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# Highlights from the IV International Symposium of Thrombosis and Anticoagulation (ISTA), October 20–21, 2011, Salvador, Bahia, Brazil

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**Abstract** To discuss and share knowledge about advances in the care of patients with thrombotic disorders, the Fourth International Symposium of Thrombosis and Anticoagulation was held in Salvador, Bahia, Brazil, from October 20–21, 2011. This scientific program was developed by clinicians for clinicians and was promoted by three major clinical research institutes: the Brazilian Clinical Research Institute, the Duke Clinical Research Institute of the Duke University School of Medicine, and Hospital do Coração Research Institute. Comprising 2 days of academic presentations and open discussion, the symposium had as its primary goal to educate, motivate, and inspire internists, cardiologists, hematologists, and other physicians by convening national and international visionaries,

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thought-leaders, and dedicated clinician-scientists. This paper summarizes the symposium proceedings.

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## Introduction

Venous and arterial thrombosis cause more than 50% of deaths in the developed world (http://www.cdc.gov/nchs/fastats/deaths.htm). Anticoagulants and antiplatelet drugs are the main tools used by physicians to prevent the formation of pathologic clots. During the first decade of the 21st century, dozens of clinical trials have been undertaken to evaluate promising new antithrombotic agents that offer the possibility of simpler treatment with either better efficacy, reduced toxicity, or both.

The Fourth International Symposium of Thrombosis and Anticoagulation was held in Salvador, Bahia, Brazil, from October 20–21, 2011; this congress offered its attendees the rare opportunity to network with each other while hearing about cutting-edge clinical research and discussing its implications for clinical practice with internationally recognized experts. This scientific program was developed for practicing clinicians in multiple specialties, and the meeting was endorsed by three major clinical research institutes: the Brazilian Clinical Research Institute, the Duke Clinical Research Institute of the Duke University School of Medicine, and Hospital do Coração Research Institute. It was also supported by the Brazilian Societies of Internal Medicine, Cardiology, Intensive Care Medicine, and Vascular Surgery, by the Latin American Group of Thrombosis and Hemostasis, and by the Anticoagulation Forum from the United States. The chairmen of the meeting were Dr. Renato D. Lopes and Dr. Richard C. Becker, both from Duke University School of Medicine and the Duke Clinical Research Institute, and Dr. David Garcia from the University of New Mexico.

After reading this summary of the symposium proceedings, we are confident the reader will agree that the symposium met its main goal: to educate, motivate, and inspire internists, cardiologists, hematologists, and other physicians to thoughtfully apply the best available evidence to the care of their patients with (or at risk for) thrombotic disease.

## Platelet biology

Platelets are small cellular fragments devoid of a nucleus, derived from the megakaryocytes, with diameters ranging from 1.5 to 3.0 μm. In steady state, platelets assume a discoid shape that completely changes during activation. The half-life of platelets in circulation is approximately 8–12 days. Platelets contain large deposits of adenosine diphosphate (ADP) and adenosine triphosphate (ATP); thus, they have a high capacity for energy metabolism that is similar to that of smooth muscle cells. However, because platelets are devoid of a nucleus, they have limited ability for protein synthesis.

The main function of platelets is to ensure primary hemostasis. However, in several clinical scenarios (such as acute and chronic coronary syndromes and cerebrovascular diseases), platelets play a negative role and are considered the main elements responsible for the physiopathology of these serious diseases.

The platelet membrane is composed of proteins, carbohydrates, and lipids. Lipids represent 35% of the membrane composition and are anti-symmetrically arranged when the platelets are in steady state (not activated), with the negatively charged phospholipids arranged in the internal portion of the membrane. The external surface of the membrane is rich in receptors, among which are the glycoprotein complex (GP) Ib/V/IX that preferably binds von Willebrand factor (vWF); GP VI that strongly binds collagen; and GP IIb/IIIa that binds fibrinogen, allowing platelet aggregation. Also in the platelet membrane, proteins such as the p-selectin are expressed. These work as chemo-attractants for leukocytes.

Cytoplasmic organelles are also very important for platelet function. These include dense peroxisomes (responsible for lipid metabolism), mitochondria (oxidative metabolism), lysosomes (only released in response to very powerful stimulations; able to cause local injury), and dense granules and alpha granules. Dense granules contain calcium at high concentrations, as well as ADP, ATP, and serotonin. Alpha granules contain great variety of substances with pro-coagulant, mitogenic, and inflammatory functions (e.g., vWF, fibrinogen, cytokines, and platelet factor 4). The release of these granules varies according to platelet stimulation.

The platelet cytoskeleton is essentially undone and remodeled during platelet activation, changing from a discoid to a spherical shape. Also during platelet activation, phyllopods are formed. Contraction of the cytoskeleton contraction is one of the basic steps of platelet activation that allows secretion of dense and alpha granules.

Platelet function can be categorized into three actions: adhesion, activation, and aggregation. An initial trigger for platelet adhesion is vascular injury, with exposure of the subendothelial content (vWF and collagen). This vascular injury can be spontaneous or iatrogenic (e.g., during percutaneous coronary intervention [PCI]). Once vWF and collagen are exposed in the circulation, platelets initiate adhesion, through binding of the GP Ib/V/IX receptor to vWF and GP VI to collagen.

The degree of platelet activation depends on several vascular injury characteristics, such as: depth of the injury, vessel site, hematocrit level, flow speed at the site concerned, and vessel diameter. The activation process is initiated right after adhesion, and both continue to occur simultaneously. Four steps are fundamental during activation: mobilization of intracellular calcium (which works as the most powerful second messenger within the platelet); cytoskeleton contraction (with change in platelet shape); secretion of alpha and dense granules (with release of platelet agonists with autocrine and paracrine action; thus, enhancing the activation signal); and exposure of negatively charged phospholipids in the external portion of the membrane (with consequent activation of coagulation cascade and thrombin generation).

The more important platelet agonists are: thromboxane A2 (TP receptor), which stimulates initial activation and local vasoconstriction; ADP (acts on $P2Y_1$ and $P2Y_{12}$ receptors), which stimulates more stable activation; thrombin (acts on PAR 1 and 4 receptors), which primarily stimulates activation in pathological conditions and is considered the most powerful agonist; and collagen (GP Ib and GP VI), which stimulates activation.

Platelet aggregation is considered the final step in platelet response to injury and involves the conformational change of the GP IIb/IIIa receptor, which moves from a low-affinity steady state to a high-affinity activated state. The activated GP IIb/IIIa receptor binds fibrinogen, forming platelet-fibrinogen-platelet aggregates and a stable platelet plug.

Platelets interact directly with the coagulation system in many ways. The interaction can be physical, such as through exposure of negatively charged phospholipids on the external surface of the membrane, or chemical, through release of pro-coagulant granules. Platelets also interact similarly with inflammatory cells through exposure of p-selectin, leading to recruitment of leukocytes and exposure of the CD40 receptor from the surface of macrophages.

In short, platelets are important structures responsible for primary hemostasis, but play a negative role in several clinical scenarios. Platelet biology is very complex because platelets have to interact with other systems, including the coagulation cascade**.**

## Measures of platelet function: are we ready to use them?

In the treatment of coronary disease, inhibition of platelet activation and aggregation is critical to the prevention of cardiovascular atherothrombotic outcomes. Clopidogrel, a $P2Y_{12}$ receptor antagonist, improves outcomes among patients with acute coronary syndrome (ACS) and after PCI. However, clopidogrel is a biologically inactive prodrug that requires several steps of metabolism for active effect. In part because of these activation steps, substantial inter-individual variability in pharmacodynamic response has been previously observed. Individual variation in response to antiplatelet therapies is in part predicated on intrinsic factors (such as genetic polymorphisms affecting absorption and/or metabolism of drug) and in part related to clinical factors such as patient non-compliance with therapies or drug–drug interactions.

There are several methods for assessment of platelet response to therapy. The current gold standard is light transmission platelet aggregometry, which involves introduction of a platelet agonist such as ADP with a light-based assay that ultimately assesses platelet aggregation. The requirement for high technical expertise, as well as substantial processing times to generate platelet-rich plasma, render this assay an unwieldy tool for clinical use. Point-of-care aggregation tests involving whole blood samples—such as the VerifyNow assay—employ the same principles in a cartridge-based fashion and have been validated against the gold standard. The vasodilator activated phosphorylation (VASP) assay measures intra-platelet phosphorylation in response to $P2Y_{12}$ receptor activation; higher VASP phosphorylation levels are observed with superior inhibition of the $P2Y_{12}$ receptor by agents such as clopidogrel. Yet, like light transmission aggregometry, this is a tool largely used for research purposes due to its technically demanding laboratory processes. Another platelet function testing modality, the multi-plate assay, examines the degree of platelet adhesion and aggregation on the sensors' surface by quantifying electrical resistance between the two central wires.

