Guided Antithrombotic Therapy: Current Status and Future Research Direction

Report on a National Heart, Lung and Blood Institute Working Group

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The National Heart, Lung, and Blood Institute (NHLBI) convened a working group to develop a research agenda to enhance the understanding and effectiveness of antithrombotic therapy. The working group brought together cardiologists, hematologists, interventionists, clinical trialists, genetic epidemiologists, basic scientists, and other stakeholders to review (1) coagulation, platelet activation and aggregation, and antithrombotic therapy; (2) issues surrounding antithrombotic therapy failure – how to define it, how to predict and diagnose it, available tests and how to optimize them; (3) the factors that affect the efficacy, safety, and predictability of antithrombotic therapies; (4) how to optimize antithrombotic therapy, improve on present interventions, and individually tailor therapy to increase efficacy and safety and to avoid failure; and (5) the clinical applicability and cost-effectiveness of individually tailored antithrombotic therapy based on functional and genetic testing. The working group characterized and discussed challenges for guided antithrombotic therapy in 4 domains: therapeutic strategies, antithrombotic metrics, pharmacology and pharmacogenetics, and stakeholders’ roles. Overall, the working group identified and prioritized the most pressing clinical needs to focus future research and translational efforts. This report presents highlights of these reviews and a summary of suggested research directions.

Gaps of Knowledge in Clinical Thrombosis

There has been tremendous progress in the field of thrombosis in the past 2 decades. The ramifications on cardiovascular care have been profound. A greater appreciation of the central role of platelets in atherothrombosis and an increased understanding of the receptors involved in platelet activation and aggregation have led to pivotal randomized controlled trials (RCTs) of novel agents. Many of these agents have been associated with substantial reductions in adverse cardiovascular outcomes. Simultaneously, an appreciation of the complexity of the coagulation cascade and the artificiality of separating it from cellular and platelet interactions has promoted a deeper understanding of thrombosis and, consequently, identification of pharmacological targets to prevent thrombosis.

Excessive thrombosis is highly relevant to a variety of disease states. Atrial fibrillation, many forms of stroke, acute and chronic coronary artery disease (CAD), prosthetic heart valves, and venous thromboembolism are all large areas of cardiovascular medicine in which thrombosis is a major part of the pathology. In each of these areas, recent data have expanded our knowledge and clinical armamentarium, with more options available to clinicians than ever before. Nevertheless, large gaps in our knowledge persist in each of these areas.

Atrial Fibrillation

Atrial fibrillation is an important risk factor for stroke and is common in older adults. Its prevalence in the United States is projected to exceed 5.5 million individuals (~1%–2% of the population) by the year 2050. The 2011 American College of Cardiology/American Heart Association (2011 ACC/AHA) Guidelines for the Management of Atrial Fibrillation (2011 ACC/AHA/ESC Guidelines for the Management of Atrial Fibrillation) recommended oral anticoagulation in most patients with atrial fibrillation for stroke prevention. Despite these recommendations, many patients remain undertreated or receive unnecessary treatment. The National Cardiovascular Data Registry, a comprehensive quality improvement organization for cardiovascular care in the United States, reported that only 53.6% of Medicare beneficiaries with atrial fibrillation received oral anticoagulation in 2013.
Cardiology Foundation/American Heart Association/Heart Rhythm Society Guidelines for the management of patients with atrial fibrillation recommend that the selection of the appropriate antithrombotic agent (including aspirin monotherapy) should be based on the absolute risks of stroke and bleeding and the balance of risk and benefit for a given patient.10 Defining these parameters is therefore critical in optimizing outcomes for patients with atrial fibrillation.

Currently, recommended therapy is aspirin in patients without risk factors for stroke, aspirin or warfarin in patients with 1 moderate risk factor, and warfarin in patients with 1 high-risk factor or >1 moderate risk factor.11 Alternative prognostic models for thromboembolic risk include the CHA2DS2-VASc (Cardiac failure, Hypertension, Age, Diabetes, Stroke [Doubled]) and CHA2DS2-VASc risk scores.12,13 Although CHA2DS2-VASc may identify more patients who may benefit from anticoagulation,14 even better risk stratification among low-risk patients would provide clinical value, especially in the setting of newer anticoagulants that are associated with less major or intracranial bleeding in comparison with warfarin.14,15 The validation in larger populations of the incremental utility of imaging data that are specific for thrombosis within the left atrium, such as atrial size, blood stasis, and appendage velocities, would be particularly useful. Development of better risk models and risk scores for bleeding on anticoagulant therapy, particularly the new oral anticoagulants, is also critical.16,17

Warfarin therapy has several limitations, including a narrow therapeutic window, a wide variation in metabolism and numerous food and drug interactions, a requirement for regular laboratory monitoring and dose adjustment, and slow onset and offset of pharmacodynamic effects. Aspirin is less effective than warfarin for nonvalvular atrial fibrillation and is only recommended in patients with low risk for thromboembolism or contraindications for warfarin. Dual antiplatelet therapy with aspirin and clopidogrel is also inferior to warfarin in the setting of atrial fibrillation, although it is superior to aspirin alone.18,19

The safety and efficacy of several new oral anticoagulants in comparison with warfarin have been examined in RCTs of nonvalvular atrial fibrillation. In the open-label Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial, the direct thrombin inhibitor dabigatran 150 mg twice daily significantly reduced the risk of stroke or systemic embolism with a similar risk of major bleeding as warfarin.20 A dose of 110 mg twice daily was also tested in RE-LY but is not approved in the United States. Because dabigatran is cleared primarily by the kidneys, patients with chronic kidney disease may be at increased risk for bleeding. Based on pharmacokinetic data, the US Food and Drug Administration (FDA) approved a dose of 75 mg twice daily in patients with diminished renal function, although there are no large outcome data with this dose. Future research will need to determine the wisdom of approving doses on pharmacokinetic grounds as opposed to large clinical trial evaluation, especially in drugs that need to balance ischemic and thrombotic reduction with bleeding concerns.

Rivaroxaban and apixaban are oral factor Xa inhibitors. In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial, rivaroxaban 20 mg daily was noninferior to warfarin according to the primary intent-to-treat analysis for the prevention of stroke or systemic embolism with similar rates of bleeding and superior to warfarin according to the per-protocol, as-treated analysis,14 whereas in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, apixaban 5 mg twice daily was superior to warfarin in preventing stroke or systemic embolism with less major bleeding.15 These randomized trials differed significantly in their designs, the baseline stroke risk in the populations studied (eg, CHADS2 scores), and time within therapeutic range on warfarin. A comparative trial of the safety and efficacy of direct thrombin (factor IIa) inhibitors versus factor Xa inhibitors is needed, Exploratory pharmacogenomic analyses are required to identify more precisely patients in whom a particular agent would provide greatest benefit. The conclusions about dabigatran, rivaroxaban, and apixaban were derived from RCTs. Clinical trials and/or registry results in all-comer populations will be needed to prove superiority, noninferiority, or inferiority to warfarin in actual clinical practice. Furthermore, real-world registries are required to assess bridging and reversal strategies for patients with different degrees of thromboembolic risk who need to interrupt therapy with one of the newer anticoagulants for planned or emergent procedures.21

