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# Highlights from the fifth international symposium of thrombosis and anticoagulation (ISTA V), october 18–19, 2012, Belo Horizonte, Minas Gerais, Brazil

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**Abstract** To discuss and share knowledge about advances in the care of patients with thrombotic disorders, the Fifth International Symposium of Thrombosis and Anticoagulation was held in Belo Horizonte, Minas Gerais, Brazil, on October 18–19, 2012. 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, thought-leaders, and dedicated clinician-scientists. This paper summarizes the symposium proceedings.

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## Introduction

The Fifth International Symposium of Thrombosis and Anticoagulation was held in Belo Horizonte, Minas Gerais, Brazil, on October 18–19, 2012; 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 and Cardiology, 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.

We are confident that readers of this summary of the proceedings 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.

## New paradigms in thrombosis

Thrombosis within the circulatory system is characterized by both intravascular and extravascular events leading to thrombin generation and fibrin formation. While the biochemistry of thrombosis is relatively well described, several recent observations suggest that the overall process is much more complex than originally believed. In particular, platelets, regardless of the relative proportion in a developing thrombus, play a pivotal role by releasing polyphosphates, microparticles, and proinflammatory mediators, and by interacting with neutrophils to generate DNA-histone-granule constituent complexes. These nuclear materials induce platelet adhesion, activation, and aggregation, factor V/Va and von Willebrand factor (vWF) expression, prothrombinase assembly, and thrombin generation.

Cells that die as a result of acute injury or necrosis, as typically seen in stroke, acute myocardial infarction (MI), and numerous malignancies, and neutrophils responding to a hostile environment, typically swell and burst, releasing their contents in a highly detrimental inflammatory and prothrombotic event (Fig. 1). Upon activation, neutrophils release granule proteins, histones, and chromatin, which together form extracellular fibers referred to as neutrophil extracellular traps (NETs).The nuclei of neutrophils, upon stimulation, lose their shape, and both the eu- and heterochromatin homogenize. The nuclear envelope and granule membranes disintegrate, allowing the mixing of NET components. The NETs are formed as the cell membrane breaks. This particular cell death process is distinct from apoptosis. Programmed cell death is characterized by cell shrinkage, condensing cytoskeleton collapse, nuclear envelope disassembly, and fragmentation of nuclear DNA. In many instances, changes within the cell prompt rapid phagocytosis before significant leakage of cellular contents.

Unraveling the complexity of thrombosis will ultimately lead to a better understanding of associated diseases and their treatment.

## Update on new antiplatelet and anticoagulant agents

Antiplatelet agents have been used in clinical medicine for over a century, while their younger cousins, anticoagulants, are now entering their 6th decade of use. Although aspirin has a proven benefit for a wide range of conditions—including primary and secondary prevention of MI, arterial stenting, peripheral vascular disease, and ischemic stroke—newer, more potent antiplatelet therapies can be added to aspirin to achieve even better outcomes. Indeed, following the landmark CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial over a decade ago, the combination of aspirin plus clopidogrel became the standard of care for patients with acute coronary syndromes (ACS). More recently, even more potent oral antiplatelet drugs (i.e., prasugrel and ticagrelor) have been carefully studied and offer significant benefits over clopidogrel. In parallel, very potent intravenous antiplatelet drugs have been evaluated in clinical trials, although their role is more limited to the peri-procedural setting.

The past 5 years have seen a sea change in the oral anticoagulant field, as several promising drugs have been developed that are at least as good as, if not better than, warfarin in preventing embolic stroke in patients with atrial fibrillation (AF) and in preventing and treating venous thromboembolism (VTE). In addition, very low dose oral anticoagulation appears promising as a third antithrombotic (in addition to aspirin and clopidogrel) in high-risk patients with ACS. Physicians also have four choices in parenteral anticoagulation: unfractionated heparin, low-molecular-weight heparin, bivalirudin, and fondaparinux.