All of the above platelet function testing modalities have been shown to correlate with post-PCI outcomes. For VerifyNow, platelet reactivity unit levels $> 235$ are associated with increased risk of cardiovascular death, non-fatal myocardial infarction (MI), and stent thrombosis. The Do Platelet Function Assays Predict Clinical Outcomes in Clopidogrel-Pretreated Patients Undergoing Elective PCI study compared VerifyNow to traditional light transmission aggregometry and noted good correlation between these two tests in their ability to discriminate future thrombovascular outcomes. For VASP phosphorylation, low post-treatment response defined as platelet reactivity $> 50\%$ was associated with future risk of cardiovascular events. Similarly for the multi-plate assay, low responders were associated with a higher incidence of stent thrombosis.

The role of platelet function testing in tailoring therapy for individual patients remains to be elucidated. The multicenter Gauging Responsiveness With A VerifyNow

Assay—Impact on Thrombosis and Safety (GRAVITAS) trial focused on patients who had residual high-on treatment platelet reactivity measured by VerifyNow testing and randomized these patients to standard-dose clopidogrel (75 mg daily) versus higher-dose (150 mg daily). Unfortunately, no differences in clinical outcomes were noted between groups, which may in part be attributed to persistently high platelet reactivity even among the higher-dose group. While this study examined the impact of dose doubling, we look to studies such as the Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and a Interruption Versus Continuation of Double Antiplatelet Therapy (ARCTIC) trial, which will examine the role of tailored therapy using alternative agents, such as prasugrel or ticagrelor, that have been shown to provide more potent and consistent inhibition of platelet function.

One important question that has been raised is: what is the appropriate timing of platelet function testing? In a study by Campo et al., PCI patients had serial measurements at baseline and at one month. Among patients who were full responders at baseline, 4% became poor responders by 30 days; in contrast, among patients who were poor responders at baseline, 70% became full responders by one month. Further, patients who were poor responders both at baseline and at one month and those who were full responders at baseline but became poor responders at one month had worse ischemic outcomes by one year. These results suggest that the 30-day time point may be a more relevant time to test.

Another question is whether platelet function testing can be used to define a therapeutic window for antiplatelet therapies similar to the international normalized ratio (INR) for warfarin therapy. To date, the ability of existing platelet function tests to predict bleeding outcomes is limited. One modestly positive study by Sibbing et al. showed that bleeding was associated with an area under the curve $\leq$188 using multi-plate technology.

In summary, several testing modalities are currently available to assess on-treatment platelet response to antiplatelet therapies. While these tests provide important prognostic information for ischemic events, their potential for bleeding prediction appears limited. Platelet function testing may someday be helpful for therapeutic selection; however, further evidence is necessary.

## Vitamin K antagonists: is this the beginning of the end?

For centuries, thrombosis has been recognized as a major pathological finding in many significant and often fatal clinical conditions. Parenteral anticoagulants, specifically unpurified heparin, led the way in the pharmacological treatment of thromboembolic diseases. Its main drawback was that it was not available for oral use. Shortly after, there came the anti-vitamin K oral anticoagulants—dicumarol and warfarin—which have been used widely since the 1950s for treatment and prevention of thromboembolic diseases, such as deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of cerebral vascular embolism in conditions such as atrial fibrillation (AF), artificial cardiac valves, and ventricular thrombi.

Use of vitamin K antagonists was, from the very beginning, recognized as troublesome due to the very narrow therapeutic range of anticoagulation, which led to lack of protection when suboptimal and to hemorrhagic events when in excess of prescribed limits. Furthermore, many natural nutrients and medicines can interfere with the pharmacological action of vitamin K antagonists, requiring frequent monitoring of the anticoagulant status via repeated measurements of the prothrombin time. The INR (a standardized reporting method) must be maintained within a narrow therapeutic range to maximize the benefit of warfarin. Several observational studies and well-controlled trials have documented the challenges of long-term warfarin use. Among observational studies, the percent time in therapeutic range has ranged only from 50 to 55% and, in the controlled trials, from 58 to 65%.

All of these difficulties probably explain the under-use of oral vitamin K anticoagulants worldwide. The recent development of new oral anticoagulants with better pharmacological profiles and easier use has raised hopes that, in the near future, vitamin K antagonists will be replaced, assuming that the newer agents prove as successful in long-term surveillance as they have been demonstrated to be in relatively short-term trials.

## New anticoagulants and new hematologic dilemmas

The development of novel anticoagulant medications has become a high priority for pharmaceutical companies. Enthusiasm for novel agents has resulted from the observation that about 50% of the population of the western world dies from either heart attack or stroke and that millions of people have AF, many of whom are inadequately treated using current oral anticoagulants. Additionally, our current armamentarium of anticoagulants (consisting predominantly of heparin, low-molecular-weight heparin [LMWH], oral vitamin K antagonists, and a selection of relatively infrequently used newer agents such as fondaparinux, hirudin, argatroban, and bivalirudin) are often perceived to be "old" and may have significant limitations that restrict their use. With the exception of the oral vitamin K antagonists, all of these medications are parenteral,

and many are expensive. Oral vitamin K antagonists are highly effective but have a slow onset and offset of action, large between-person variability in their dose requirements, are subject to food and drug interactions, and are complex to reverse. Despite these drawbacks, the oral vitamin K antagonists have been proven to reduce thromboembolism in a wide variety of settings, including patients with AF, mechanical heart valves, MI, and after orthopedic surgery. They are also effective for the secondary prevention of DVT, PE, and MI.

The "ideal" anticoagulant would be orally administered, have a rapid onset and offset of action, predictable pharmacokinetics and pharmacodynamics, a low propensity for food and drug interactions, be administered in fixed doses, be "reversible" in cases of bleeding, have a wide therapeutic window, and not require routine monitoring, but have a form of monitoring available should it be required. Oral vitamin K antagonists do not possess many of these characteristics.

Recent developments in the field of anticoagulants leave us at a crossroads; many clinicians are considering whether it is time to abandon the oral vitamin K antagonists. The rationale for reducing or eliminating use of oral vitamin K antagonists include eliminating the need for monitoring, having less variability in the dosing of the oral anticoagulant, and potentially reducing bleeding. However, eliminating oral vitamin K antagonists will be difficult. In some settings, they are the only proven therapy (e.g., patients with antiphospholipid antibody syndrome or those with mechanical heart valves). Additionally, oral vitamin K antagonists are inexpensive, they have 100% brand recognition internationally (thereby reducing the likelihood of medication errors), and the ability to monitor these drugs improves compliance. Finally, oral vitamin K antagonists can be rapidly reversed.

The development of novel anticoagulant medications has been facilitated by a comprehensive analysis of the coagulation cascade. Coagulation is initiated at sites of vascular injury when tissue factor binds with circulating activated factor VIIa. This complex converts factor X to factor Xa and factor IX to factor IXa. Factor Xa then acts in concert with factor Va to convert prothrombin to thrombin. Thrombin is the "engine" of coagulation. It converts fibrinogen to fibrin, facilitates a positive feedback loop leading to activation of coagulation, activates factor XIII, which cross-links fibrin stabilizing the clot, and has a number of other important roles in coagulation.

A clear understanding of the coagulation cascade has allowed the development of highly specific inhibitors of coagulation. Initially, these agents were developed using recombinant DNA technology modeled after naturally occurring anticoagulants. Perhaps the best example of this is the development of the hirudins, modeled after the anticoagulant present in the saliva of the medicinal leech. More recently, knowledge of the structure of the coagulation enzymes has allowed the development of molecules using computer-assisted design. These molecules are of low molecular weight, can be made orally bioavailable, and when carefully designed are highly specific to their enzyme target. Development of these agents has revolutionized the approach to anticoagulation.

Polypeptide drugs tested as inhibitors of coagulation include tissue factor pathway inhibitor, nematode anticoagulant peptide C2 (rNAPC2), active site-blocked factor VIIa, activated protein C, soluble thrombomodulin, and the hirudins. Low-molecular-weight inhibitors include rivaroxaban, apixaban, edoxaban, and dabigatran. Additional agents are under development.

In general, polypeptide drugs are falling out of favor, except for their use in acute situations such as ACS or in unstable patients with extensive thromboembolic disease. These drugs are used less and less frequently because of their high cost and need for parenteral administration. Furthermore, the effectiveness of many of these drugs has recently been questioned. For example, recombinant activated protein C was recently withdrawn from the worldwide market (http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2011/2011_142-eng.php, accessed November 14, 2011). Some of these drugs (e.g., rNAPC2) are being studied for other indications, such as the treatment or prevention of cancer.