Although the direct thrombin and factor Xa inhibitors possess several advantages, the rates of major bleeding with these agents are not insignificant, particularly when considering that the duration of treatment is indefinite. In the ARISTOTLE trial, the rate of major bleeding according to the International Society of Thrombosis and Hemostasis criteria in patients randomly assigned to apixaban was 2.13% per year, and the rate of any bleeding event was 18.1% per year.15 Mechanical approaches to stroke prevention such as transcatheter left atrial appendage (LAA) occlusion may reduce the risk of stroke without exposing the patient to the long-term bleeding hazard of anticoagulation. In a randomized clinical trial involving 707 patients and 1065 patient-years of follow-up, LAA occlusion with the WATCHMAN device was noninferior to warfarin for the prevention of stroke, systemic embolism, or cardiovascular death, at the cost of more frequent procedural complications,22 although procedural safety has improved with increased operator experience.23 The safety and efficacy of this strategy is being explored further in the Prospective Randomized Evaluation of the WATCHMAN LAA Closure Device In Patients with Atrial Fibrillation versus Long Term Warfarin Therapy (PREVAIL) trial. Rigorous, prospective, and preferably randomized data in comparison with anticoagulant therapy are required to determine the relative safety and efficacy of other mechanical approaches to stroke prevention, such as surgical exclusion of the LAA and catheter-based LAA ligation. Furthermore, studies that compare clinical outcomes between LAA occlusion and newer anticoagulants would help ascertain the appropriate role of a mechanical approach within the current paradigm of pharmacological therapies. Comparative trials of different approaches to LAA occlusion would also be
useful, and further research into the appropriate target populations, such as patients with atrial fibrillation and stroke while they are receiving anticoagulation therapy, as well.

Another mechanical approach that may decrease thromboembolic consequences of atrial fibrillation is catheter ablation. Although primarily used to treat patients with symptoms due to atrial fibrillation that are refractory to medical therapy, there may be an additional role in preventing stroke and systemic embolism, although this hypothesis remains controversial and unproven. Preliminary data appear mixed. However, further randomized data are needed to determine any impact of catheter ablation on subsequent stroke risk and the durability of any effect.

Coronary artery disease is common in patients with atrial fibrillation. Treatment of patients with atrial fibrillation who require dual antiplatelet therapy after acute coronary syndrome and/or percutaneous coronary intervention (PCI) is a common clinical dilemma. Triple therapy after PCI with warfarin and dual antiplatelet therapy is associated with a substantial risk of bleeding; in 10 observational studies involving 1349 patients on triple therapy, the pooled rate of major bleeding at 30 days was 2.2% (95% confidence interval, 0.7%-3.7%). Current treatment recommendations are based on expert consensus and follow the general principle of considering the anticipated risk of bleeding and the risk of stent thrombosis for a particular individual. One current approach in patients with atrial fibrillation and a stent is to give 1 to 3 months of triple therapy, followed by an anticoagulant plus an antiplatelet agent. Delineation of the appropriate role, timing, and duration of triple therapy in these patients is required, particularly with the factor Xa and direct thrombin inhibitors, for which clinical experience is limited. Furthermore, which patients ought to be on dual therapy with 1 antiplatelet agent and 1 anticoagulant or those who should only be on anticoagulation 12 months after a stent are all areas that require further research.

Gaps of Knowledge in Atrial Fibrillation and Stroke

From the above review of data, it is clear that there have been significant advances in anticoagulation for atrial fibrillation. The major gaps that were identified are as follows:

- The need for a comparative trial of oral direct thrombin inhibitors versus factor Xa inhibitors, and a comparative trial of alternative factor Xa inhibitors, including comparison of once daily versus twice daily regimens, as well.
- Strategies to improve adherence, which become even more important with therapies that do not require international normalized ratio monitoring.
- Study of mechanical versus pharmacological approaches to thrombus prevention in atrial fibrillation, and maintenance of sinus rhythm as a potential antithrombotic strategy, including with catheter ablation, as well.
- Better risk stratification at the lower end of the thromboembolic risk spectrum and potential incorporation of imaging modalities such as echocardiography and MRI to risk stratification algorithms.
- A registry of bridging strategies.
- Development of novel oral anticoagulants that are not cleared by the kidneys and are safe during pregnancy.
- Delineation of the role of triple antithrombotic therapy after stenting and/or acute coronary syndromes.
- Development of a single point-of-care assay for antiplatelet drugs and anticoagulant agents that provides a global measure of thrombotic risk.
- Study of atrial fibrillation in the setting of valvular heart disease.

Noncardioembolic Ischemic Stroke

Carotid artery and brain imaging are performed using duplex ultrasonography, computed tomography angiography, magnetic resonance angiography, or catheter-based contrast angiography. Although computed tomography and magnetic resonance imaging for screening patients at increased risk for ischemic stroke is becoming more sophisticated, the predictive value and cost effectiveness will need to be proven to move them from research tools to routine clinical practice.

Aspirin is recommended to prevent thromboembolic events in patients with carotid artery disease, whereas warfarin is recommended in patients with mechanical heart valves or atrial fibrillation. Optimal medical therapy also includes angiotensin-converting enzyme inhibitors, β-blockers, statins, and control of risk factors to target levels. Carotid surgery and stenting increase blood flow to the brain and change the atherosclerotic substrate. Whereas there has been great interest in comparing carotid endarterectomy and stenting in asymptomatic patients, neither has been compared with optimal medical therapy in the contemporary era. Given that a significant proportion of revascularization procedures are performed in asymptomatic patients, the added benefit of carotid revascularization in comparison with optimal medical therapy alone needs to be shown to justify continuing this widespread practice.

Major efforts have been made to increase the public awareness of the signs and symptoms of stroke. More success is needed in promoting the importance of calling 911 to activate emergency medical services shortly after symptom onset and improving the emergency response system. Developing integrated regional stroke networks that will decrease barriers to rapid treatment is necessary to decrease the fragmentation of stroke care that currently exists in many communities. The implementation of prehospital, emergency department, and interhospital transfer acute stroke protocols is critically important. Improving time-to-treatment will require the same effort and outcomes research that has been pursued in ST-elevation myocardial infarction. The ability to develop an imaging tool that could be used in the ambulance to make the diagnosis of stroke and facilitate prehospital activation of the Stroke Team would be a major advance and might allow the investigation of prehospital initiation of fibrinolytic therapy.

Stroke centers have the capability of rapidly performing computed tomography or magnetic resonance brain imaging and initiating intravenous fibrinolytic therapy in patients who meet treatment criteria. It is possible that bolus intravenous therapy with reteplase or tenecteplase has advantages over alteplase, particularly if prehospital therapy becomes possible. More research is needed comparing intravenous fibrinolytic therapy with selective intra-arterial fibrinolytic therapy.
Selective catheter-based reperfusion is another rich topic for investigation.

In patients with a history of noncardioembolic ischemic stroke, antiplatelet drugs are recommended for the prevention of recurrent ischemic stroke. Aspirin monotherapy, clopidogrel monotherapy, and the combination of aspirin and dipyridamole are recommended options for initial therapy. Although combining aspirin and clopidogrel is contraindicated for routine secondary prevention of stroke, limited-duration combination therapy is indicated in patients with recent acute coronary syndrome and/or vascular stenting.

Prasugrel is contraindicated in patients with a history of stroke or transient ischemic attack (TIA), and ticagrelor is contraindicated in patients with a history of intracerebral hemorrhage. However, intracranial bleeding risk might be lower for patients with a history of TIA than with stroke. It is possible that prasugrel or ticagrelor monotherapy could be superior agents for ischemic stroke prevention in patients with a history of TIA. Determining whether there are differences in the response to antithrombotic therapy between TIA and stroke could increase treatment options for TIA. Dabigatran, rivaroxaban, and apixaban are anticoagulant options that also deserve evaluation. There have been no trials of treatment options in patients who have recurrent events on antithrombotic therapy. Options include adding or switching agents.

