behavior

Head-to-Head Interventions

We also looked for head-to-head interventions, and found only four relevant studies. These studies showed no difference for telephone versus video reminders, physician versus research staff in delivering decision aids, high versus low intensity in nurse case management. Shared decision making was superior to clinician decision making.

KEY QUESTION 4 RESULTS

Vulnerable populations

We looked for evidence on vulnerable populations for example, low health literacy, co-morbid disease or severe illness, elderly, low income, under– or uninsured, inner city or rural populations. We saw a low strength of evidence of benefit for African American patients with depression and diabetes, patients with depression (including major and severe depression) and co-existing hypertension, and elderly patients with diabetes, hyperlipidemia, heart failure and hypertension. We found insufficient or no evidence for other vulnerable populations.

KEY QUESTION 5 RESULTS

Harms

Only three studies gave us insights into the potential harms of efforts to improve adherence, and these were heterogeneous in terms of interventions and outcomes, providing insufficient evidence.

Limitations

Limitations of this body of evidence included:

- Heterogeneity in adherence measures
- Poor reporting on intervention characteristics
- Lack of focus on mediators
- Limited information on QOL, patient-reported outcomes, and patient satisfaction
- Limited information on costs and long term health outcomes

Conclusion

Numerous pathways provide opportunities to improve medication adherence across a spectrum of clinical conditions, and research shows a subset of these effective interventions relate better adherence to better health outcomes. Further research is needed to explore:

- Interventions that work best in vulnerable populations
- How interventions compare with one another
- The additive effect of combining interventions
- What specific elements of interventions best improve adherence
- How adherence can be further linked to health outcomes

Julie Kuhle, BS Pharm
Senior Director Performance Measurement, Pharmacy Quality Alliance

Adherence as a Performance Measure for Newer Anticoagulant Therapies

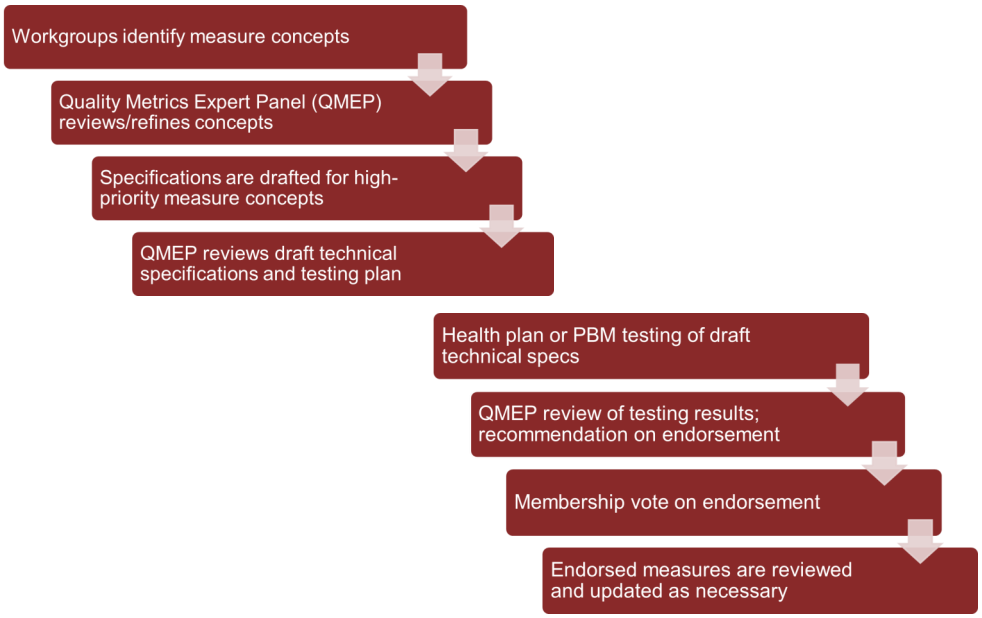
The Pharmacy Quality Alliance (PQA) was established in 2006 as a public-private partnership. The organization was formed in response to the Medicare Modernization Act of 2005, which required medication use performance measures for health plans. In brief, the mission of PQA is to improve the quality of medication management and use.

PQA is a consensus-based, non-profit, alliance with more than 80 member organizations, including: health plans and pharmacy benefits managers, pharmacies and professional associations, Federal agencies (CMS, FDA), pharmaceutical manufacturers, consumer advocates, and technology and consulting groups.

Some of the key activities of our organization include the development of quality measures for pharmacy services and drug plans, the formation and collaboration of workgroups to identify key measure concepts in areas such as safety, adherence, clinical appropriateness, the development and testing of technical specifications, the maintenance and updating of approved measures, and the implementation of demonstration projects for pharmacy quality measures. We also provide education for pharmacists on quality measures and performance improvement, connect pharmacy to healthcare quality initiatives, and conduct several "best practices" seminars and forums throughout the year and at our annual meeting.