Recent research has focused on inhibition of factor Xa or thrombin, given their seminal roles in coagulation. Rivaroxaban, apixaban, and edoxaban are all highly active, orally bioavailable inhibitors of coagulation. Each has been extensively tested in diverse clinical situations, and each holds promise as a therapy for the prevention and treatment of both venous and arterial thrombosis. Dabigatran is the only thrombin inhibitor currently available; although it has reduced bioavailability, it has demonstrated its effectiveness as an agent for the prevention and treatment of thrombosis.

Novel agents should not be regarded as a panacea; although they address many of the perceived concerns with novel anticoagulants, they have their own limitations. These include cost, a lack of familiarity among the medical community (leading to the likelihood of medical error), a much less broad set of indications (given their development in a more restrictive regulatory environment), and a lack of antidotes or reversibility. Although there has been early work on the development of specific antidotes for both the direct Xa inhibitors and dabigatran, none of these agents has reached even early-phase clinical trials in patients with active bleeding.

Given the excitement surrounding novel anticoagulant medications, it is very likely that a great deal more research

describing their utility and toxicities will be undertaken in the coming years.

## Antiplatelet agents under development

The evolution of antiplatelet therapy over the past decade has witnessed clear advances, with the development of increasingly potent and response-consistent $P2Y_{12}$ receptor antagonists, including prasugrel, and more recently ticagrelor, a non-thienopyridine agent that may also offer benefit through prolonged inhibition of adenosine re-uptake by erythrocytes. A wealth of information from phase three clinical trials highlights the broad potential of new-generation antiplatelet agents but also underscores the importance of patient selection, aspirin dosing, and uncommon yet potentially life-threatening hemorrhagic complications involving the gastrointestinal tract and brain. These adverse events serve as a reminder that platelets play an important role in hemostasis and the maintenance of vascular integrity, including the blood–brain barrier.

Future investigations will likely focus on strategies and technologies to optimize patient-centered therapies and platelet antagonists that attenuate thrombosis while preserving hemostatic potential and vascular reparative capacity.

## Anticoagulation in ACS patients managed invasively: a time for change or a time of choice?

Earlier studies demonstrated that the use of enoxaparin in non–ST-segment elevation ACSs (NSTE ACS) patients managed conservatively reduced the rates of death or MI by approximately 20% both at 8 and 42 days compared with unfractionated heparin (UFH). More recent studies, however, indicated that an invasive strategy with early catheterization and angioplasty was associated with improved outcomes compared with a conservative approach. When enoxaparin was compared with UFH in the setting of an early invasive strategy, similar efficacy outcomes, regardless of anticoagulation therapy, were seen. In contrast, patients treated with enoxaparin had a significant 30% increase in severe bleeding as evaluated by the TIMI scale.

Recently, a great deal of evidence has suggested that bleeding is a major determinant of clinical outcomes in ACS patients. Both moderate and important bleeding are associated with worse outcomes after adjustment for potential confounders. In a pooled analysis of 26,452 patients with ACS, severe bleeding increased more than five times the odds of 30-day mortality or MI.

Drugs recently developed, such as factor Xa inhibitors and direct thrombin inhibitors, have an improved safety profile. In the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial, the indirect Xa inhibitor fondaparinux reduced major and minor bleeding by more than 50% in NSTE ACS patients. This resulted in a significant 11% reduction in mortality at six months. Similarly, the thrombin blocker bivalirudin reduced severe bleeding by almost 40% in ST-segment elevation MI patients, leading to a 30% reduction in all-cause mortality. This benefit extended to three years of follow-up.

The results of these trials indicate that safer anticoagulant drugs with similar efficacy profiles are currently available and that new treatment combinations may reduce mortality. Therefore, it is a time for change to the newer agents in ACS. At this point, it is very important that the guidelines and future studies focus on these new therapeutic options; clinicians can benefit from more evidence when choosing the best clinical setting for each particular agent.

## Oral anticoagulants after ACS

Current guidelines recommend dual antiplatelet therapy after ACS, but the risk of recurrent ischemic events remains elevated in these patients. Meta-analyses of clinical trials on the addition of warfarin to aspirin after ACS indicate that this intervention is associated with a reduced rate of ischemic events at the cost of increased risk of major bleeding. Moreover, warfarin therapy requires frequent monitoring and is also associated with food and drug interactions. With the development of oral agents that directly inhibit thrombin or drugs that are direct inhibitors of factor Xa, a new opportunity for secondary prevention after ACS has emerged. These agents have predictable dose-dependent pharmacokinetics and pharmacodynamics and, therefore, do not require frequent monitoring. Some have also been shown to be effective and safe in the management of AF. Dabigatran, a direct inhibitor of thrombin, was compared with placebo on top of dual antiplatelet therapy in the Reduction by Dutasteride of Clinical Progression Events in Expectant Management (REDEEM) phase two trial in 1861 patients. The administration of newly developed direct factor Xa inhibitors on a background of single or dual antiplatelet therapy has also been evaluated by phase two trials. In the Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With ACSs (ATLAS ACS TIMI-46) trial, different doses of rivaroxaban were compared with placebo in 3491 patients. Darexaban was also evaluated in the dose-ranging Study Evaluating Safety, Tolerability and Efficacy of YM150 in Subjects With ACSs (RUBY) trial with 1279 patients, and apixaban was evaluated in the Apixaban for Prevention of Acute Ischemic

Events (APPRAISE) dose-ranging trial with 1714 patients. The results of these phase two trials in patients after ACS are remarkably consistent, by showing a dose-dependent increase in major bleeding with little or no significant effect on the reduction of cardiovascular events. In agreement with these findings, a phase three trial, APPRAISE-2, with 7392 patients, was prematurely terminated because of an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events.

The role of factor Xa inhibitors in the secondary prevention after ACS became even more complex after the results of the ATLAS-ACS 2 TIMI 51 trial, which evaluated more than 15,526 patients randomized to placebo or to two doses of rivaroxaban. Results of this highly anticipated trial demonstrated that ACS patients receiving standard therapy, including dual antiplatelet therapy, may benefit from the addition of the factor Xa inhibitor rivaroxaban, although at the cost of some additional bleeding complications. Both rivaroxaban doses reduced the primary end point of cardiovascular death/MI/stroke at the cost of increased bleeding rates. The 2.5-mg twice-daily dose had the better benefit/risk balance, due to lower bleeding risk, than the 5-mg twice-daily dose. Surprisingly, the lower dose of rivaroxaban resulted in a significant reduction in death from cardiovascular causes (2.7% vs. 4.1%, $P = 0.002$) and in all-cause mortality (2.9% vs. 4.5%, $P = 0.002$). These benefits were not observed in higher-dose rivaroxaban, and the difference between the two doses of rivaroxaban was significant. Rivaroxaban-treated patients experienced more major bleeding and intracranial hemorrhage than controls, but without a significant increase in fatal bleeding. It is possible that the addition of very-low-dose anticoagulation with rivaroxaban may represent a new treatment strategy in patients with a recent ACS. However, it is important to note that the ATLAS-ACS 2 trial had relatively small percentages of elderly patients, female patients, and patients with impaired renal function, suggesting that the results may not be entirely replicated with higher-risk patients in the real world.

In summary, as mentioned in the editorial by Matthew Roe and E. Magnus Ohman, "a new era of secondary prevention after an ACS has begun and will be characterized by the need to balance ischemic versus bleeding risks when selecting the type, number, and duration of antithrombotic therapies for individual patients."

## New antiplatelet agents in ACS patients: how should we choose?

Treatment options for patients with ACS continue to expand. Most recently, two new potent oral inhibitors of the platelet $P2Y_{12}$ receptor, prasugrel and ticagrelor, were found in randomized clinical trials to be superior to clopidogrel in preventing death, MI, or stroke in patients presenting with ST-segment elevation MI and NSTE ACS and are now available for clinical use. However, their availability only adds to the complexity of treatment selection. Considering combinations of oral and intravenous (IV) antiplatelet agents, anticoagulants, and their use and timing relative to the use and timing of PCI, there are at least 144 different possible combinations for treatment of an individual patient. Given this complexity, a number of factors should be considered in selecting therapy.

First and foremost, the evidence supporting efficacy and safety of the agent must be considered. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, clopidogrel reduced the risk of death, MI, or stroke relative to aspirin alone by 20% with acceptable incremental bleeding. However, the CURE trial was conducted prior to the current era of invasive treatment for NSTE ACS and did not include ST-segment elevation MI patients. In addition, clopidogrel levels and platelet responsiveness to clopidogrel are highly variable across patients, in part related to polymorphisms in CPY2C19, an enzyme in the cytochrome P450 system responsible for converting clopidogrel from a pro-drug to its active form. Unfortunately, there is no evidence to date that increasing the dose of clopidogrel is effective in reducing clinical events in patients with reduced function polymorphisms of CYP2C19 or in reducing death, MI, or stroke in ST-segment elevation MI and NSTE ACS patients overall.