More information is needed to prove that aspirin actually prevents ischemic stroke in primary prevention. It is not known whether prasugrel or ticagrelor are superior to aspirin or clopidogrel monotherapy for primary prevention of ischemic stroke. Nor is it known whether aspirin 81 mg daily is as effective as or safer than aspirin 325 mg daily for cerebrovascular disease.

**Gaps of Knowledge in Noncardioembolic Ischemic Stroke**
Ischemic stroke is an area that is ripe for improvement. Critical areas of research were identified.

- A randomized, controlled trial of optimal medical therapy alone versus revascularization for asymptomatic carotid artery stenosis, potentially incorporating better brain and carotid imaging for risk stratification.
- Differentiate the cause of stroke and TIA more precisely, and antithrombotic management, as well, respectively.
- Expand the role of regional prehospital diagnosis/treatment of ischemic stroke.
- Evaluate the potential role of stroke imaging in the ambulance.
- Catheter-directed therapy trial for ischemic stroke, as has been done with ST-elevation myocardial infarction.
- Determination of what to do with patients who experience recurrent events on treatment; should one add or switch antithrombotic agents?

**Acute and Chronic CAD–Smarter Antithrombotics**

**Hemostasis and Thrombosis**
Platelets are critical in the initiation, progression, and thrombotic complications of atherosclerosis. Although new antiplatelet agents (eg, prasugrel, ticagrelor) have been developed to further reduce ischemic events when added to aspirin therapy, these therapeutic advances are associated with an increase in severe bleeding. Given the association between bleeding and increased mortality, balancing the efficacy and safety of new antiplatelet agents and multidrug antithrombotic regimens has taken on even greater importance. It is in this context that there is great interest in emerging experimental data from animal models raising the intriguing possibility that physiological hemostasis and pathological thrombosis might represent 2 mechanistically different processes (Figure 1), thereby permitting the targeting of thrombosis, but not hemostasis (ie, decreased bleeding risk).

Sachs and Nieswandt have catalogued 34 genetically modified mouse strains studied in vivo for thrombus formation (typically ferric chloride or photochemical carotid injury or laser-induced injury of the cremaster microvasculature) and hemostasis (ie, tail bleeding time). These mouse strains broadly cover the complex interplay involving a large number of platelet surface receptors, signaling pathways, and enzymatic cascades that mediate platelet tethering and adhesion.
platelet activation, and platelet aggregation and thrombus propagation. Interestingly, only 6 of 34 targets—namely, platelet P2X$_4$, CD150, Gas6, CD40L, and coagulation factors XI and XII—have been reported to regulate thrombosis, but not hemostasis.

**Inflammation and Thrombosis**

New lines of research suggest that thrombosis and hemorrhage may also be uncoupled at the interface of pathways controlling thrombosis and inflammation. Leukocyte–platelet interactions induce bidirectional signals that amplify proinflammatory and prothrombotic cellular responses. One remarkable example is spleen tyrosine kinase (Syk), a 72-kDa signaling protein with kinase and scaffolding activities. Several in vitro lines of evidence suggest that inflammatory and thrombotic signaling pathways converge on Syk. In platelets, phosphorylation of Syk has been reported following activation by multiple receptors. Syk is also a mediator of signaling events induced by high shear stress. In leukocytes, Syk promotes the recruitment of these cells to both inflamed and injured blood vessels. Recent studies using a novel and highly selective pharmacological inhibitor of Syk (PRT060318; 2-(((1R,2S)-2-aminocyclohexylamino)-4-(m-tolylamino)pyrimidine-5-carboxamide), coupled with genetic experiments, demonstrate that Syk inhibition ameliorates both the acute and chronic responses to vascular injury without affecting hemostasis. PRT060318 strongly inhibited arterial thrombosis in vivo in multiple animal species while having a minimal impact on bleeding. Furthermore, leukocyte–platelet–dependent responses to vascular injury were markedly inhibited by PRT060318. Dose-response studies will be required to establish whether a strategy aimed at targeting the kinase activity of Syk in a chronic setting is feasible and safe. The therapeutic potential of Syk may exemplify a new class of antiatherothrombotic agents that target the interface between thrombosis and inflammation.

**Gaps of Knowledge in Acute and Chronic CAD: Antithrombotic**

The knowledge base in acute and chronic CAD has grown exponentially. Remaining potentially high-yield targets for research include:

- Identification of molecular targets that dissociate bleeding and thrombosis.
- Development of a polypill for secondary prevention, which may ensure better adherence (although at the risk of greater nonadherence to all included medications).
- Evaluation of different dosing strategies of reversible agents to prevent myocardial infarction during noncardiac surgery.
- Personalized care with genetic and point-of-care assays.
- Development of better animal models of bleeding and thrombosis that are organ specific (brain, heart, gastrointestinal, etc).
- Development of better nonanimal models for thrombosis.

**Prosthetic Heart Valves and Thromboembolism**

Consensus guidelines recommend the addition of aspirin 75 to 100 mg once daily to vitamin K antagonists (VKAs) for all patients with mechanical heart valves and for those patients with biological valves who have risk factors for thromboembolism. Clinical evidence in support of this recommendation is provided by a review of 11 RCTs involving 2428 patients. The combination of aspirin plus a VKA resulted in a 42% relative risk reduction in thromboembolic events. Beneficial effects were offset by an increase in major bleeding (odds ratio of 1.66), an apparent dose-dependent effect seen with aspirin that has led to the recommendation for the use of low-dose aspirin plus a VKA.

The beneficial effects associated with the combination of aspirin plus a VKA for the prevention of thromboembolic events identifies an important gap in our knowledge. Tests have been developed and implemented to quantify the effects of anticoagulants and antiplatelet agents, yet no single test has been developed to provide a global assessment of antithrombotic effects. Such a test may be useful to identify patients at greater risk of thromboembolic events and, conversely, those patients at greater risk of bleeding complications. The availability of such a test would be particularly useful to guide therapy in patients who require interruption in their antithrombotic therapy and in patients who are likely to have different antithrombotic requirements.

Pregnancy in association with a prosthetic heart valve entails substantial risk to both the mother and fetus. Our gap in knowledge is perhaps greatest in this situation. It has long been believed that both warfarin and heparin pose risks to the mother and fetus. More recent data suggest that the risk of embolopathy with warfarin, especially at doses of 5 mg daily or less, may have been overestimated. Changes in volume status and the apparent volume of distribution of the VKA, combined with changes in the synthesis of coagulation factors, add to the complexity and mandate regular testing. A global assessment of antithrombotic effects would be particularly useful to develop effective antithrombotic strategies in pregnant women who have prosthetic heart valves. More data are needed as to the optimal anticoagulation approach for the duration of pregnancy.

New direct-acting anticoagulants inhibit coagulation factor Xa or thrombin (factor IIa). The more consistent antithrombotic effects of these agents may be useful in patients with prosthetic heart valves. The dire consequences of valve thrombosis present serious challenges to investigating new regimens; however, preliminary studies in vitro suggest that dabigatran may prevent valve thrombosis as effectively as heparin. Once again, a global assessment of antithrombotic effects that is sensitive to the effects of all anticoagulants would aid in development. Ideally, comparative testing of different direct-acting anticoagulants would indicate whether inhibiting thrombin or factor Xa is preferable for preventing thromboembolic events.