PQA accomplishes its work through workgroups, with about 4 to 10 representatives from the member organizations on each workgroup. These workgroups meet monthly by phone to accomplish their work. PQA has an Adherence Workgroup and, given the growing interest in adherence as a performance measurement, this year formed a second Adherence Workgroup to meet the high degree of interest in this area right now.

PQA's process for the development of performance measures is complex. It involves the following steps:



Driver for Adherence — Medicare Star Ratings

One driver for adherence to medications is the Medicare Part C and D Star Ratings, which are based on a number of different domains and quality measures. Medicare Part D plan sponsors receive a summary rating on quality, as well as four domain scores (18 individual measures in total). There are five measures from PQA that Medicare Part D implements or uses within their Star Ratings. These are:

- 2 measures of medication safety
  - — High risk medications in the elderly
  - — Appropriate treatment of blood pressure in persons with diabetes
- 3 measures of medication adherence
  - — Oral diabetes medications
  - — Cholesterol medication (statins)
  - — Blood pressure (renin-angiotensin-aldosterone inhibitors)

Due to the higher weighting of clinically relevant measures, the PQA measures account for 47% of Part D summary ratings in 2012.

Money as a Driver of Adherence

Medicare Advantage plans have a new payment system that started in 2012. This is very important now, because the star ratings will affect payment to Medicare Advantage plans wherein higher-rated plans get higher payment. Quality Bonus Payments (QBPs) will be awarded on a sliding scale according to star ratings, and the 2013 payments are based on 2012 ratings which were based on 2010 data. Stand-alone Part D plans will have marketing advantages related to star ratings, but not QBPs.

Stars Rating	QBP Percentage for 2012/2013	QBP Percentage for 2014
Less than 3 stars	0%	0%
3 stars	3%	3%
3.5 stars	3.5%	3.5%
4 stars	4%	5%
4.5 stars	4%	5%
5 stars	5%	5%

QBP is a percentage increase in payment to the plan above the standard rate. For plans with less than 5 stars, the standard rate may be capped at pre-ACA rates. For more details, https://www.cms.gov/MedicareAdvtgSpecRateStats/

This will be a huge driver and plans will be looking to increase their scores, or their overall star ratings, to obtain the QBPs or marketing advantages. Right now, prescription drug plans are trying to figure out how to do this. By analyzing the data, plans can determine how to target certain populations with poor adherence scores. Plans may make adjustments to help patient receive medication with fewer barriers, such as reduced copayment or zero copayment or they can provide patients information about the importance of adherence.

Adherence Measures

There are several methodologies that could be used to measure adherence, but percentage of days covered or PDC is the one used by PQA. PDC is a widely accepted measure and also generally accepted by the National Quality Forum. PDC measures the percentage of days that a patient is covered by a prescription claim in that category, or by a certain drug, throughout the year. PQA looks for a PDC threshold of 80%. The PDC threshold is the level above which the medication has a reasonable likelihood of achieving the most clinical benefit. Clinical evidence provides support for a standard PDC threshold of 80%.

There are two problems, however, that we do need to address. First, we recognize that if a patient has the drug we can't be sure that they are adherent. Even if they open the bottle, we can't be certain that they actually took the medication. Second, an 80 percent adherence or threshold rate is the standard reported in the literature, and we want to look at a threshold that will allow patients to have positive outcomes. However, we don't know exactly what that threshold should be for each therapeutic class of medications. Therefore, we are working with the 80% threshold. For HIV/AIDS, the adherence threshold is 90%, because adherence to these medications is so important. It has been suggested that for OACs we too should consider a 90% threshold.

Rationale for Adherence Measure for Non-Warfarin Oral Anticoagulants

The rationale for PQA's adherence measure is:

- Adherence to all anticoagulants is important.
- Adherence to non-warfarin oral anticoagulants may be more critical to monitor since there isn't a surrogate lab value such as INR.
- Warfarin was not included in this adherence measure due to frequent dosing adjustments to therapy, which makes an accurate calculation of adherence based on prescription claims improbable.

Description of Adherence Measure

The description for PQA's adherence measure is:

- The percentage of patients 18 years and older who met the Proportion of Days Covered (PDC) threshold of 80% during the measurement period for: Non-warfarin oral anticoagulants or apixaban, dabigatran, rivaroxaban.

Denominator

Importantly, the data source is prescription claims data, as Part D Prescription Drug Plans do not have diagnosis data. Without diagnostic data, PQA needed to construct a denominator to ensure that they were only looking at patients using the medication chronically. Therefore, the denominator is:

- Patients who filled at least two prescriptions for a non-warfarin oral anticoagulant on two unique dates of service at least 180 days apart during the measurement period AND who received greater than 60 days supply of the medication during the measurement period. Patients who received one or more prescriptions for warfarin, enoxiparin, daltiparin, fondaparinux, heparin are excluded.