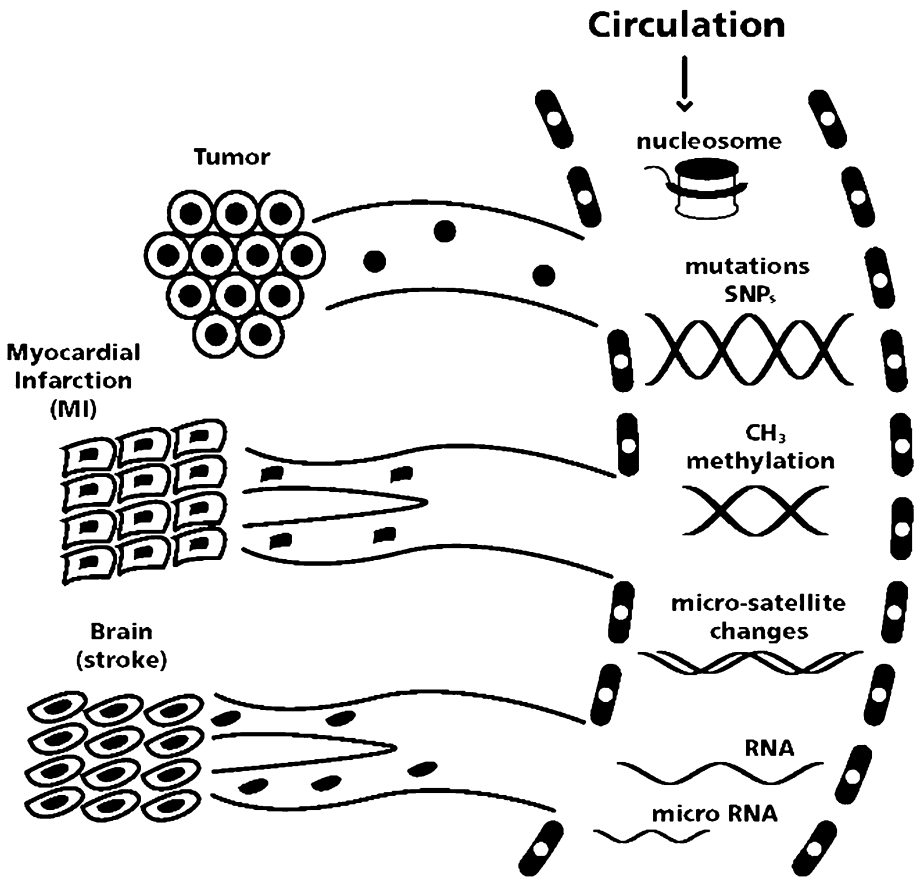


**Fig. 1** Nuclear materials released into the circulation, including DNA fragments, RNA, microRNA, histones, and nucleosomes, can be probed for important diagnostic and prognostic information

## Carotid intima-media thickness test: an update of how to use it in clinical practice

Cardiovascular disease (CVD) remains the leading cause of death in the Western world. Understandably, there is great interest in identifying patients at high CVD risk who would be candidates for more intensive medical interventions.

Atherosclerosis begins early in childhood; during progression of the disease, changes in the arterial wall are characterized by gradual thickening of the intima and media layers. B-mode ultrasound can measure this thickening through direct visualization of the arterial wall. Carotid intima-media thickness (CIMT) is defined as the thickness between the intimal-luminal and the medial-adventitial interfaces of the carotid artery.

Consensus documents provide protocols and recommendations for the use of carotid ultrasound to identify and quantify subclinical vascular disease and to evaluate CVD risk in clinical practice. High-quality ultrasound images of the distal 1 cm of the far wall of each carotid common artery should be obtained and compared with values from a normative data set. CIMT values greater than or equal to the 75th percentile are considered high and indicative of increased CVD risk.

Several studies have demonstrated that CIMT can be useful for refining CVD risk assessment in at-risk patients and can predict major adverse CVD events. Patients who (1) have a family history of premature CVD in a first-degree relative, (2) are less than 60 years old with a single risk factor and would otherwise not be candidates for medical treatment, and (3) are women younger than 60 years with at least two CVD risk factors also might be considered for CIMT testing.

Although population assessment of CIMT as a risk predictor in individuals is plausible, the association between CIMT progression assessed from two ultrasound exams and CVD risk in the general population remains unproven. The ability to serially assess CIMT progression and regression awaits further advances in technologies such as real-time three-dimensional imaging systems and ultrasound contrast agents.

## Recent important changes in the ACCP guidelines

The American College of Chest Physicians (ACCP) sponsored the development of the *Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College*

*of Chest Physicians Evidence-Based Clinical Practice Guidelines*; a print copy of the executive summary and an on-line version of the complete text were published in *Chest* in February 2012. Overall, this version of these guidelines contains fewer strong (Grade 1A) recommendations than the previous edition. There are several reasons that the number of 1A recommendations has decreased.