Patients with prosthetic valves require periodic interruption of antithrombotic therapy. By limiting the duration during which the patient is not anticoagulated, the thromboembolic risk is reduced. The rapid onset of action of direct-acting anticoagulants shortens the interval during which the patient is not anticoagulated. The availability of an agent that could reverse the drug’s effect could also shorten this interval. In
addition, such an agent would be useful when spontaneous major bleeding occurs.

The risk of thromboembolism is influenced not only by valve type (mechanical or bioprosthesis), but also by associated conditions such as atrial fibrillation and systolic heart failure. The development of new anticoagulants, new antiplatelet agents, and new methods to implant aortic valves (transcatheter replacement) has created important gaps in our knowledge regarding the most effective antithrombotic therapy. Additional clinical trials are needed. The success of these trials would be enhanced by the availability of an accurate and precise measure of global antithrombotic effects.

**Gaps of Knowledge in Prosthetic Heart Valves and Thromboembolism**

Progress in antithrombotic therapy for prosthetic valvular heart disease has been relatively slow, in part, because of the dire consequences of valve thrombosis. Important areas to address are:

- Anticoagulation bridging for invasive procedures: who, when, how?
- Role of new direct thrombin and factor Xa inhibitors in pregnancy.
- Role of acute and chronic antithrombotic therapy in transcatheter valve replacement.
- Testing direct thrombin and factor Xa inhibitors for artificial valves and a comparative trial of direct thrombin and factor Xa inhibitors.
- Antidotes for direct thrombin and factor Xa inhibitors.

**Venous Thromboembolism**

There has been considerable progress in the prevention, diagnosis, and treatment of venous thromboembolism (VTE) in recent years. The risk factors for VTE have been better defined, and the armamentarium of drugs for the prevention and treatment of VTE has expanded with the introduction of new oral anticoagulants that target factor Xa or thrombin. Nonetheless, several challenges remain.

First, anticoagulants have long been the mainstay for primary and secondary prevention of VTE. However, there has been a resurgence in the use of antiplatelet drugs for this indication; many orthopedic surgeons routinely use aspirin in place of anticoagulants for thromboprophylaxis after hip or knee replacement surgery, and a recent study demonstrated a ∼40% reduction in recurrent VTE when aspirin was compared with placebo for secondary prevention in patients with unprovoked VTE who had been treated with a 6- to 18-month course of conventional anticoagulation. Aspirin is easier to administer than warfarin or injectable anticoagulants. Building on these findings, there is a need for studies to compare aspirin with the new oral anticoagulants for primary and secondary VTE prevention.

Second, although it is clear that patients with VTE in the setting of a transient risk factor, such as surgery or trauma, have a low risk of recurrent VTE after a 3-month course of anticoagulant therapy, this is not the case with unprovoked VTE. Unprovoked VTE is a chronic disease; the risk of recurrence when anticoagulant therapy is stopped in such patients is ≈10% at 1 year and 30% at 5 years even after a 2-year course of anticoagulation. Because of this high risk of recurrence, some experts recommend long-term anticoagulation, which is not only inconvenient for patients and costly for the healthcare system, but also places patients at risk for bleeding. These concerns identify several unmet needs. These include (a) the need for a global test or testing strategy that identifies patients at high risk for recurrent VTE so that these patients can be targeted for extended anticoagulant therapy, (b) the need for trials comparing anticoagulants (including the new anticoagulants) with aspirin for secondary prevention, and (c) the need for trials to determine whether lower doses of the newer anticoagulants will have similar efficacy, but better safety, than full doses for secondary VTE prevention.

Third, special populations of patients with VTE continue to pose challenges. These include pregnant women and patients with cancer. There are no licensed oral anticoagulants for prevention or treatment of VTE in pregnancy. Based on preclinical assessments in animals, at least 2 of the new oral anticoagulants appear to be safe in pregnancy (dabigatran and apixaban); clinical studies are needed to evaluate this possibility. Patients with VTE in the setting of cancer are particularly difficult to manage and are often given extended treatment with low-molecular-weight heparin, which necessitates a daily subcutaneous injection. Studies are needed to determine whether the new oral anticoagulants are as effective and safe as low-molecular-weight heparin in this setting. Finally, certain subsets of patients receiving systemic combination chemotherapy for treatment of cancer are at high risk for VTE. Preliminary studies indicate that prophylaxis with injectable anticoagulants lowers this risk. Better risk stratification schemes are needed to identify high-risk patients. In addition, to streamline thromboprophylaxis in this vulnerable patient population, the new oral anticoagulants need to be compared with injectable agents.

Fourth, advances in our understanding of the molecular mechanisms of coagulation have enabled the identification of thrombophilic conditions that predispose patients to VTE. Although some of these abnormalities can be identified in 40% to 50% of patients with hereditary forms of VTE, at least half of the patients with VTE do not have recognized abnormalities, and many patients with thrombophilia do not experience VTE. Genome-wide association studies (GWAS) have failed to identify new genetic defects in VTE. Therefore, we need to use other approaches to identify novel genetic factors leading to thrombophilia, such as whole genome analysis and deep sequencing. In addition, more information is required about the influence of environmental factors and modifier genes on the phenotype in these patients.

Finally, there is increased emphasis on personalized medicine. Point-of-care genotyping can identify common polymorphisms that influence warfarin metabolism and average dose requirements. Incorporation of this information into warfarin-dosing algorithms may streamline the achievement of therapeutic levels of anticoagulation. Studies are ongoing to determine whether genotyping improves patient outcome. With the move to new oral anticoagulants, there is a need for additional genetic studies to determine whether a patient-centered approach can be used to optimize the efficacy and safety of these agents.
Gaps of Knowledge in Venous Thromboembolism

The main challenges in VTE are:

- Definition of the role of aspirin and/or other antiplatelet agents in primary and secondary prevention in at-risk patients.
- Prediction of recurrent thrombosis and determination of optimal duration of antithrombotic therapy.
- Management of special patient populations, including pregnant women, patients with VTE in the setting of cancer, and patients with thrombophilia.
- Genetic and functional point-of-care testing to identify risk and personalize treatment of VTE.

Prioritizing Future Directions in Clinical Thrombosis

As discussed above, there are several knowledge gaps in thrombosis as it pertains to cardiovascular medicine. Atrial fibrillation, stroke, acute and chronic CAD, prosthetic heart valves, and VTE all have important knowledge deficits and unmet clinical needs. The highest priority studies in our opinion are summarized below:

- Comparative trials of evolved oral direct thrombin inhibitors and factor Xa inhibitors in patients with atrial fibrillation.
- Mechanical versus pharmacological approaches for stroke reduction and maintenance of sinus rhythm in atrial fibrillation.
- Optimal medical therapy versus revascularization for asymptomatic carotid stenosis, with consideration of better brain and carotid imaging for risk stratification.
- Catheter directed therapy trial for stroke (as has been done with ST-elevation myocardial infarction).
- Identification of molecular targets that dissociate thrombosis from bleeding, to the extent possible.
- Anticoagulation bridging for invasive procedures: who, when, how?
- Predictors of recurrent VTE and determination of appropriate length of therapy.

As is apparent, these studies would encompass RCTs, translational work, and basic investigation. The knowledge generated would have an enormous public health impact by addressing fundamental unresolved clinical issues for some of the most prevalent cardiovascular conditions worldwide.

Personalized Antithrombotic Therapy

Warfarin therapy has long been guided by a functional assay, the international normalized ratio of the prothrombin time. Although there has been interest in the use of genetic assays (VKORC1 and CYP2C9) to guide warfarin dosing (see Role of Genetic Testing), the field appears to be moving in a different direction: namely, the use of newer anticoagulants, drugs, either direct thrombin inhibitors (eg, dabigatran) or factor Xa inhibitors (eg, rivaroxaban, apixaban, and edoxaban) that do not require routine coagulation monitoring.