Numerator

The numerator in this measurement is the number of patients in the denominator who met the PDC threshold during the measurement year. There are several steps to determine this for each patient in the denominator:

- Step One — Determine the patient's measurement period
- Step Two — Count the days the patient was covered by at least one drug in the class based on fill dates and days supply
- Step Three — Divide the number of covered days by days in the measurement period, multiply by 100, report as percentage for each patient
- Step Four — Count the number of patients who had a PDC of $\geq$ 80%, then divide by the total number of eligible patients

Questions for Testing

Several health plans tested this measure, addressing questions from the PQA workgroup and quality metrics expert panel. These questions were:

- What is the nature of the population?
  — Size, to ensure that the population is large enough
  — Age distribution
  —Percentage of low income subsidy
- How many subjects in the denominator?
  —Of the population, who fit the denominator by age, and how many were excluded due to warfarin.
- How many subjects in the numerator?
  —Split by age
- How many subjects in the denominator have ICD-9 codes for DVT, thrombophlebitis? This was done to look for a more acute population still captured in the denominator.

Testing Results

In the chart below, the four plans — Plan A, Plan B, Plan C and Plan D — appear on the left. Plans A, B and C are Medicare plans. Plan D is a commercial plan, and therefore it's population is going to be younger.

Plan / # of members	Members in age range	Age range (years)	Denominator #	Numerator #	Rate
Plan A / 126,024	56,503	19-74	385	323	83.9%
Plan A / 126,024	126,024	19+	1315	1126	85.6%
Plan B / 194,253	106,173	19-74	365	273	74.8%
Plan B/ 194,253	194,253	19+	1218	927	76.1%
Plan C / 1,770,000	n/a	n/a	7351	5238	71.3%
Plan D / 1,690,000	n/a	n/a	774	577	74.6%

PQA relies on their member organizations to provide the testing information requested, sometimes not all of the information is provided. Plans C and D, for example, only provided the denominator, the numerator and a percentage. However, plans A and B did provide all information requested, allowing us to look at age break-down based on our measure and to see who fell into the numerator and denominator.

Most important to note with these results is that the rate varied. A variation in rate, as we see in these results, is a very important factor for a good quality measure, because it demonstrates that there clearly is room for improvement.

A few other points to note: Plan B had a high low-income subsidy (LIS) and their adherence rate is less. This is similar to other adherence measures where a high LIS population often has a lower adherence rate. Also, since Plan D is commercial, they had a smaller population that fell into the numerator and denominator, because they had a much younger overall population in their plan. Also important to note, we were concerned about age and whether there would be a change or variation in PDC based on age. We didn't see that. The younger population of 19–74 doesn't vary much from those in the older age group. Also, when we included the group aged 75 and older, the population for the denominator jumps significantly, which means we would be missing a majority of people taking these OACs if we were to limit the measure to a younger population.

Additional results

The chart below shows some additional results with the same four plans. Important to note here, we wanted to look at the health plan's total population and determine how many people fell into the denominator, or in the population how many people are using OACs chronically. We see in Plan D, with the younger population, that fewer were using OACs chronically, but with Plan A and Plan B it is more significant. Lastly, looking at Plan A, which also included medical and diagnostic data, or the number of patients using OACs relative to an ICD-9 for DVT, we see a low percentage for this acute indication.

Plan / age range	Members in age range	Denominator	% members in denom (by age)	# / % of pts in denom w/ ICD-9 for DVT
Plan A 19-74	56,503	385	0.68%	19 patients with ICD-9 4.9% of denominator
Plan A 19+	126,024	1315	1.04%	57 patients with ICD-9 4.3% of denominator
Plan B 19-74	106,173	365	0.34%	
Plan B 19+	194,253	1218	0.63%	
Plan C Medicare	1,770,000	7351	0.42%	
Plan D commercial	1,690,000	774	0.05%	

Testing Take Away Points

From this testing, PQA learned that:

- The measure is feasible
- Variation exists between different plans
- There is room for improvement
- Adherence is lower in populations with higher LIS
- Denominators increase significantly with inclusion of 75+
- Variation in PDC rate by age doesn't appear to be significant
- Percent of patients in denominator treated for non-AF indications appears to be low

Next Steps

PQA will share results of testing and take comments and questions from its membership. PQA will call for endorsement of this measure during its Annual Meeting in May 2013.