First, a clinical trial methodologist (who could review available evidence without any intellectual or financial conflict of interest) was appointed as the lead editor of each section. In addition to being able to interpret the evidence without historic (or other) bias, these individuals maximized the consistency and rigor with which the criteria for strong (vs. weak) recommendations were applied. When such criteria were applied strictly, much of the available evidence was categorized as being of low or medium quality.

Second, asymptomatic deep vein thrombosis (DVT)—a surrogate endpoint used in many primary VTE prevention studies—was not considered when recommendations were drafted. Eliminating this endpoint (which itself is not important to patients) from many treatment comparisons changed the strength, or in some cases the direction, of many recommendations in the VTE prophylaxis sections.

Finally, the Executive Committee formally surveyed the guideline panelists about the relative importance of various outcomes. The survey results—not available to previous guideline authors—were used to quantitatively rate the "disutility" of possible endpoints (e.g., ischemic stroke vs. intracranial hemorrhage [ICH]) and significantly influenced the ratings of recommendations, since their strength was largely based on risk–benefit trade-offs.

Examples of some of the most noteworthy changes in the guidelines are listed in Table 1.

## Highlights of key studies presented in 2012

In 2012, several significant studies were presented at the most important international scientific meetings in cardiology. During the American College of Cardiology (ACC) Scientific Sessions in Chicago, a study that received substantial attention was TRA 2P TIMI-50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events—Thrombolysis in Myocardial Infarction 50), a multinational, randomized trial comparing vorapaxar, a protease-activated receptor-1 (PAR-1) platelet receptor blocker, with placebo in 26,449 patients with atherosclerosis characterized by a history of MI, ischemic stroke, or peripheral arterial disease. Two years into the study, vorapaxar was discontinued in patients with prior stroke due to increased ICH. However, at 3 years, the use of vorapaxar decreased the primary composite endpoint of cardiovascular death, MI, or stroke (9.3 vs. 10.5 %; hazard ratio [HR] 0.87; 95 % CI 0.80–0.94; $P < 0.001$). The rates of Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) moderate or severe bleeding, including ICH, were increased in patients on vorapaxar (4.2 vs. 2.5 %; HR 1.66; 95 % CI 1.42–1.93; $P < 0.001$). More importantly, at the European Society of Cardiology (ESC) 2012 meeting, results were presented for the subgroup of 17,779 patients with prior MI. In this subgroup, there was a 20 % reduction of the primary endpoint with vorapaxar (8.1 vs. 9.7 %; $P < 0.001$), with an increase in moderate or severe bleeding (3.4 vs. 2.1 %; HR 1.61; 95 % CI 1.31–1.97; $P < 0.001$) but not ICH. Based on these results, Merck is seeking US Food and Drug Administration (FDA) and European Medicines Agency approval for vorapaxar for secondary prevention use in patients with prior MI. The

**Table 1** 2012 American College of Chest Physicians guidelines—key changes from the 2008 edition

| AT9 recommendation | Difference from AT8 | Comment |
|---|---|---|
| Aspirin listed among VTE prevention options after orthopedic surgery | Change from a strong recommendation *against* aspirin use in this setting | Re-interpretation of exisiting evidence; LMWH still *preferred* over aspirin |
| Weak recommendation against catheter-directed thrombolysis for proximal DVT | Change from a weak recommendation in favor | Acknowledges low quality of available evidence and highlights important |
| Weak recommendation to consider extended anticoagulation in patients with idiopathic VTE | Change from a stronger recommendation in the same direction | More recognition that the burdens and hazards of anticoagulant therapy can often outweigh benefits |
| Strong recommendation against VTE prophylaxis in *low-risk* patients with medical illness | No specific recommendation for this risk group | Text discusses the challenge of defining low-risk patients |
| Aspirin recommended for all patients over 50 years old | Not addressed | Based on combination of cardiovascular benefits *and* anticancer effects of aspirin |

*AT9* Antithrombotic Therapy and Prevention of Thrombosis, 9th ed, *AT8* Antithrombotic Therapy and Prevention of Thrombosis, 8th ed, *VTE* venous thromboembolism, *LMWH* low molecular weight heparin, *DVT* deep vein thrombosis

results of TRA-2P, similar to other secondary prevention trials, suggested that dual antithrombotic therapy might be important for the prevention of cardiovascular events in patients with a history of coronary artery disease, but at the expense of increased bleeding risk.