Like clopidogrel, prasugrel is a thienopyridine and administered as a pro-drug, but is more potent than clopidogrel in inhibiting platelet function with less variability in response across individuals. Additionally, prasugrel is less susceptible to the effects of CYP2C19 polymorphisms than clopidogrel.

Ticagrelor is a non-thienopyridine, reversible inhibitor of the $P1Y_{12}$ receptor that is more potent than clopidogrel and is administered as the active drug. Briefly, compared with clopidogrel in patients with both NSTE ACS and ST-segment elevation MI, prasugrel (administered after coronary anatomy was known and PCI was planned) and ticagrelor (administered as upstream therapy) reduced the risk of death, MI, or stroke by 19 and 16%, respectively, over treatment of approximately 12 months. Importantly, treatment with ticagrelor resulted in a significant 21% reduction in cardiovascular mortality. Efficacy results were consistent across major subgroups, with a possible enhanced benefit of prasugrel among diabetic patients and reductions in stent thrombosis with both agents. There was a significant treatment-by-region interaction in the Platelet Inhibition and Patient Outcomes (PLATO) trial, such that the point estimate for treatment effect favored clopidogrel

in North America. Subsequent analyses suggested that aspirin dose explained the majority of the difference in treatment response by region, and ticagrelor now carries a Food and Drug Administration (FDA) black box warning for use only with low-dose aspirin (<100 mg).

Although there was a higher rate of major bleeding with ticagrelor compared with clopidogrel, there was no increase in intracranial or life-threatening bleeding. However, prasugrel resulted in a 32% higher rate of major bleeding than clopidogrel, which included significant increases in life-threatening and fatal bleeding and an increase in intracranial hemorrhage in patients with prior transient ischemic attack or stroke. Net clinical benefit was also not favorable for prasugrel in patients over age 75 years and those with body weight <60 kg. Therefore, prasugrel has an FDA black box warning restricting use in these subgroups.

A practical consideration in selecting treatment is cost, particularly with the expectation that clopidogrel will become available in generic form in May 2012. Present pricing for consumers in the United States is approximately $200 per month for clopidogrel, $215 per month for prasugrel, and $260 per month for ticagrelor. Compliance is also a practical concern. Both clopidogrel and prasugrel were developed for once-daily dosing, but ticagrelor was developed to be given twice daily, which may affect compliance in some patients. Additionally, ticagrelor causes symptomatic dyspnea in some patients, which may lead to lower compliance.

Selection among the new antiplatelet agents and clopidogrel should consider local practice patterns, including such things as what agents are available in institutional formularies and in local pharmacies and how familiar physicians at the treating facility are with the properties of the agents and their potential benefits and risks. Finally, a systematic approach is recommended for oral antiplatelet treatment selection that considers these factors, as well as local interventional and referral patterns, and that simplifies the approach to selection of all antithrombotic therapy for treatment of ACS at an institution.

## Bleeding and mortality in patients with ACS

Bleeding occurs commonly during the treatment of ACS, an observation that has been made in both clinical trials as well as in observational registries of community practice. However, the incidence of bleeding depends on the definition applied, and unfortunately varying definitions have been applied historically across trials. For example, in the TIMI trials, major bleeding is defined as fatal or life-threatening bleeding, intracranial hemorrhage, hemoglobin drop ≥5 g/dL, or hematocrit drop ≥15%. In contrast, the Acute Catheterization and Urgent Intervention Triage Strategy definition of major bleeding includes intracranial, retroperitoneal, intraocular, or access-site hemorrhage requiring surgical intervention, hematomas ≥5 cm in diameter, as well as more conservative hemoglobin drops depending on whether an overt source of bleeding is observed. The use of blood product transfusions has been variably incorporated into these definitions as well and contributes further to the variation and incidence of bleeding due to varying institutional thresholds for transfusion. The Bleeding Academic Research Consortium (BARC) assembled a working group to provide standardized bleeding definitions for cardiovascular clinical studies. This group acknowledged several challenges in creating a universal bleeding definition but proposed a consensus classification for bleeding evaluation or treatment. Type II bleeding includes clinically overt signs of bleeding that are actionable but do not meet criteria for other BARC bleeding. Type III is clinical, laboratory, and/or imaging evidence of bleeding with specific health care provider response. Type IV includes coronary artery bypass graft (CABG)-related bleeding, and Type V is defined as fatal bleeding.

Bleeding has important prognostic complications as it has been associated with an increased longitudinal risk of mortality. The severity of bleeding correlates with worse outcomes. Bleeding is costly, not only because it prolongs length of hospitalization, but also because it is associated with additional diagnostic and treatment interventions. Bleeding can also result in decreased use of evidence-based therapies. In a study of patients with ACS, patients who developed bleeding complications were less likely to be discharged on antiplatelet therapy such as aspirin and thienopyridine. Six months after a bleeding event, these patients remained less likely to receive these evidence-based therapies. Even nuisance bleeding is associated with a high rate of antithrombotic treatment discontinuation.

Bleeding also often leads to the transfusion of blood products. Tremendous variation in transfusion practices exists across health care organizations. However, a common theme is that older patients, female patients, and patients with renal insufficiency are more likely to receive transfusion therapy. Transfusion in the ACS setting has been independently associated with worse outcomes. Appropriate thresholds for transfusion have not been well established within the cardiovascular arena. The only randomized clinical trial on this topic was conducted by the Canadian Clinical Trials group in 1999, which randomized 838 critically ill patients to a liberal versus restrictive transfusion strategy. No difference in 30-day mortality was noted between transfusion strategies, although there was a suggestion of benefit for the more liberal strategy among patients with coronary disease.

There is increased focus on bleeding avoidance strategies. First and foremost would be the prediction of bleeding risk. The Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) bleeding risk score was developed and validated in a cohort of patients with NSTE ACS, and it identified eight clinical factors that are associated with increased bleeding risk: female sex, prior history of diabetes, heart failure, peripheral vascular disease, or clinical and laboratory evidence of risk including lower creatinine clearance, higher heart rate on admission, lower systolic blood pressure on admission, and lower admission hematocrit. A key first step to bleeding avoidance is the appropriate dosing of antithrombotic therapies. Patients who are older or who have worsening renal function are particularly vulnerable to excess antithrombotic dosing. Appropriate dosing, particularly in these high-risk patients, may alleviate the relationship between these risk characteristics and increased bleeding risk. The use of safer antithrombotics may also be considered. Bivalirudin, for example, has been well studied in both the ST-elevation and NSTE ACS settings and has been shown to have efficacy comparable with the traditional combination of heparin and GP IIb/IIIa inhibitors but an enhanced safety profile with reduced bleeding risk. Arterial access for cardiac catheterization may also play a role in bleeding avoidance. The recent Radial Versus Femoral Access for Coronary Angiography and Intervention in Patients with Acute Coronary Syndromes (RIVAL) study compared clinical outcomes between patients who underwent radial versus femoral arterial access. Although the primary outcome of death, MI, stroke, and non-CABG-related major bleeding at 30 days was not significantly different between groups, secondary outcomes, including the occurrence of large hematomas or major vascular access site complications, were substantially reduced with radial access.

In summary, bleeding is an important event associated with increased mortality among patients with ACS, and bleeding avoidance should be prioritized while reducing ischemic risk with antiplatelet interventional therapies. Strategies that achieve this balance are associated with improved survival.

## Thromboprophylaxis in critically ill patients

Critically ill patients have an increased risk of DVT due to their acute illness, procedures such as central venous catheterization, and immobility. Among patients in the intensive care unit (ICU), DVT is an important problem because thrombus propagation and embolization can lead to potentially fatal PE. The effects of thromboprophylaxis with LMWH compared with UFH on venous thromboembolism (VTE), bleeding, and other outcomes were uncertain in critically ill patients. To address this question, The Prophylaxis for Thromboembolism in Critical Care (PROTECT) trial (NCT00182143) was planned.

PROTECT was a randomized, stratified, concealed international trial comparing subcutaneous injection of UFH 5000 IU or the LMWH dalteparin 5000 IU once daily plus once-daily placebo for the duration of the ICU stay. The objectives of PROTECT were to examine, among medical-surgical critically ill patients, the effect of the LMWH versus heparin on the primary outcome of proximal leg DVT and the following secondary outcomes: DVT elsewhere, PE, any venous thromboembolism (DVT or PE), and the composite of VTE or death, bleeding, and heparin-induced thrombocytopenia. Patients were followed up to death or hospital discharge. Venous thromboembolism events were included after ICU discharge. All patients, families, clinicians, research personnel, outcome adjudicators, and the trial biostatistician were blinded to allocation. Data were analyzed according to the intention-to-treat principle.