Updated Outcome

At the PQA Annual Meeting, May 28-30, 2013, in Washington, DC, PQA *members voted to endorse the following new performance measure:* Adherence to Non-Warfarin Oral Anticoagulants. The measure, *Adherence to Non-Warfarin Oral Anticoagulants*, addresses the percentage of patients 18 years and older who met the Proportion of Days Covered (PDC) threshold of 80 percent during the measurement period for the non-warfarin oral anticoagulants apixaban, dabigatran and rivaroxaban. Adherence to all anticoagulants is important to decrease risk of stroke, pulmonary embolism and deep vein thrombosis. This measure addresses an important safety concern because adherence to these new drugs cannot be monitored through a surrogate lab value, such as INR. The half-life of these medications is short (in comparison to warfarin), so adherence to these non-warfarin anticoagulants may be more critical to monitor.

Margaret Fang, MD, MPH

Associate Professor of Medicine, Division of Hospital Medicine, UCSF
Medical Director, UCSF Anticoagulation Clinic

As a hospitalist and researcher, I've seen first-hand many of the barriers that lead patients to nonadherence, but I've also seen the ability of patients to adhere to OACs.

Adherence is often viewed as the patient's responsibility, with the health system and provider reinforcing the ability of the patient to adhere. Persistence, or the planned duration of therapy, is determined more from a clinician's perspective.

The management or control of OACs is strongly connected to clinical outcomes. Moving too far in one direction results in elevated bleeding risk; moving too far in the other direction results in elevated thrombosis risk. We know this is true of OACs like warfarin, and it's clear that this will be the case with the newer OACs as well.

Despite knowing adherence is vital and important to efficacy, adherence and persistence rarely reach 100 percent in clinical practice:

- Patients on warfarin for atrial fibrillation are in target INRs only ~55% of the time
- ~22%-33% of patients newly started on warfarin for atrial fibrillation discontinue therapy within the first year of treatment
- Effectiveness of anticoagulation is compromised by inadequate treatment

(Baker et al, J Manag Care Pharm 2009)

ATRIA Study

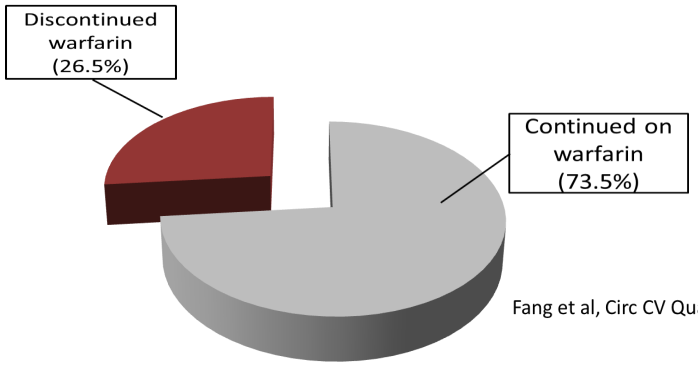
In the ATRIA study, we looked at the issue of persistence. This study involved a community based cohort of patients enrolled in Kaiser Permanente of Northern California. These are patients who all have a prescription drug plan. More than 80 percent of these patients were enrolled in a dedicated AC clinic or standardized AC management clinics.

We studied 4,188 patients who were newly starting warfarin for AF and followed them for a median of 4.6 years. We followed them based on a metric of adherence we developed to show whether a patient filled/refilled a prescription and had regular INR measurements. To navigate the issue of dosing or changes in dosing, we tied pharmacy and prescription data into these metrics.

The goal was to describe the persistence of therapy when newly started and hopefully identify risk factors for discontinuation to help modify interventions to maintain adherence in the future.

Findings: Warfarin Discontinuation in the First Year

Despite being in an integrated health system with pharmacy coverage – we found that more than one in four (26.5%) patients we studied had discontinued therapy within the first year.

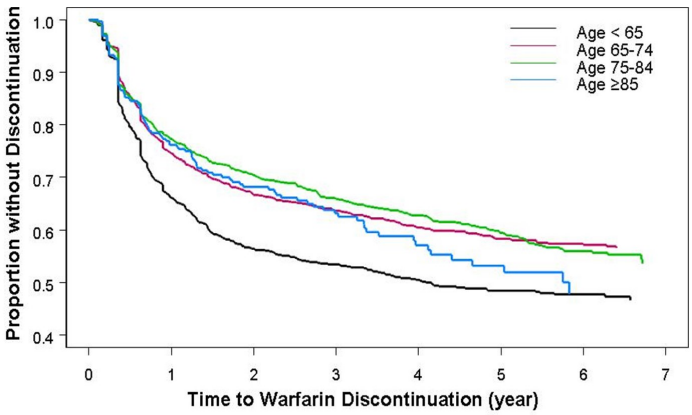


Fang et al, Circ CV Qual Outcomes, 2010

Discontinuation by Age

Then we looked at who had discontinued by age, hypothesizing that older patients in the cohort might have more problems maintaining therapy.

What we found, however, was the opposite: The youngest patients discontinued therapy the fastest, and there was no significant difference in discontinuation rates among the older patients.