In contrast, because of the variation in response to antithrombotic therapy, there is great interest in the use of functional and genetic assays to guide such treatment. Possible mechanisms of aspirin and clopidogrel “resistance,” hyporesponsiveness, or high on-treatment platelet reactivity include: bioavailability (nonadherence, underdosing, poor absorption [enteric-coated aspirin]); interference (nonsteroidal anti-inflammatory drugs/aspirin, atorvastatin/clopidogrel, proton pump inhibitors/clopidogrel); single-nucleotide polymorphisms (CYP2C9*2, ABCB1 for clopidogrel); platelet interactions with other cells (endothelial cells and monocytes synthesize thromboxane A2, and its precursor, prostaglandin H2, as well, both of which may be taken up by platelets, thereby bypassing the cyclooxygenase-1 inhibition by aspirin); platelet function (accelerated platelet turnover, with introduction into the bloodstream of newly formed, drug-unaffected platelets; stress-induced cyclooxygenase-2 production in platelets; underlying platelet hyperreactivity).

Role of Platelet Function Testing

Platelet function tests for measuring the response to aspirin include those with thromboxane as the end point (serum thromboxane B2, urinary 11-dehydro thromboxane B2), arachidonic acid as the stimulus (turbidometric platelet aggregometry, impedance platelet aggregometry, the VerifyNow Aspirin assay, the thromboelastogram PlateletMapping system, the Impact cone and plate(let) analyzer, flow cytometric assays of platelet surface P-selectin, platelet surface activated GPIbβ [GPIIb/IIIa], and/or leukocyte-platelet aggregates) and others (eg, PFA-100). Platelet function tests for measuring the response to clopidogrel use ADP as the stimulus and include: phosphorylase of vasodilator-stimulated phosphoprotein measured by flow cytometry, turbidometric platelet aggregometry, impedance platelet aggregometry, the VerifyNow P2Y12 assay, the thromboelastogram PlateletMapping system, the Impact cone and plate(let) analyzer, flow cytometric assays of platelet surface P-selectin, platelet surface activated GPIIb/IIIa, and/or leukocyte-platelet aggregates). Prostglandin E1 can be used to better focus the test on the P2Y12-mediated (ie, clopidogrel-dependent) pathway of platelet signaling, and this reagent is included in the commercially available vasodilator-stimulated phosphoprotein assay (BioCytest) and VerifyNow P2Y12 assay (Accumetrics). Point-of-care assays (also referred to as point-of-service assays) have potential advantages over laboratory-based tests. For example, point-of-care assays can inform immediate decision making about the type and dose of antiplatelet therapy in the intervention cardiology suite. A rigorous definition of a point-of-care assay is one that meets all of the following criteria: use at or near the patient bedside, easy to use without special skills, no sample processing, no pipetting, and a rapid readout. The only currently available test that meets these criteria is the VerifyNow assay.

The concept of guiding antiplatelet therapy based on platelet function testing can be considered in 3 steps. First, is there interpatient response variability to the antiplatelet agent as judged by a specific platelet function test? The answer to this first question is yes for both aspirin and clopidogrel. Second, in patients on antiplatelet therapy, is hyporesponsiveness in a platelet function test predictive of major adverse cardiovascular events (MACEs) (when other risk factors are accounted for)? The answer to this second question is also yes for both aspirin and clopidogrel with stronger evidence for clopidogrel. Third, and most important, does guided antiplatelet therapy based on the results of platelet function testing decrease MACE? The answer to this third question is
unknown for aspirin and, based on very limited data, possibly yes for clopidogrel. However, the data are currently insufficient to recommend platelet function testing to guide antiplatelet therapy in the clinical setting.

In comparison with clopidogrel, newer P2Y<sub>12</sub> antagonists (eg, prasugrel and ticagrelor) produce greater and more consistent inhibition of ADP-dependent platelet function and decrease MACE to a greater extent. Nevertheless, there is still interpatient variability in on-treatment platelet reactivity with these antiplatelet agents, albeit less than with clopidogrel. With these newer P2Y<sub>12</sub> antagonists, the relationship between high on-treatment platelet reactivity and MACE, and the role (if any) of guided therapy, is unknown.

Randomized controlled trials are needed to address the hypothesis that modification of antiplatelet therapy in individual patients based on platelet function testing reduces MACE without increasing bleeding. There have been no such RCTs of personalized aspirin therapy. Because aspirin is not patent protected, such trials are unlikely to be funded by industry. In contrast, there have been several RCTs of personalized clopidogrel therapy. Small, short-term studies of adjusted clopidogrel loading doses according to the vasodilator-stimulated phosphoprotein phosphorylation index showed a decreased MACE rate in PCI patients with high on-treatment platelet reactivity. The GRAVITAS study showed that, among patients with VerifyNow-defined high on-treatment platelet reactivity (P2Y12 reaction units >230) after PCI and implantation of drug-eluting stents, doubling the dose of clopidogrel and comparison with standard-dose clopidogrel did not reduce the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis. However, the GRAVITAS study had limitations, including a low MACE rate and only a fixed doubling of the clopidogrel dose, whereas the small, but successful vasodilator-stimulated phosphoprotein studies specifically tailored the clopidogrel dose to up to 4 times baseline. Furthermore, in a post hoc analysis of the GRAVITAS study in which the P2Y12 reaction unit cutoff at baseline was reduced to <208 P2Y12 reaction units, there was a lower risk of MACE, even after adjustment for other predictors. The RECLOSE 2 ACS study, which had similar limitations to GRAVITAS, also did not show benefit to guided clopidogrel therapy based on ADP-induced platelet aggregation. The ARCTIC trial (http://clinicaltrials.gov/ct2/show/NCT00327411) is in progress.

**Future Directions in Platelet Function Testing**

Important issues to be resolved in future randomized trials include:

- Study populations with a sufficiently high risk of MACE to provide appropriate statistical power.
- Selection of the appropriate platelet function test(s), ideally those that can identify both risk of thrombosis and risk of bleeding.
- Optimal time(s) to measure platelet function, because platelet function has been shown to vary over time, and high on-treatment platelet reactivity is associated with acute coronary syndromes. Multiple measurements may therefore be needed to optimally tailor antiplatelet therapy (analogous to what is currently done with low-density lipoprotein cholesterol, for example).
- Identification of optimal cutoff values for the platelet function test(s).
- Integration of the result of the platelet function test(s) with the results of genetic tests (see Role of Genetic Testing).
- Development of algorithms that combine clinical, procedural, and demographic data.
- Although the focus of this research field has been on clopidogrel, questions remain about the non–cyclooxygenase-1-dependent effects of aspirin and their correlation with clinical outcomes.
- Nonadherence plays a potentially critical role. If a patient does not take an antiplatelet drug, a platelet function test will record the patient as being nonresponsive to the drug. Behavioral studies of prescribers and patients with regard to adherence and adoption of new drugs and monitoring strategies are therefore needed, and implementation of targeted interventions to enhance adherence by patients, with a focus on reversible drugs that require more than once-a-day therapy (eg, ticagrelor).
- See also the last item in the Future Directions in Genetic Testing.

**Role of Genetic Testing**

Whereas rare Mendelian genetic disorders of platelet biology and hemostasis have been recognized for more than a century, the influence of more common genetic variants on platelet biology, hemostasis, the predilection for thrombosis, and the response to antithrombotic therapies has only recently been appreciated.