The main results of the PROTECT trial suggested that there was no significant between-group difference in the rate of proximal leg DVT, which occurred in 96 of 1873 patients (5.1%) receiving dalteparin versus 109 of 1873 patients (5.8%) receiving UFH (hazard ratio in the dalteparin group, 0.92; 95% confidence interval [CI], 0.68–1.23; $P = 0.57$). The proportion of patients with pulmonary emboli (a key secondary outcome measure) was significantly lower with dalteparin (24 patients, 1.3%) than with UFH (43 patients, 2.3%) (hazard ratio, 0.51; 95% CI, 0.30–0.88; $P = 0.01$). There was no significant between-group difference in the rates of major bleeding (hazard ratio, 1.00; 95% CI, 0.75–1.34; $P = 0.98$) or death in the hospital (hazard ratio, 0.92; 95% CI, 0.80–1.05; $P = 0.21$).

## Does aspirin have a role in venous thromboembolism prevention?

Patients undergoing orthopedic surgery are at high risk for VTE. Anticoagulant agents (e.g., LMWH or fondaparinux) significantly reduce the risk of VTE after orthopedic surgery, but the role of aspirin in VTE prevention has been controversial, in part because platelets are thought to be less important than fibrin in venous thrombosis. Guidelines published by the American Academy of Orthopedic Surgeons recommend aspirin as one of several acceptable VTE prevention strategies for the majority of patients undergoing major orthopedic procedures. In contrast, the eighth edition of the American College of Chest Physicians'

Evidence-based Guidelines on Antithrombotic Therapy strongly recommends that aspirin *not* be used for VTE prophylaxis.

A recent systematic review of all evidence relevant to aspirin suggests that aspirin is almost certainly more effective than placebo for the prevention of VTE following orthopedic surgery. The most important data come from two sources: a meta-analysis published by the Anti-Platelet Trialists' Coalition (APTC) in 1994 and the Pulmonary Embolism Prevention (PEP) study published in 1999. The APTC meta-analysis included data pooled from almost 9000 patients who had participated in VTE prevention trials following orthopedic surgery, as well as other clinical settings. Although the results indicated that, compared with placebo, aspirin reduced the rate of PE by more than 50%, the validity of the findings was questioned because many of the trials from which these data were abstracted had serious methodologic flaws (e.g., open-label design, sub-optimal DVT detection methods, non-uniform antiplatelet drugs and doses across studies).

The PEP trial was undertaken to address the fact that many physicians (especially non-surgeons) had rejected the APTC results. Over 17,000 patients in five countries were randomized to receive either aspirin 160 mg or placebo, started pre-operatively and continued for 35 days. The majority of patients underwent surgery to repair a hip fracture, but about one quarter of participants had an elective total hip arthroplasty. This well-designed, very large randomized trial with almost 100% follow-up for clinical end points found that aspirin reduced the risk of fatal and non-fatal PE; the relative effect was very similar to that seen for aspirin in the APTC meta-analysis. Based on data from PEP and APTC combined, it appears that, compared with placebo, aspirin could prevent 5–10 PEs per 1000 patients treated. Aspirin use following major orthopedic surgery would be expected to increase the number of patients who require transfusion by approximately 3–6 per 1000. Although a few direct comparisons between aspirin and anticoagulant agents in this setting have been published, the available evidence is too sparse and too inconsistent to draw definitive conclusions about the net clinical benefit (or harm) of anticoagulants versus aspirin in this setting. Pending further study, it seems reasonable to conclude that aspirin should have *some* role as a VTE prevention strategy after orthopedic surgery; without more data, however, we can expect ongoing disagreement about the patients for whom it would be most appropriate.

## Should patients with cancer receive primary VTE prophylaxis?

The association between cancer and thromboembolic phenomena has been recognized since 1865. It was first described by Armand Trousseau (1801–1867) as a sign of occult pancreatic cancer, but there is wide variation in the relative risk of VTE in different cancers. The presence of an active cancer should be one of the leading risk factors recognized by physicians when assessing VTE risk during hospitalization. In the algorithm used for electronic alert to prevent VTE created by Kucher and colleagues, the presence of cancer carries a score of 3, while a score $\geq 4$ reflects a high thrombotic risk. Some other scores evaluate the VTE risk in patients with cancer and on chemotherapy. The most important single message is that physicians should perform a systematic evaluation of each cancer patient, taking into account both factors linked to the patient (such as age, type and stage of the disease, previous history of VTE, known thrombophilia), as well as factors linked to the treatment (type of chemotherapy, hormonal therapy or an anti-angiogenic agent, such as thalidomide in association with corticosteroids, immobilization during hospitalization, and surgery).

VTE is one of the most frequent complications in cancer patients (4–20%). The risk of VTE is 3–5 times higher in cancer patients undergoing surgery than in those without cancer, and, as a consequence, among hospitalized cancer patients who die, one in every seven do so from PE. Also, when cancer patients develop a thrombotic event, they have a three-fold increased risk of recurrence, even years after the first VTE episode. Compared with similar patients without malignant disease, cancer patients have twice the incidence of bleeding during anticoagulant treatment. Furthermore, the development of VTE is independently associated with lower survival rates. At the same time, there is growing evidence that the use of anticoagulants lowers the risk of death; however, this hypothesis requires further research.

With regard to preventing thromboembolic disease in cancer patients, the patients who have been studied most often are those undergoing surgical intervention for their cancer. Low-dose UFH and LMWH are effective in preventing both DVT and fatal PE in general and in oncological surgical patients undergoing laparotomy. It has been demonstrated that cancer itself is a risk factor for the development of perioperative bleeding complications independent of pharmacological thromboprophylaxis type.

Cancer patients admitted to the hospital but not undergoing surgical intervention should be treated as other acutely ill hospitalized medical patients and provided with thromboprophylaxis when appropriate. The use of routine anticoagulation for patients with central venous catheters is no longer recommended. Although older studies suggested that the use of low-dose vitamin K antagonist or LMWH was associated with a benefit in reducing the frequency of thrombosis associated with central catheters, some more contemporary studies with the same agents fail to demonstrate a benefit.

At least three major guidelines for thromboprophylaxis in cancer patients have been published in recent years—the European Society for Medical Oncology, the American Society of Clinical Oncology, and the American College of Chest Physicians, 8th edition—and may help physicians in their clinical practices. Some of the key points about primary prophylaxis in cancer patients are as follows:

- LMWH, low-dose UFH, and vitamin K antagonist are not routinely indicated to prevent catheter-related thrombosis or during chemotherapy, if patients are ambulatory, except in multiple myeloma patients receiving thalidomide or lenalidomide or dexamethasone.
- Routine use of VTE prophylaxis with low-dose UFH or LMWH or fondaparinux in cancer patients undergoing medium and large surgical procedures is recommended.
- VTE prophylaxis should be maintained for at least 7–10 days and considered for up to 28 days in curative pelvic and abdominal cancer procedures.
- Routine use of prophylaxis should be considered in cancer patients hospitalized with an acute medical illness.

## Managing anticoagulation in patients undergoing surgical procedures: diminishing bleeding and ischemic risks

Excessive bleeding leads to early instability and postoperative complications, and blood transfusion is clearly related to late mortality after cardiac surgery. Measures to prevent bleeding and avoid blood transfusion are very important to improve surgical outcomes. Preoperative anticoagulation and antiplatelet therapy comprise one of the six major risk factors for prediction of surgical bleeding.

Consequently, there are two situations in which coagulation status must be managed prior to surgical procedures to diminish bleeding and ischemic risk: in patients using an anticoagulation agent and in those receiving dual antiplatelet therapy. Aspirin is not a problem anymore. Although in the past it was recommended to cease aspirin use 3–5 days prior to surgery, this is no longer the case as guidelines now recommend that aspirin be administered prior to CABG because it has been shown to be related to better surgical outcomes. Thus, aspirin may be avoided only before special surgical procedures such as ophthalmic or intra-cerebral procedures.

### Anticoagulants

Warfarin is by far the most widely used anticoagulant. In some regions, fenprocoumon is preferred because of its longer half-life. Newer agents, such as dabigatran, apixaban, and rivaroxaban, for example, have not yet been completely incorporated into the routine clinical armamentarium. Anticoagulants are mostly used for preventing arterial and pulmonary embolism in atrial fibrillation, for implanted mechanical valves, DVT, and PE. The main advantages of the newer anticoagulants are that they do not require monitoring and have a shorter half-life, which could facilitate management around the time of a surgical procedure. But there is very limited published evidence regarding those new drugs in surgery.

Warfarin might not be interrupted for low-risk endoscopic procedures. For patients at high risk for thrombosis who undergo procedures with low bleeding risk, it is recommended to stop use 3–5 days preoperatively. When the thrombosis risk is high and there is also high bleeding risk, it is recommended to stop warfarin 3–5 days preoperatively and monitor the INR. In the presence of an implanted mechanical heart valve, there is need to employ a bridge therapy prior to surgery, interrupting warfarin and introducing unfractionated or low-molecular-weight heparin until the moment of the procedure, and restarting warfarin the day after surgery. In this setting, a practical approach to perioperative anticoagulation would be: Discontinue warfarin 5 days preoperatively if INR is between 2 and 3 and for 6 days if INR is between 3 and 4.5. Observe that aging is associated with a slow resolution of anticoagulant effect.