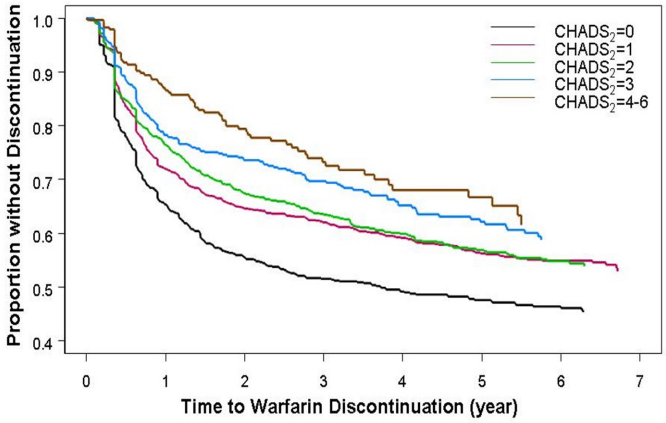


Discontinuation by $CHADS_2$ Scores

We also looked at the appropriateness of therapy. We often think of adherence in terms of being "good" and nonadherence being "bad." We have to consider appropriateness of therapy however.

When we stratified our population by $CHADS_2$ Score, the lower the score the more likely a patient was to discontinue therapy. The higher a $CHADS_2$ score, the more likely the patient was likely to stay on therapy. We found, however, that even the patients at highest stroke risk didn't have 100% adherence.

This finding shows that stroke risk may affect adherence and persistence of therapy.



Hemorrhage Leading to Discontinuation of Therapy

There also are situations where it is clinically appropriate to discontinue therapy, with hemorrhage probably being the most prominent cause. We looked at rates of major hemorrhage in the first year, and it was just 2.3% of the cohort. Of the 263 patients in our study who were hospitalized for hemorrhage, 65% subsequently discontinued warfarin therapy.

Predictors of Discontinuation

Taking clinically indicated discontinuation out of the equation, we ran our model to look for some of the other predictors for discontinuation and we found:

- Younger people are more likely to discontinue therapy
- Men are more likely to discontinue therapy
- The less time spent in therapeutic range (INR), the more likely a person will discontinue therapy
- People with lower $CHADS_2$ Scores are more likely to discontinue therapy.

We tried to limit known or planned discontinuation (e.g., ablation or cardioversion). However, there may be alternative clinical explanations for why patients discontinue therapy that we were unable to measure.

Risk factor	Adjusted Hazard Ratio (95% CI)
Age	
<65	1.33 [1.03-1.72]
65-74	1.14 [0.88-1.46]
75-84	1.01 [0.79-1.30]
≥85	Referent
Female	0.86 [0.76-0.96]
% time in therapeutic INR range (per 10% decline)	1.46 [1.42-1.49]
CHADS2 Score	
0	2.54 [1.86-3.47]
1	1.98 [1.46-2.70]
2	1.65 [1.20-2.25]
3	1.22 [0.87-1.71]
4-6	Referent

Lastly, what we're not able to ascertain from this study is what happens in discussions between patients and clinicians, in terms of patient preferences, perceptions of risk, and the shared decision-making process that can also influence adherence.

A study similar to ours — published from the *Get with The Guidelines/Stroke* project — and the AVAIL Registry, pointed to these types of factors. In this study involving 106 US centers, 31% of 180 stroke survivors prescribed warfarin discontinued therapy within the first year. When surveyed, one-quarter of these patients said it was a provider-driven decision.

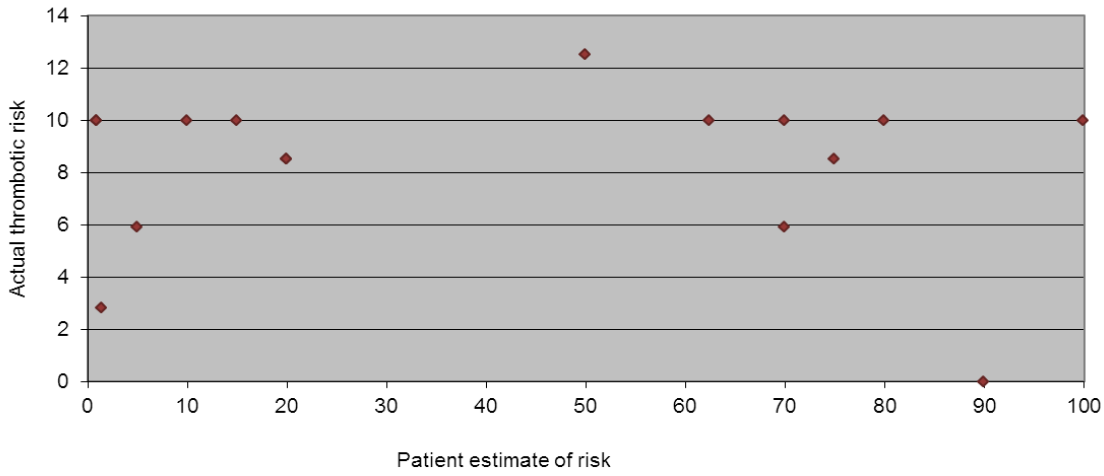
Therefore, again, it's not always all one factor or another. Rather, it's an intersection of patient, provider, and the larger healthcare system. This study reinforced the idea that adherence is related to beliefs about medication and treatment, and whether patients perceive the medications as beneficial or they have specific concerns about a medication, as well as the stability of the medication routine. The way in which these factors intersect with provider interactions and the larger health system will influence or impact adherence. (O'Carroll et al, Ann Behav Med, 2011; Chambers et al, Br J Health Psych, 2010)