Studies from the Framingham Heart Study demonstrated that heritable factors accounted for 20% to 30% of the overall variance in platelet aggregation in response to agonists such as epinephrine. A subsequent GWAS in 2 cohorts (Framingham Heart Study and Genetic Study of Atherosclerosis Risk) identified associations of 7 loci with platelet aggregation near or within GP6, PEAR1, ADRA2A, PIK3CG, JMJ1D1C, MRVII, and SHH. In addition, a recent large GWAS has reported 68 genomic loci associated with platelet count and volume, underscoring the role of genetic factors in megakaryopoiesis and platelet formation.

In terms of antiplatelet therapies, aspirin irreversibly inhibits cyclooxygenase-1 and -2. In platelets, cyclooxygenase-1 catalyzes the conversion of arachidonic acid to prostaglandins G<sub>2</sub> and H<sub>2</sub>, resulting in downstream synthesis of thromboxane A<sub>2</sub>. Variability in aspirin-mediated antiplatelet effects has been noted, with potential associations with adverse cardiovascular outcomes. Genetic polymorphisms may play a role in individual response to aspirin, but consistent, validated associations remain to be established.

Clopidogrel, an oral thienopyridine, is a prodrug, ≈85% of which is metabolized by esterases in the gut to form an inactive carboxylic acid derivative. The remaining 15% is biotransformed into the active compound by hepatic metabolism involving 2 sequential cytochrome P450–mediated steps, with CYP2C19 involved in both steps. The active thiol metabolite then irreversibly binds the P2Y<sub>12</sub> ADP receptor, leading to partial inhibition of ADP-dependent
platelet activation and aggregation. Variability in clopidogrel response has been observed: on-treatment platelet reactivity in clopidogrel-treated patients approximates a bell-shaped distribution, and individuals with high on-treatment platelet reactivity have higher rates of ischemic events, including stent thrombosis.98

In a study of healthy Amish persons given clopidogrel for 7 days, the platelet response to clopidogrel was highly heritable ($r^2=0.73$). A GWAS identified 13 single-nucleotide polymorphisms on chromosome 10q24 within the CYP2C19–CYP2C19–CYP2C9–CYP2C8 region that were associated with a diminished response to clopidogrel.99 The lead -nucleotide polymorphism was in strong linkage disequilibrium with the CYP2C19*2 variant, which involves a single base pair mutation of G→A at position 681, creating an aberrant splice site that leads to the synthesis of truncated nonfunctional CYP2C19 protein.100 This locus accounted for 12% of the variation in platelet aggregation to ADP. The *2 variant is carried by $\approx30\%$ of whites, $40\%$ blacks, and $55\%$ of East Asians.101 In comparison with noncarriers, carriers of at least 1 copy of the CYP2C19*2 allele or other loss-of-function CYP2C19 variants have $\approx30\%$ lower levels of active clopidogrel metabolite and $\approx25\%$ less platelet inhibition.102

Moreover, among patients with acute coronary syndromes and planned PCI treated with clopidogrel, carriers of at least 1 copy of a CYP2C19 loss-of-function variant had a 50% increase in the risk of cardiovascular death, myocardial infarction, or stroke and a 3-fold increased risk of stent thrombosis.103 These observations have been seen in a total of 9 clinical studies involving patients treated with clopidogrel predominantly for PCI.104 Based on the totality of the data to date, both heterozygotes and homozygotes appear to be at increased risk. The clopidogrel label has been updated by the FDA to include a boxed warning about the impact of genetics on the response to clopidogrel. A recent meta-analysis showed a less robust association, but the study was questionable with regard to its relevance to current clinical use, because it included nonstented patient populations in which clopidogrel has modest or no efficacy, did not restrict analyses to events while patients were on clopidogrel, and included noncardiovascular outcomes unaffected by clopidogrel.104

Other variants have been found that have been associated with the pharmacological and clinical responses to clopidogrel. The ABCB1 gene (also known as MDRI) encodes for the xenobiotic efflux p-glycoprotein pump involved in intestinal absorption of clopidogrel. In some but not all studies, the CYP2C19TT genotype has been associated with an increased rate of cardiovascular events in the setting of treatment with clopidogrel therapy after an acute myocardial infarction.105

The PON1 gene encodes for paraoxonase-1, an esterase synthesized in the liver and associated with high-density lipoprotein cholesterol in the blood. Although 1 study found the PON1 Q192R polymorphism to affect variability in clopidogrel efficacy and to confer increased risks for definite stent thrombosis,106 these observations have not been replicated in multiple subsequent studies.109,110

The CLOVIS-2 and ELEVATE-TIMI 56 trials have demonstrated, respectively, that tripling the loading and tripling the maintenance doses of clopidogrel in patients with poor antiplatelet responses to standard doses can achieve on-treatment platelet reactivity comparable to that observed with standard dosing in wild-type, responsive patients.111,112 Alternatively, prasugrel and ticagrelor are third-generation ADP receptor antagonists whose efficacy is not influenced by CYP2C19 loss-of-function genetic variants.107,113

In terms of anticoagulants, warfarin interrupts hepatic vitamin K recycling by inhibiting vitamin K epoxide reductase and vitamin K quinine reductase. Warfarin is ingested as a combination of active R- and S-warfarin enantiomers, with the S-enantiomer $\approx3$ to 5 times more potent. S-warfarin is inactivated by CYP2C9-mediated hydrolysis; the less active R-enantiomer is metabolized by CYP3A4 enzymes. GWAS studies have confirmed the association between genetic polymorphisms in VKORC1 and CYP2C9 and warfarin dosing variability.114,115 CYP2C9 and VKORC1 genotype information accounts for $\approx40\%$ of the variability in warfarin dosing. In 2007, the FDA updated the warfarin label to note that VKORC1 and CYP2C9 variants may influence the warfarin dosage requirement. In 2010, the label was further updated with inclusion of a pharmacogenetic-guided dosing scheme for initiation of warfarin therapy (factoring in the presence or absence of VKORC1-1369 G→A and CYP2C9*2 or CYP2C9*3).

Algorithms incorporating a patient’s genotype, demographic factors, and comediations have been developed in an attempt to improve the prediction of initial warfarin dosing; these algorithms provide the greatest benefit in patients requiring extremes of warfarin dosage ($\pm21$ mg per week or $\pm49$ mg per week).116 Several small studies have suggested that genotype-based warfarin dosing can result in smaller and fewer dose adjustments117 however, no impact on clinical outcomes has yet been demonstrated in prospective studies. Several large-scale prospective studies are underway to further elucidate whether genotype-guided algorithms improve clinical outcomes. Novel anticoagulants, including dabigatran, rivaroxaban, and apixaban, have emerged as alternatives to warfarin that are not influenced by these pharmacogenetic interactions.

**Future Directions in Genetic Testing**

Five areas of study for the genetics of antithrombotic therapy are recommended:

- Identify and characterize the full spectrum of genetic variants associated with platelet biology, hemostasis, and thrombosis phenotypes, and the pharmacokinetic and pharmacodynamic responses to antiplatelet and anticoagulant therapies, as well. Such characterization could be accomplished by GWAS or whole exome sequencing. Quantitative phenotypes such as platelet aggregation and coagulation parameters permit adequate statistical power in studies of relatively smaller numbers of individuals. More challenging is attempting to apply such approaches to clinical outcomes because the sample sizes required rise steeply. One cost-efficient approach would be to support ancillary genetic studies in existing or planned clinical studies.
- Perform functional validation and characterization of discovered genetic loci. Understanding the mechanisms underlying observed associations between loci and the afore-
mentioned phenotypes will be important for both furthering our knowledge of basic biology and developing drug targets. Such investigation will likely require a combination of cell-based and animal-based models, and ex vivo and in vivo human studies, as well.