### Antiplatelet drugs

As already mentioned above, earlier guidelines recommended interruption of aspirin use some days prior to any operation. This is no longer true, especially in cardiac surgery, because with modern management, bleeding is seldom related to aspirin administration. Current guidelines do not recommend aspirin interruption, and the recently published American College of Cardiology/American Heart Association guideline for CABG surgery includes a Class I recommendation for the administration of aspirin in patients who are not taking it and who are undergoing CABG because it is related to better surgical outcomes.

Thienopyridines are related to postoperative bleeding and should be avoided or require specific management during the perioperative period. Because there are some different characteristics between the two most commonly used drugs of this class, they will be commented on separately below:

#### *Clopidogrel*

This is the most widely used ADP $P2Y_{12}$ inhibitor. Because its effect on platelets is irreversible, its use must be interrupted 5–7 days preoperatively, providing sufficient time for the platelet population to be renewed. The impact of exposure to clopidogrel in patients with ACS requiring coronary artery

bypass surgery was studied in a multicenter analysis for the end points of reoperation, major bleeding, and length of hospital stay. It was found that the adjusted risk for reoperation was 9.80 (95% CI: 2.18–43.95; $P = 0.01$) in the clopidogrel patient group. Interestingly, the management of patients undergoing CABG on clopidogrel seems to be improving, as bleeding and associated mortality have been reduced in recent reports as compared with the last two decades. There is variability in the patient's response to clopidogrel, due to genetic characteristics. For this reason, some would argue that there is a place for point-of-care testing to evaluate its action in the individual patient, although there is no formal recommendation for such testing. More studies to clarify the role of these tests in this setting are warranted.

*Prasugrel*

As with clopidogrel, this drug irreversibly binds the ADP $P2Y_{12}$ receptor. It has not been used as frequently as clopidogrel because it was more recently approved for clinical use. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) found it to be rather efficacious despite a higher bleeding tendency in ACS. In patients receiving CABG, however, prasugrel was related to a 21.9% incidence of surgical bleeding, compared with 4.1% related to clopidogrel. It is reasonable to recommend stopping prasugrel for at least 7 days prior to CABG and to take special precautions to prevent perioperative bleeding.

*Ticagrelor*

This drug has some advantages over the above-mentioned thienopyridines because its effect is reversible and diminishes within 48 h, so that major surgical procedures can be done without fear of excessive bleeding. In the PLATO trial for ACS, ticagrelor was related to reduction of vascular death and MI but not stroke, compared with clopidogrel. There is little clinical evidence regarding the impact of ticagrelor on surgical outcomes. In a recently published analysis comparing ticagrelor with clopidogrel in the PLATO trial, among patients receiving CABG for whom ticagrelor/placebo was to be withheld for 24–72 h and clopidogrel/placebo for 5 days preoperatively, there was reduced cardiovascular and total death without an increase in major bleeding in the ticagrelor group.

## Perioperative management in patients under dual antiplatelet therapy

As aspirin can be safely maintained during the surgical period, management is focused on the second antiplatelet drug. Taking clopidogrel as the paradigm drug and adjusting management for the others drugs, general measures can be summarized as below.

It is recommended as Class I in Society of Thoracic Surgeons (STS)/Society of Cardiovascular Anesthesiologists (SCA) guidelines to stop medications that inhibit the platelet $P2Y_{12}$ receptor before operation to decrease bleeding events. The timing of discontinuation depends on the pharmacodynamic half-life for each agent, as well as the potential lack of reversibility.

European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines state that, for preoperative management of patients treated with dual antiplatelet therapy and considered for cardiac and non-cardiac surgery, one should proceed as follows: (1) emergent case: proceed to surgery; (2) semi-elective and urgent: "case-by-case" clinical decision; (3) elective: wait until completion of mandatory dual antiplatelet regimen. The decision-making process should balance the risk of thrombosis against the risk of bleeding, leading to continued use of aspirin + clopidogrel in low bleeding risk cases and continued use of aspirin but stopping of clopidogrel or even of both drugs in high bleeding risk cases.

The above-mentioned large meta-analysis on safety of clopidogrel being continued until CABG in ACS proposes an algorithm: (1) For stable elective CABG with no drug-eluting stent: stop clopidogrel for >5 days; (2) For stable elective CABG in the presence of drug-eluting stent implanted for <1 year: consider operating on clopidogrel or switch to IV tirofiban plus heparin as a bridge to surgery; (3) For non-elective CABG in emergent or urgent ACS: operate on clopidogrel, unless it is a reoperation, there is a bleeding disorder, or troponin is negative, favoring a multidisciplinary decision.

Lysine analogues, epsilon-aminocaproic acid, and tranexamic acid are very useful as they reduce total blood loss and decrease the need for blood transfusion during cardiac procedures and are indicated for blood conservation as Class I (Level A) in STS/SCA guidelines. Their effect is beneficial, even in routine CABG cases, for reducing postoperative thorax blood drainage. It might be advisable and is accepted in some centers for emergency ACS patients facing an intervention to avoid antiplatelet drugs until an anatomical coronary arteries diagnosis is obtained for deciding to proceed with a percutaneous intervention or surgery, or even excluding a non-coronary cause, such as aortic dissection, maintaining free use of aspirin and heparin.

Finally, some practical management tips based on surgical experience and previous literature are listed below:

- If possible, delay surgery for 3–5 days (clopidogrel or prasugrel) or 2–3 days (ticagrelor) if the patient is

relatively stable, balanced against severity and instability.
- If the patient is stable but the lesion is critical, give IV UFH until the effect of the antiplatelet drug wears off.
- No prophylactic preoperative transfusion of blood products.
- Do not stop heparin and give a full dose of heparin before bypass.
- Use tranexamic acid 10 mg/kg before surgical incision, plus 10 mg/kg on beginning of bypass.
- Generously use platelet transfusion after administration of protamine if diffuse bleeding, 0.2 units/kg.
- In the post-operative period, proceed to judicious surgical re-exploration, platelets infusion, and tranexamic acid when needed.
- Use reduced hemo-dilution under normothermia, modified ultrafiltration; minimize cardiopulmonary bypass circuits and priming.
- Employ good operative technique, including topical hemostasis, plus sealants or biological glues.
- Improve blood salvage methods and neutralize heparin with protamine on a titration basis.

## Venous thromboembolism in heart failure patients: how should we manage this special population?

Venous thromboembolism and congestive heart failure (CHF) are among the most commonly encountered medical conditions, particularly in the elderly and hospitalized population. It is well recognized that CHF patients develop a hypercoagulable state that involves abnormalities in all three components of the Virchow's triad, which places these patients at an increased risk for VTE. Unfortunately, VTE has generally been regarded to be an end point of secondary importance in large, randomized CHF trials, and therefore, its actual incidence in this population has not been well studied.

Multiple autopsy studies have confirmed a very high prevalence of VTE in CHF patients. A case-controlled study has also shown that CHF is an important risk factor for VTE in ambulatory outpatients and that the risk progressively increases with worsening of the ejection fraction. Large, randomized CHF trials have suggested in retrospective analyses that the incidence of PE in mildly symptomatic ambulatory patients is probably low (<1%/year). On the other hand, hospitalized CHF patients with impaired mobility have an incidence of VTE as high as 21%, although most of the events are asymptomatic distal DVT. In a recent prospective study involving severe CHF patients admitted to a coronary care unit, PE was diagnosed in 9.1% during the hospitalization period, despite adequate prophylaxis in 70% of the cases. It is also important that PE patients with CHF have a higher mortality than those without CHF, and that PE is an independent predictor of death and rehospitalization in CHF patients.

The diagnosis of VTE in CHF patients is an increasingly frequent and challenging problem. There is a substantial overlap in symptoms and signs of both conditions, and some of the diagnostic tests for VTE do not perform as well in the heart failure population. D-dimer levels are already elevated in the majority of CHF patients; thus, its utility for suspected VTE in this population is severely compromised. Lung scintigraphy is often non-diagnostic, but computed tomography maintains its accuracy and is the preferred imaging test to evaluate suspected PE in CHF patients. The therapeutic options in CHF patients with VTE are the same and include the commonly used anticoagulants, fibrinolytics, and catheter or surgical embolectomy. Nonetheless, comorbidities, numerous medications, and renal dysfunction—all commonly seen in CHF patients—pose serious challenges to the management of patients with PE.