There are multiple barriers to effective adherence, and in studies of the secondary prevention of stroke, we see several. In one such study among 600 inner city stroke survivors, interviews with these subjects showed some of these additional barriers were:

- Increased concerns about medications
- Low trust in doctor
- Problems with communicating with doctor due to language
- Perceived discrimination by the healthcare system
- Difficulty accessing healthcare and poor continuity of care

To attempt to highlight how patients perceive or process information, we conducted a pilot study in our AC clinic. We surveyed 16 patients newly started on OAC therapy in our clinic. Most of these patients had been hospitalized and had counseling sessions with our inpatient pharmacists and clinicians, helping educate them about their condition and stroke risk. In this pilot study, we asked them to answer the following question*: If you didn't take warfarin, how likely do you think it is that you would have a stroke or DVT within the next year*?

The results varied widely:



In some cases, patients said they were 100% likely to have a stroke, for example, and others said they had zero risk. Interestingly, their answers had no relationship to their actual clinical risk.

Perhaps the most important information this pilot study revealed is that the way we present information or the way we participate in shared information and decision making clearly needs some improvement. This is an area where additional work needs to be done.

Will the Newer Oral Anticoagulants Improve Adherence and Persistence?

The question of whether or not the newer OACs will improve adherence and persistence has been raised. Although we don't know that answer yet, one school of thought is that they perhaps can, because they are easier to use and they don't require INR monitoring or dose adjustments. While the newer therapies may be more costly, the patient may no longer have a clinic co-pay or transportation costs associated with routine blood monitoring. These factors may make these newer medications more convenient than warfarin.

One thing to note is that efforts to quantify the effect of warfarin on quality of life have found relatively small effects even compared to daily oral aspirin therapy, which doesn't require monitoring. In the BAATAF randomized trial, no significant differences in quality of life were found between warfarin and aspirin (Lancaster et at, Arch Intern Med, 1991). Therefore, it remains unclear whether these newer OACs will offer any quality of life benefits compared to warfarin.

Comparative Discontinuation Rates

Discontinuation rates in recent trials comparing adjusted dose warfarin to a fixed dose oral comparator — including aspirin, clopidogrel, and the newer OACs — show that the rate of discontinuation is remarkably similar.

Obviously, these are clinical trial situations where patients are selected for adherence and there is a system to help encourage adherence.

What will happen in a real world setting? Perhaps this will be different, but we don't know yet.

Trial	Warfarin	Comparator	Comparator Treatment
ACTIVE W	7.8%	13.8%	Clopidogrel + ASA
BAFTA	33%	24%	ASA
SPORTIF III	14%	18%	Ximelagatran
SPORTIF V	10.6%	10.0%	Ximelagatran
RE-LY	10.2%	15.5%	Dabigatran
ROCKET-AF	22.2%	23.7%	Rivaroxaban
ARISTOTLE	27.5%	25.3%	Apixaban

Effective AC Management:

Focus on Promoting and Simplifying Adherence

Adherence and Persistence

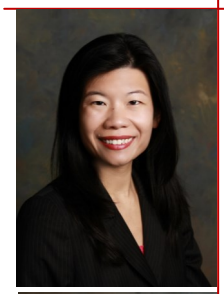
It's not clear that compliance with therapy will be substantially improved with newer oral anticoagulants. The consequences of poor adherence may be more consequential given the lack of ability to monitor adherence via INRs, as well as the shorter half-life of these newer OACs compared to warfarin.

Therefore, it will continue to be important to assess patient perceptions about the risks and benefits of therapy and to screen for potential barriers to adherence.

Working Group Sessions

Atrial Fibrillation Group Moderator: Margaret Fang, MD, MPH
Associate Professor of Medicine, Division of Hospital Medicine, UCSF
Medical Director, UCSF Anticoagulation Clinic

Venous Thromboembolism Group Moderator: Scott Kaatz, DO, MSc
Chief Quality Officer, Director, Hospitalist Program, Hurley Medical Center



During this symposium, two Working Groups were conducted to gain insights and input from all symposium participants. The larger group of symposium participants was broken into two groups: One group focused on oral anticoagulant (OAC) adherence relative to atrial fibrillation (AF), the other group was focused on OAC adherence relative to venous thromboembolism (VTE). The AF Working Group was moderated by Margaret Fang, MD. The VTE Working Group was moderated by Scott Kaatz, DO.