- Characterize second-order interactions. Acknowledging the complexity of the biology of thrombosis and antithrombotic therapy, both gene–gene and gene–environment interactions will need to be defined. Data already suggest that the clinical implications of certain pharmacogenetic interactions (such as CYP2C19 and clopidogrel) depend on the patient’s clinical status (eg, whether they have undergone PCI or not). Screening methods for these second-order interactions could include both wet laboratory and bioinformatics approaches.

- Bring genetic testing into clinical practice. For genetics to be readily incorporated into clinical practice, genotyping must move from research laboratories and send-out tests to rapid-turnaround or even rapid point-of-care testing. To that end, there have been several recent successful demonstrations of point-of-care testing for genotyping for CYP2C19 loss-of-function alleles. Down the road, comprehensive hemostasis/thrombosis arrays or even sequencing may be readily available. As genome-wide genetic data become increasingly available to clinicians, support for integrating such information into clinical practice will be needed.

- Determine the utility of platelet function and genetic testing in clinical practice. Studies will need to be done in appropriately sized cohorts with sufficient statistical power for major adverse cardiovascular outcomes. For evidence-based use, data from platelet function and genetic testing will need to be integrated with clinical characteristics. Both thrombotic and bleeding outcomes should be examined. For platelet function testing, as results change over time, multiple measurements may be needed to optimally tailor therapy. Moreover, the optimal cutoff values will need to be determined. Although a dedicated RCT comparing clinical outcomes in patients who undergo testing versus those who do not would represent the highest level of evidence, such a trial would need to be exceedingly large to be adequately powered for clinical outcomes. Thus, 1 objective is to identify a range of more practical trial designs. For example, 1 such design, which is analogous to what has been done for other high-risk features such as diabetes or an elevated troponin, is to use platelet function testing or genotyping to define subgroups within RCTs of therapies. Moreover, testing might be used to identify high-risk subgroups for enrollment into trials (somewhat akin to what is done in oncology).

### The Stakeholder’s Roles

Because antithrombotic therapy is critical to the treatment of the world’s leading causes of death and disability (CAD, stroke, and atrial fibrillation), many stakeholders have an interest in developing new therapies and in understanding existing therapies better. Further, as information becomes increasingly available, policymakers are envisioning the global therapeutic development enterprise in a much more sophisticated manner than in the past (Figure 2).118

In an ideal system, adequate investment in preclinical thrombosis research would lead to conceptual advances. These advances would, in turn, be translated into novel molecules capable of inhibiting or enhancing selective elements of the coagulation system in a well-defined manner. Following preclinical proof-of-concept evaluation, early-stage clinical trials would be performed to winnow out unfavorable approaches. Ultimately, approaches that showed the greatest promise in early studies would be selected for testing in trials designed and powered to provide a clear estimate of the balance of risk and benefit associated with the use of such treatments in clinical practice. Definitive trial results would be translated into clinical practice guidelines, and the most clear-cut results would inform performance indicators once it became clear that a given therapy should or should not be given in a particular clinical circumstance. Finally, the sum of this information and knowledge would be stored in databases and knowledge repositories to drive a system of continuous learning.

Although we have yet to attain this ideal in practice, multiple societal entities can help move us closer to achieving an ideal learning health system, and the field of antithrombotic therapy represents an important possible prototype for such a system. One distinctive element of an ideal learning health system is that multiple stakeholders must be involved: pharmaceutical, biotechnology, and device companies (ie, the medical products industry); academic health and science systems (AHASs); medical practitioners and providers; Patient Advocacy Groups/Voluntary Health Organizations (PAG/VHOs); and government agencies. Furthermore, although opportunities to develop therapies with high-quality evidence are expanding, so too is the organizational complexity of biomedical research as it evolves into a truly global enterprise.

### The Medical Products Industry

The medical products industry develops drugs and companion diagnostics along a continuum that reaches from the preclinical arena through clinical trials and marketing. How-
ever, the industry has been under economic and regulatory pressures for some time, and many believe that its current financial models are not sustainable because of the enormous costs of bringing new treatments to market.\textsuperscript{119} Although the particulars of the cost estimates can be debated (including the cost of all developmental failures and the opportunity costs of the delay on return on investment),\textsuperscript{120} the view that the cost of developing new therapies has escalated is largely undisputed.

Moreover, as the risks associated with treatments have become better understood, the evidentiary standards of regulatory agencies have become stricter, further increasing the cost and risk of development and marketing. Many have expressed worry about a diminution in both venture capital for cardiovascular drug development and investment in large pharmaceutical companies at later stages of drug development. Nevertheless, given the enormous market occasioned by vascular disease as a cause of death and disability in the economically developed world, the reward for developing a successful drug can be significant. Accordingly, the medical products industry likely will continue to invest in new therapies, and, it is hoped, in an increasing number of personalized treatments in which companion diagnostics can be used to determine which patients will achieve the best results with specific drugs or combinations of drugs. However, as companies face escalating costs and the uncertainties of a crowded market, the need for public-private partnerships to stimulate development is likely to prove increasingly critical.

An important development in the medical products industry is the reduction in fundamental research and development due to the financial pressures described above. Shrinking corporate research and development budgets mean that the National Institutes of Health (NIH) and academia will have to take on added responsibility to fill the pipeline with discoveries that will lead to new and better drugs. One countervailing trend of note is the increasing willingness of pharmaceutical companies to enter into creative agreements with academia in the preclinical development arena.

Because the medical products industry appears to have limited interest in comparative effectiveness research, government and academia have to fill this important need. Given the large number of patients required for comparative effectiveness trials and the high cost of these studies, it will be critical to form partnerships that can identify the most important questions to be answered and can conduct studies efficiently. The Patient-Centered Outcomes Research Institute\textsuperscript{121} represents a major effort by the US government to create a partnership in which the medical products industry can contribute to the design of comparative effectiveness trials without having to fund those studies.

**Academic Health and Science Systems**

Over the past few years, academic institutions—typically medical schools with affiliated hospitals—have evolved into entities with an array of institutions needed to support integrated health systems, or AHASs.\textsuperscript{112} AHASs produce the scientists and clinicians who will develop and use antithrombotic agents. As pharmaceutical and device companies continue to pare down their research and development budgets, there is a corresponding growth of interest in forging novel relationships with AHASs. Although these relationships hold great promise for joint efforts in laboratory research, numerous issues regarding financial conflicts of interest and the not-for-profit status of American academic centers await resolution. Effective consulting by knowledgeable academics to provide input and guidance into corporate decision making will likewise be critical to success. AHASs will also likely play a key role in conducting clinical trials as the field seeks more efficient methods in this arena.

**Medical Practitioners and Providers**

Medical practitioners will ultimately use therapies developed by the medical products industry and AHASs and conduct necessary clinical trials. Professional societies representing the cardiovascular medicine community, including the American College of Cardiology (ACC), the American Heart Association, and the European Society of Cardiology all play central roles in developing clinical practice guidelines and performance measures. These groups are also developing and implementing registries that integrate clinical quality assessment and postmarketing surveillance.\textsuperscript{123–125}

The medical products industry must address the remaining health needs of the population as defined by the providers who prescribe their products. There is general agreement among providers that we need antithrombotics with better risk-benefit profiles, and a better understanding of how combinations can be used together in practice, as well. Given the financial constraints enumerated above, there will be a persistent gap between the available evidence and the needed evidence until providers form more efficient research groups, using methods such as integration of registries and electronic health records into randomized trials. These essential studies may range from intensive study groups focused on biological mechanisms to global trials networks and health system–based postmarketing surveillance efforts.