In summary, CHF is an important risk factor for VTE, with an incidence that varies widely from <1% to 20% depending on the severity of the disease and the clinical context. Both conditions negatively affect each other's prognosis, and therefore a high index of suspicion should be maintained in patients presenting with decompensated CHF. The preferred method for confirming and excluding the diagnosis of PE in the CHF population is the computed tomography scan. Treatment should be promptly initiated once the diagnosis is suspected, and careful attention should be paid to the choice, dosing, and management of antithrombotic therapy, as several physiologic abnormalities place these patients at a particularly high risk of bleeding complications.

## Anticoagulation in atrial fibrillation: an important issue

Atrial fibrillation strokes are associated with a 30-day mortality of 24%. Warfarin has been shown to reduce the risk of stroke by 66%. Despite its proven efficacy, warfarin is underused in clinical practice. The dose response of warfarin is affected by age, sex, weight, liver function, dietary vitamin K, drugs, and pharmacogenomic factors. The narrow therapeutic window, coupled with a highly variable dose response, mandates frequent monitoring of the INR, which poses a barrier to warfarin's effectiveness in clinical practice. Several alternatives to warfarin have been evaluated in clinical trials. The first, dabigatran, is a direct oral thrombin inhibitor. Both rivaroxaban and apixaban inhibit factor Xa. All three of these agents reduced the risk of stroke (composite end point of ischemic and

hemorrhagic stroke) among patients with AF. The reduction in intracranial hemorrhage is unprecedented and is one of the most remarkable features of these drugs. Apixaban and the lower dose of dabigatran (110 mg) also reduced major extracranial bleeding compared with warfarin. These new oral anticoagulants are characterized by shorter half-lives compared with warfarin, do not require monitoring, and have fewer drug interactions. The degree of renal clearance is an important distinguishing feature of these drugs, as is the dosing frequency. Approximately 80% of dabigatran is eliminated by the kidneys, 66% of rivaroxaban (36% as unchanged drug), and 25% of apixaban. Both dabigatran and apixaban are dosed twice daily, and rivaroxaban is taken once daily.

Translating the efficacy of the novel anticoagulants from randomized trials into clinical practice will require heightened vigilance around medication adherence and changes in renal function. Creatinine clearance needs to be measured prior to initiation of these agents and then periodically throughout the duration of therapy. Although drug interactions are significantly less common with the new anticoagulants compared with warfarin, all are substrates of the P-glycoprotein (P-gp) transporter, so the potential for interaction with P-gp inhibitors and P-gp inducers exists. In addition, both apixaban and rivaroxaban are metabolized via CYP3A4. The short half-life and rapid onset of action obviate the need for perioperative bridging in most instances, but also highlight the importance of hemostasis prior to initiation following invasive procedures. The safety of these agents in combination with dual antiplatelet therapy warrants further study. In addition, data are needed regarding reversal of these anticoagulants in the setting of trauma, urgent surgery, and major hemorrhage. The ability to monitor the anticoagulant effect in select clinical situations remains a priority for real-world practice. The new oral anticoagulants represent a major advance in the prevention and treatment of thromboembolic disease. Current and planned studies will continue to inform their optimal use.

## Stroke and bleeding in atrial fibrillation: how should we assess them?

The prevalence of AF in the United States is expanding rapidly. By 2050, estimates project that there will be over 5 million Americans with AF. Patients with both paroxysmal and persistent AF face elevated risks for stroke and systemic emboli. This risk can be successfully mitigated if patients are treated with chronic anticoagulation, yet use of such therapy can also cause serious bleeding events including intracranial hemorrhage and even death. Thus, selection of anticoagulant therapy should ideally be individualized, guided by a patient's specific risks for stroke with AF and bleeding with anticoagulation.

These risks can now be accurately estimated used several published risk prediction models. The $CHADS_2$ risk score uses a simple additive sum of five clinical features (CHF, hypertension, age $\geq$ 75 years, diabetes, and stroke [weighted = 2]) to stratify risk for stroke in AF. The $CHAD_2$-VASc score extends this simple risk score by adding in three additional risk factors: vascular disease, age 65–75 years, and sex = female). This modification provides for slightly more accurate risk estimation, particularly among lower-risks groups. Clinical trials have demonstrated that the benefits of warfarin therapy are linearly associated with patient risks. Based on these data, current U.S. and European guidelines recommend initiation of anticoagulation in all patients with moderate-to-high stroke risk.

The risks of bleeding with warfarin therapy are also associated with certain patient-related risk factors, which can be summated using published risk scores. These include the HAS-BLED, ATRIA, and HEMORR2HAGES bleeding risk scores. While these scores can stratify risk, the scores are often based on retrospective factors (such as labile INR results), thereby limiting their use in prospectively selecting a given patient for drug initiation. These bleeding scores also unfortunately demonstrate that many patient factors associated with stroke risk (including age, hypertension, and stroke) are also risk factors for bleeding. For example, the choices for anticoagulation therapy in older patients with multiple comorbidities will require a trade-off of high benefit and high risks.

The individualization of therapy does not end with these risk factors but is also determined, in part, by provider and system factors. For example, concomitant medications can also raise a patient's risk for bleeding. Specifically, combining use of aspirin and/or an ADP-inhibitor with warfarin can substantially raise a patient's risk for bleeding. Additionally, the effective and safe therapeutic window for warfarin therapy is narrow. Therefore, close patient monitoring and appropriate dose titration are needed to achieve optimal results. However, data indicate that this is rarely achieved in current U.S. clinical practice, where patients on warfarin are within the recommended therapeutic range less than 55% of the time. Newer anticoagulant therapies, including the direct thrombin inhibitor (dabigatran) and the new factor Xa inhibitors (apixaban and rivaroxaban), offer the promise of reducing anticoagulation-related bleeding risks, particularly the dreaded risk of intracranial hemorrhage. Yet, while these novel drugs may not require such careful therapeutic titration, patients must still closely and continuously adhere to instructions for the drugs to be safe and effective. These later points emphasize the importance of considering patient, provider, and system factors when

selecting AF treatment, as well as highlight future opportunities for quality improvement in AF care.

## Triple therapy

Overlapping indications for antithrombotic therapy may lead to the need for "triple therapy," defined currently as aspirin, clopidogrel, and oral anticoagulation.

As the population ages, more patients will have both ACS and AF; accordingly triple therapy may be used more frequently. Prior studies have shown that, with more antithrombotic therapy, risk of bleeding increases. Many antiplatelet and anticoagulant drugs are part of the foundation for treatment of ACS and AF, making the decision about the right combination of these agents challenging. However, limited evidence is available to guide therapeutic decision-making about triple therapy. Registry information, subgroup analyses from clinical trials, and overviews of single-center experiences have been published, but no randomized trials evaluating different strategies of triple therapy have been completed.

Multiple guidelines and consensus statements from national societies provide recommendations for clinicians concerning the use of triple therapy. A simple flow diagram can be used by physicians to guide decisions about the need for dual antiplatelet therapy or triple therapy based on the assessment of patient bleeding and stroke risk. Five additional factors should be considered: (1) use of the lowest dose of antiplatelet therapy; (2) use of bare metal stents versus drug-eluting stents to minimize the duration of antiplatelet therapy; (3) optimal INR within a range of 2.0–2.5; (4) gastric protection with proton-pump inhibitors; and (5) minimization of the duration of triple therapy. It is also important to re-evaluate regularly the need for triple therapy. The risk of stent thrombosis will decrease over time, whereas bleeding risk will remain constant.

The ongoing What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) trial is a prospective, multicenter, open-label randomized trial that aims to determine whether the combination of oral anticoagulants and clopidogrel 75 mg/d reduces the risk of bleeding and is not inferior to triple therapy (clopidogrel + oral anticoagulants + aspirin) with respect to the prevention of thrombotic complications. The primary outcome of the study will be the occurrence of bleeding up to 30 days and one year. Major adverse cardiac events will be the secondary outcomes. Sample size is 496, and the estimated study completion date is October 2011 (www.clinicaltrials.gov, NCT00769938).

The Triple Therapy in Patients on Oral Anticoagulation After Drug-Eluting Stent Implantation (ISAR-TRIPLE) study, an interventional, randomized, open-label trial, was designed to compare the six-week versus six-month clopidogrel treatment regimen in patients with concomitant aspirin and oral anticoagulants following drug-eluting stenting. The composite of death, MI, definite stent thrombosis, stroke, or major bleeding will be the primary outcome. The secondary outcomes will be the composite of cardiac death, MI, stent thrombosis, or ischemic stroke, as well as major bleeding complications. Estimated enrollment is 600, and the completion date is July 2012 (www.clinicaltrials.gov, NCT00776633). These two studies will also provide important insights about the use of triple therapy in clinical practice.