Each group was asked to address and record their input relative to four central topics for discussion:
1. Risk Factors for nonadherence
2. Patient selection relative to adherence intervention
3. Tools and interventions currently in use
4. Additional considerations, future research needs

Working Group Input

The results of these Working Groups, outlined below, were then presented by Drs. Fang and Kaatz:

Question 1. Risk factors for nonadherence

There were several key points related to barriers to adherence that emerged from this discussion. One key point involved the concept of "universal precautions," in other words, standard elements for high quality, safe OAC management. "Universal precautions" relating to OAC management and adherence will encompass many domains, such as accounting for costs of care, the way the system is structured, and adherence to evidence-based standards of OAC management. It is also important to acknowledge that "one size does not fit all," understanding that anticoagulation is an individualized experience that should account for patient experiences/preferences.

- Proposed Action Item: The development of a spectrum of educational materials that are "universal" for HCPs, the OAC patient population (AF and VTE), and the public. These would reflect the core or universal information/education needs in OAC management and adherence. However, with the notion that "one size does not fit all," the individualized adaption or customization of these core materials is recommended to reflect select patient profiles and better meet and target specific HCP and patient information needs. Such diverse materials might range from brochures and DVDs, for example, to infographics, OAC-specific telephone reminder apps, web-based materials, and public health education initiatives.

Question 2. Risk factors for nonadherence

There are likely to be universally recognized barriers (e.g., physical disability, financial difficulties) to nonadherence, as well as nonadherence due to inadequate performance feedback or challenges to effective population management. It was agreed that we need to "diagnose" patients who may be nonadherent, but even if we do so successfully, we still may not have the tools we need to successfully address barriers to nonadherence.

- Proposed Action Item: Develop a system or mechanism that will enable us to assess patient comprehension and understanding in a rigorous way in AC management. Once that system or mechanism is developed, then we can identify tools to help "diagnose" or identify nonadherence, which in turn will drive the development of tools or interventions to help promote adherence.

Question 3. Tools and interventions currently in use

Both groups were in agreement that we need high quality, evidence based, informational tools, and tools that are adaptable to different settings: clinicians, patients, primary care physicians, specialty AC clinics. The role of external agencies or drivers also was discussed, with the idea that there could be great value in some type of public reporting relative to AC clinics (e.g., a national AC Clinic directory, including a description of services with criteria for quality assessments). In this regard, transparency of performance and wide scale dissemination of information was considered a very interesting target of intervention.

Further, two models for HCP education/training also were identified: 1) The University of Wisconsin's method of having an AC Clinic serve as an arm of outreach to other clinics to promote best practices and 2) The National Blood Clot Alliance online curriculum for HCPs.

An important issue that was raised was what the future role of AC clinics should be? Do AC clinics have a role in this era of target specific OACs? It was proposed that a future role of AC clinics might be in the dissemination of best practices, assisting with quality reporting and population management, and the delivery of specialized education and consultation, particularly with newer agents. And, finally, AC clinics also might be able to leverage their collective experience to identify or intervene upon barriers to adherence.

- Proposed Action Item: The research and development of a diverse spectrum of tools that will help healthcare professionals stratify and address or leverage AC management/adherence risks, and also to help AC clinics expand their services to include AC adherence.

Question 4. Additional considerations, future research needs

There was a lot of interest expressed in terms of developing a risk stratification score (similar to a $CHADS_2$ score) for nonadherence. Also, again, it was agreed that core materials need to be developed and continuously updated for newer agents and newer developments. Also, the group expressed interest in exploring ways to link clinical outcomes to newer OACs. In this regard, questions posed included: Should we follow patients on these newer therapies in clinic? Should we order blood tests? What's the best way to optimize outcomes?

- Proposed Action Item: Explore unknowns in the management of newer OACs to help establish a role for AC Clinics to help optimize outcomes in this arena.

Gary Raskob, PhD
Dean, College of Public Health, and Professor, Epidemiology & Medicine, University of Oklahoma Health Sciences Center, and incoming Chair, NBCA MASAB

Closing Remarks

As co-chair of this symposium, I would like to take this opportunity to thank Dr. Jack Ansell, my co-chair, Alan Brownstein, NBCA's CEO, and Lisa Fullam, the Program Director for this symposium, for the work they did to help us achieve the vision we first had for this meeting. We began planning this event just three months prior to the meeting, and the results in the end were quite impressive. I'd also like to thank our faculty for their direction and input, and extend NBCA's appreciation to everyone who attended the meeting, particularly the patients directly affected by AF and VTE who joined us.