Providers also have an important role as advocates for continued development by the medical products industry and by government. Given that typical drug development processes do not clarify which alternatives are best for particular groups or individual patients, provider groups must advocate for funding for comparative effectiveness studies from industry and/or government. Such arguments, however, will be more persuasive if providers have developed more cost-efficient methods for performing these trials.

**Patient Advocacy Groups/Voluntary Health Organizations**

PAG/VHOs are emerging as major forces in therapeutic development. In diseases such as cancer, HIV–AIDS, multiple myeloma, and cystic fibrosis, PAG/VHOs have become a significant source for funding research and are exerting influence in shaping policies related to research and the evaluation and regulation of drugs and devices. For example, the Cystic Fibrosis Foundation invests in product development and funds a research network that performs clinical trials. In the arena of thrombosis, however, PAG/VHOs are less focused because so many different diseases are involved. For example, the American Heart Association is a potent...
advocacy organization that funds its own research, but its broad mandate limits direct influence on antithrombotic drug development. Sustained focus on the profound impact of thrombosis on human health is needed to ensure sufficient investment for developing more effective therapies.

Government Agencies

The National Institutes of Health
Multiple government agencies are involved in antithrombotic drug development, with the NIH, in general, and the NHLBI, in particular, funding much of the discovery science and applied basic science that produces new ideas about antithrombotic drugs. Defining optimal strategies for investing money allocated to the NHLBI is of vital interest to all other constituents and is the primary subject of this report. The urgent need for NIH investment in research into the basic biology of thrombosis is only heightened by the reductions in fundamental research and development spending by the medical products industry noted above. At the same time, support for the NIH is under stress, with flat budgets that actually represent a decline in scientific purchasing power. The NIH will need to carefully craft strategies for maximum leverage, applying public money in key areas where investment from the private sector is less likely.

Agency for Healthcare Research and Quality
The Agency for Healthcare Research and Quality is charged with improving the quality, safety, efficiency, and effectiveness of health care for all Americans. This broad mission includes significant efforts to aggregate research data across studies, but the agency’s ability to conduct primary research is limited by its relatively small budget.

Centers for Medicare and Medicaid Services, Department of Veterans Affairs, and Department of Defense
The Centers for Medicare and Medicaid Services, the Department of Veterans Affairs, and the Department of Defense provide services that use antithrombotic therapies. In the case of the Department of Veterans Affairs and the Department of Defense, a modest but significant research budget is allocated to focus on research pertaining to the health needs of the military and veterans. The creation of incentives aimed at stimulating research into new treatments, and the development of evidence to guide more effective use of therapies, are in the direct interest of these agencies and their beneficiaries.

Food and Drug Administration
The FDA regulates the development and appropriate use of antithrombotic drugs in the United States. Its policies and guidelines control the direction that preclinical and clinical studies take as biological concepts are translated into useful products. But as the number of available antithrombotics has grown, issues such as noninferiority trials, joint approval of new therapeutics with companion diagnostic assays, the use of biomarkers and putative surrogates, simplification of trials, and regulation of combination therapies have emerged as critical limiting or enhancing factors, depending on specific FDA precedents. The relatively new field of regulatory science creates opportunities for systematically analyzing the regulatory process related to evaluation and approval of antithrombotic therapy, with the goal of streamlining the process. The development of academic units focused on regulatory science would increase the likelihood of success and provide a cadre of experts who could spearhead evidence-based regulatory science advances.

Globalization
Until recently, the development of new drugs and accompanying devices has occurred largely within North America, Europe, and Japan. Now, however, clinical trials, including research funded by the US government, are performed globally, and the largest future markets are in Brazil, Russia, India, China, and Korea. Much of the research and development enterprise formerly centered in the United States and Western Europe is becoming globalized as well. Accordingly, as strategies for developing antithrombotics are devised, consideration must be given to parallel funding agencies, professional groups, PAG/VHOs, and government agencies on a global scale. An effective global approach that would rapidly accumulate evidence about the benefits and risks of new and competing therapies is a key public health priority for the world’s 7 billion people, given that ≈17 to 24 million persons are expected to die each year of cardiovascular diseases in the coming decades.

Conflict of Interest
To produce a successful system for developing new antithrombotic therapies, while also maintaining the ability to understand how to most effectively use the old therapies, conflicts of interest will be engendered across the spectrum of interactions. Although the conflict between the driving profit motive of industry and the not-for-profit sector has been emphasized in the past and deserves continued emphasis, it should also be noted that government agencies charged with reimbursement may not favor new, more expensive therapies; journals receive advertising and have their own biases; and the press is under increasing pressure to deliver sensational news as the mainstream press has downsized. The complexity of this situation is best handled by transparency about both financial and nonfinancial conflict of interest and instituting rational and explicit management plans, including having open discussion about the issues engendering potential bias.

Pulling It Together
The complexity of the task of developing and optimizing antithrombotic therapy is very challenging. There are 4 key areas to consider in antithrombotic development: (1) basic research into the biology of thrombosis, (2) preclinical development, (3) definitive clinical trials, and (4) comparative effectiveness. The NHLBI has a special role to play in funding research that explores the basic biology of thrombosis. Because there are no other major societal entities focused on this issue, sustained support is crucial, and in this arena the traditional peer-review system works well for identifying and promoting the best science. However, preclinical development is a key area where aggressive partnership-building efforts could enable the NHLBI to significantly catalyze more effective preclinical translational efforts. Continued work on
preclinical models, including animal models and in silico experiments, and investigation into the systems biology of thrombosis, as well, are key priorities in preclinical development. The NHLBI’s recently created mechanisms for translational units also should remain a high priority to attract more industry funding in this area.

The US clinical trials enterprise is bogged down by low throughput and high costs. Recent NHLBI workshops have suggested creative approaches to addressing this issue. In the field of thrombosis, intensive studies of human systems biology are needed, as are more efficient mechanisms for conducting large trials. Collaboration with the newly created National Center for Advancing Translational Sciences will be critical in these regards, but it is a general support system, and specific efforts aimed at furthering thrombosis research will be essential.

Finally, the areas of comparative effectiveness and the assessment of antithrombotic combinations require leadership from NHLBI. Head-to-head comparisons and evaluation of combination therapies have not been emphasized by industry because of the economic risk and the complexity of regulatory review. Over the years, the NHLBI has conducted many landmark trials that have examined marketed therapies and evaluated their value for patients. These efforts should continue and focus on antithrombotic therapy, but must now accommodate a larger number of potential partners for funding.

**Future Directions of NHLBI and Other Stakeholders**

The potential role for NHLBI as a convener in this field is shown in Figure 3.

Because of funding limitations, collaboration across traditional lines will be necessary. Given the NHLBI’s transpar-ency and the degree of public trust reposed in it, the agency should be constantly engaged in thrombosis research, bringing together the many interested parties to fund important research through creative partnerships. In many cases, the NHLBI can aggregate information and serve as the neutral ground for interpretation, thus setting the direction of research without having to provide the funding; in other cases, the research should be funded directly by public sources. The specific recommendations in this report on trials for antithrombotic agents represent an example of an effort that could be expanded to other fields.

Much of the accretion of knowledge in this field is stored in digital media. Given the accelerating rate at which these data are accumulating, there is a pressing need for a knowledge repository (encompassing precompetitive and publicly available information) that could be used and contributed to by all interested parties.

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