The optimal antithrombotic strategy for patients with ACS and AF who do or do not undergo PCI is still uncertain. Based on the available data, triple therapy offers the best protection against stroke and myocardial events but at the cost of increased bleeding. Currently, triple therapy defined as aspirin plus clopidogrel plus warfarin should be administered for the shortest period possible. Triple therapy may be redefined in the near future with new $P2Y_{12}$ inhibitors such as prasugrel and ticagrelor, newer antiplatelet agents such as PAR-1 inhibitors, other oral factor Xa inhibitors such as rivaroxaban or apixaban, and antithrombin agents such as dabigatran.

Recent data suggest that some new antithrombotic agents under development have significant potential to improve anticoagulant therapy. Their uptake and use will depend mostly on efficacy, safety, and cost relative to current medications. Moreover, a careful balance of antithrombotic efficacy and bleeding risk is now recognized as essential. Forecasting the death of vitamin K antagonists such as warfarin may be still premature, however. How to apply therapies, even when they have been shown to provide benefits in trials, will continue to be a major challenge in clinical practice. Finally, the optimal duration of triple therapy use and the population that may benefit the most from it also need to be defined.

## How to manage anticoagulation in AF patients undergoing cardioversion

The reversion of an abnormal heart rhythm to its normal state was first described by Bernard Lown in 1961. The initial experience with cardioversion of ventricular and supra ventricular arrhythmias, including atrial fibrillation and atrial flutter, was furthered by several clinicians practicing at prominent institutions, who documented successes and potential complications, among them systemic embolism and stroke.

Guidelines for the management of AF and atrial flutter to include the peri-cardioversion period have been

formulated by national and international organizations and underscore the importance of anticoagulant therapy to minimize the risk of cardioembolic events that can be life-threatening or life-altering. While either IV or oral anticoagulants can be used as thromboprophylaxis for patients undergoing cardioversion, there are two fundamental tenets of effective therapy. First, a sufficient intensity of anticoagulation must be achieved at the time of the procedure. Second, a threshold level of anticoagulation must be maintained during a vulnerable period of varied duration after successful restoration of normal sinus rhythm.

## The limitations of bleeding risk prediction rules in clinical practice

Clinicians prescribe anticoagulant therapy when they decide that the risks of such therapy (major bleeding) are outweighed by its benefits (thrombosis prevention). Estimating the benefits of anticoagulation is relatively straightforward, especially in patients with AF, where the widely accepted $CHADS_2$ score correlates well with annual stroke risk. To help clinicians determine the trade-offs associated with anticoagulation, several groups have derived prediction models that use patient characteristics to stratify an individual's annual risk for major bleeding. Although the development of these bleeding risk prediction models has helped clinicians by identifying factors (e.g., concomitant antiplatelet therapy, anemia, renal/hepatic failure, history of stroke) that are independently associated with an increased risk of warfarin-associated major bleeding, the models themselves are of limited value in clinical practice for a number of reasons. First, the majority of patients with AF stand to gain so much benefit (by reducing the risk of ischemic stroke) from warfarin that almost no calculated risk of bleeding should preclude a trial of anticoagulation. But even for the minority of AF patients whose absolute stroke risk reduction from warfarin is low (e.g., $CHADS_2$ score = 1), where these bleeding risk calculators seem more applicable, their use is impractical. All bleeding risk models estimate the annual likelihood that a patient will experience major bleeding. Unlike AF-related stroke (which is fatal or severely disabling more than 50% of the time), the "major bleeding" predicted by these models represent clinical events within a spectrum that includes both simple blood transfusion as well as fatal intracranial hemorrhage. Because warfarin-related major bleeding is fatal in fewer than 10% if cases, it is difficult to know how to weigh the information generated by a bleeding prediction model against the benefit of reducing the risk of ischemic stroke.

Even if the trade-offs were more straightforward, several of these bleeding risk scores are, unlike the $CHADS_2$ score, difficult to remember and/or calculate. In the case of the HAS-BLED score, we must know whether the patient has "labile INR values"—this is information that cannot be known to the clinicians who are trying to decide whether to initiate warfarin treatment. In the case of the model published by Shireman, the equation used to define bleeding risk is so complicated that the authors admit clinicians would be unable to commit it to memory. Other models are incomplete: the ATRIA bleeding risk score does not account for concomitant antiplatelet therapy, a factor known to increase the risk of warfarin-associated major hemorrhage more than two-fold. Finally, none of the new oral anticoagulants being studied (or recently approved) for stroke prevention in AF has been evaluated by these bleeding prediction models.

In summary, there is no doubt that the benefits of anticoagulant therapy must be balanced against the risk that they might cause major bleeding. That notwithstanding, for the reasons outlined above, the currently available bleeding risk scores/models have limited utility in everyday clinical practice.

## Thromboprophylaxis for medical patients: should it be the default?

Medical thromboprophylaxis reduces the risk of DVT, PE, and fatal PE. There is excellent quality evidence that medical prophylaxis is under-prescribed, resulting in otherwise avoidable episodes of VTE. Use of medical prophylaxis has been endorsed by numerous peer organizations and is the focus of initiatives such as Required Organizational Practices of Accreditation Canada (http://www.accreditation.ca/uploadedFiles/ROP%20Handbook.pdf, accessed November 14, 2011).

However, it is clear that not all medical patients require thromboprophylaxis. Some patients have contraindications to anticoagulant therapy (such as those who have active bleeding and those with severe acquired or congenital bleeding disorders). Mechanical forms of prophylaxis (such as intermittent pneumatic compression devices or graduated compression stockings) might be used in such patients; however, their efficacy has never been tested in well-performed prospective studies. Extrapolating from other situations, mechanical prophylaxis reduces the risk of VTE but is associated with the potential for toxicity, including reduced mobilization, spread of infection, and skin ulceration. Mechanical forms of prophylaxis are also poorly tolerated by most medical patients.

More importantly, and the focus of recent evidence, is the observation that many patients in the hospital are at very low risk of VTE. When prophylaxis is administered to these patients, it results in the potential for toxicity

(bleeding and heparin-induced thrombocytopenia), as well as expense with little likelihood of benefit (because the background rate of VTE is sufficiently low so that it is unlikely to be lowered further by therapy).

There is no doubt that all patients admitted to the hospital should receive consideration for the administration of anticoagulant prophylaxis or mechanical prophylaxis. Adherence to this recommendation will be an enhanced by the use of preprinted orders, computerized prompting, and a multidisciplinary approach to care wherein multiple individuals take responsibility for ensuring the provision of optimal prophylaxis. When patients are considered to be at sufficiently low risk, then documentation of the rationale for non-administration of prophylaxis should be provided. This could take the form of a note in the chart or a specific notation in the computerized order entry system discussing why prophylaxis is not being administered.

Various authors have attempted to provide guidance for clinicians with respect to patient selection for prophylaxis. In a widely referenced paper, Dr. Charles Francis has proposed that a combination of age more than 40 years, anticipated limited mobility of three or more days, and at least one other risk factor provide sufficient likelihood of VTE to warrant prophylaxis. Conditions associated with increased risk include, but are not limited to, CHF, MI, stroke, inflammatory bowel disease, and a history of previous VTE, recent surgery, trauma or immobilization, obesity, central venous catheterization, known acquired or inherited thrombophilic states, and, potentially, estrogen therapy. Patients meeting three or more criteria should probably receive prophylaxis. In many hospitals, this will encompass nearly all patients; however, there remains a small subset of patients who do not meet criteria and who probably have a sufficiently low risk of VTE that the use of antithrombotic prophylaxis cannot be justified.

The case against routine prophylaxis was probably most compellingly made by Barbar and colleagues in a recently published paper. One thousand one hundred and eighty consecutive patients were followed after admission to an internal medicine service for the development of VTE over 90 days. A previously validated scoring system was used to assign patients to various risk classes for the development of VTE. Fully 711 patients were found to have a low risk of venous thromboembolism, of whom 659 (93%) did not receive any VTE prophylaxis. Among the 711 patients, there were two clinically apparent episodes of venous thrombi embolism, one occurring in the 659 patients who did not receive prophylaxis and one occurring in the 52 patients who did. These observations argue compellingly against the use of routine prophylaxis because the administration of routine heparin or LMWH to the 659 patients would have exposed them to the potential for toxicity without hope of further reducing the very low risk of VTE observed in this study. There is absolutely no doubt that bleeding rates would "swamp" the potential benefit of a reduction in the rate of VTE.

In summary, the administration of pharmacologic or mechanical thromboembolism prophylaxis is a critical consideration for all patients admitted to the hospital. Many patients harbor significant risks for venous thromboembolism, and all such patient should be treated with effective forms of pharmacologic prophylaxis. However, a significant proportion of patients will have a sufficiently low risk of VTE that the risks and costs of pharmacologic and mechanical prophylaxis cannot be justified; in such patients, documentation of the rationale for the omission of therapy is required, but venous thromboembolism prophylaxis should consist simply of aggressive mobilization and early discharge from the hospital.

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