Also, on behalf of NBCA, I want to thank our sponsors — Platinum Sponsor Boehringer Ingelheim and Gold Sponsor Janssen — for their support of this important symposium.

In offering up closing or summary remarks for this meeting, I want to touch on the points that struck me as being most noteworthy, including:

- So Much Information, So Few Answers. One of the first items that struck me is how much information we have, but how little we actually know based on definitive, strong evidence. In the systematic review presented, we saw 4,124 studies or records drop dramatically to just 62 that were actually measuring adherence or interventions, of which only 33 show an increase in adherence, but only 26 of those show clinical outcomes.

  We raised several crucial questions during the course of this symposium: Is adherence a problem with the new OACs? Is it a matter of persistence, or is lack of persistence an issue for anyone who has these problems? Is there a difference in adherence seen in AF compared to VTE? Is adherence related to timing, dosing, or missing a dose? The reality today is that we don't really know the clinical importance of many of these factors. To a certain extent, we have assumed we have an adherence issue at hand, because the newer therapies do not require INR monitoring. We have been using or pointing to INR as an indicator that a patient is nonadherent, but we know that INR and TTR are influenced by a number of factors. Therefore, unless a patient tells you that they haven't taken their medication as prescribed, is the situation with warfarin really fundamentally different than what we are going to see with the newer agents? Or, are we just really comfortable with where we've been with warfarin for 60 years, and with our ability to monitor that drug.

  This is no doubt an area that we need to explore further and get in front of in the right way. Specifically, we need to research nonadherence at a finer level to determine what is actually clinically relevant.

- Communication. The presentations we heard today, as well as the input we gathered in our two working group sessions, point to the importance of communication. The skill of the provider as a communicator — in terms of content, style, consistency, and frequency, for example — was raised. We know that patients can't be expected to absorb everything when they are affected by serious health issues. We all also know that some of us are not doing as well as we should as communicators.

  However, the other side of this equation is equally important: Listening. Patient preference is very important, and the practice of evidence-based medicine is actually the intersection of clinical expertise, research evidence, and patient preference. This is an area that we have to give ample consideration to as we move forward.

- Research. Almost everyone who participated in this symposium expressed the need for more research in this area. Fundamental issues about these drugs are not known. For example: Is a fixed dose regimen good for all patients? Are there other subgroups for whom the risk/benefit tradeoffs are not quite what the main overall results should be? We need research to measure and assess adherence and how it relates to outcomes in a clinically relevant way.

  We know we face fiscal constraints, in terms of potential available funding for adherence research relative to the clinical conditions of VTE and AF. Therefore, it's imperative that we be creative and resourceful in our efforts to stimulate funding support for this much needed research. We need, for example, strong public-private partnerships to tackle this issue, we also need our partners at the National Institutes of Health, the Centers for Disease Control & Prevention, and select international bodies, to come together to leverage the crucial issue of adherence in OAC management. We also need strong advocacy, a role that, in addition to improved communications, NBCA can no doubt contribute to quite effectively. Whenever any one of us has a chance to be heard on this matter, we need to make sure that investment in this arena continues to help ensure quality care and a continued reduction in healthcare costs.

- Next Steps. Lastly, I want to touch on the next steps for this program planned by NBCA. Specifically, in upcoming months, our organization will compile and distribute the proceedings of this meeting via NBCA's website, YouTube channel, publicity and widespread distribution. We also will develop screening and educational tools, and conduct impact evaluations of these tools with select AC Forum clinics. Longer term, we will fine tune these screening and educational tools for widespread distribution and use. Also, NBCA will focus on advocacy efforts connected to reimbursement and the Affordable Care Act, seeking opportunities to bring added support to research and quality improvements in OAC management and adherence.

Again, thank you for your involvement with this meeting and your support of NBCA. We value our partnership with you.

Vision

The National Blood Clot Alliance foresees a future in which the number of people suffering and dying from blood clots in the United States is reduced significantly.

Mission

Working on behalf of a broad array of people who may be susceptible to blood clots, the National Blood Clot Alliance advances prevention, early diagnosis and successful treatment of blood clots, clotting disorders and clot-provoked strokes through public awareness building, patient and healthcare professional education and supportive public and private sector policy promotion.

For more information:

National Blood Clot Alliance
Stop The Clot®

National Blood Clot Alliance
120 White Plains Road, Suite 100
Tarrytown, NY 10591

(877) 4 NO CLOT
www.facebook.com/stoptheclot
www.stoptheclot.org

National Blood Clot Alliance
Stop The Clot®

National Blood Clot Alliance
120 White Plains Road, Suite 100
Tarrytown, NY 10591

(877) 4 NO CLOT
www.facebook.com/stoptheclot
www.stoptheclot.org