Another major study presented as a late breaking clinical trial at ACC 2012 was BRIDGE-ACS (Brazilian Intervention to Increase Evidence Usage in ACSs). This study was conducted in Brazil to evaluate the effect on compliance and clinical outcomes of a program designed to improve implementation of the guidelines of the Brazilian Society of Cardiology for the treatment of ACS in 34 public hospitals. A dedicated nurse followed chest pain patients from hospital admission to discharge, and training and teaching tools were provided to the physicians involved in patient care. The program resulted in a significantly higher proportion of patients at intervention hospitals who received all of the acute therapies for which they were eligible (67.9 vs. 49.5 % for control patients; HR 2.64; 95 % CI 1.28–5.45; $P = 0.01$). At the time of hospital discharge, 31.9 % of patients at non-intervention hospitals received recommended medications versus 50.9 % of patients at intervention hospitals (HR 2.49; 95 % CI 1.08–5.74; $P = 0.03$). The authors concluded that although compliance with evidence-based treatment is still low in developing countries, the implementation of simple measures may improve compliance with important guidelines recommended for treatment of patients with ACS.

Finally, one of the most interesting studies in 2012 was presented at the ESC congress. This investigator-initiated randomized clinical trial, WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting?), evaluated the association of two different antithrombotic regimens with ischemic and bleeding outcomes in 573 patients on oral anticoagulation undergoing stent implantation. In recent years, the indications for using both anticoagulation and antiplatelet therapy have increased. However, triple therapy is associated with increases in both the risk of bleeding and mortality. WOEST compared triple therapy with an anticoagulant agent plus aspirin and clopidogrel versus an anticoagulant and clopidogrel (no aspirin). The primary and secondary endpoints were thrombolysis in myocardial infarction (TIMI) bleeding and all-cause mortality, stroke, reinfarction, stent thrombosis, or urgent revascularization, respectively. After 1 year, patients randomized to dual therapy had significantly lower rates of bleeding compared with triple therapy (19.5 vs. 44.9 %; HR 0.36; 95 % CI 0.26–0.50; $P < 0.001$). Incremental bleeding in the triple therapy group was mostly gastrointestinal, skin, and puncture site hemorrhages, but not ICH. Mortality was significantly lower among patients on dual therapy (2.6 vs. 6.4 %; $P = 0.027$), but there were no differences between groups in the primary composite ischemic endpoint or other individual endpoints. WOEST was the first prospective randomized trial to demonstrate a significant reduction in bleeding events among patients on dual anticoagulant and clopidogrel therapy compared with triple therapy with an anticoagulant agent, clopidogrel, and aspirin. However, this trial was not powered to examine ischemic endpoints, so these results should be interpreted with caution.

## Transition from warfarin to new oral anticoagulants in patients with AF

Physicians seeing patients with AF have to make a series of important decisions about anticoagulant therapy. For patients with new AF who are candidates for anticoagulation, considerations currently include warfarin, dabigatran, or rivaroxaban. For patients with AF on warfarin therapy, considerations include continuation of warfarin or transition to a new oral anticoagulant.

Subgroup analyses in previous trials have raised the hypothesis that most of the benefit of warfarin compared with other antithrombotic strategies is in patients who are already taking oral anticoagulant therapy rather than patients who are naïve to vitamin K antagonists (VKAs) and about to start warfarin. VKA-experienced patients tended to have lower risks of major vascular events and major bleeding in contrast to patients who were initiated on warfarin without a prior history of anticoagulant exposure.

In the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF), RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy), and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF) trials, approximately 50–70 % of patients enrolled were VKA-experienced. Importantly, the overall treatment effect and safety profile observed with the novel anticoagulant compared with warfarin was consistent in VKA-naïve and VKA-experienced patients. The data from these large trials support the safe transition of warfarin to a novel anticoagulant.

## Antithrombotic therapy in new devices for heart failure: an update

End-stage refractory heart failure is a life-threatening syndrome, and few options are available to these patients: palliative care, placement of a ventricular assist device (VAD), or orthotopic heart transplantation (OHT). Unfortunately, OHT is not available for all heart failure patients

who would benefit from this procedure, due to a shortage of donor hearts. As a result, thousands of people die annually while awaiting heart transplantation.

Placement of a VAD is an effective option for treatment of acute or chronic end-stage heart failure. Use of mechanical circulatory support (MCS) is increasing as a result of improvements in continuous-flow ventricular assist systems. MCS saves lives and enables the next steps in patient treatment, such as OHT, or provides permanent treatment of heart failure. Due to the donor organ shortage, increasing numbers of patients are on lifelong support as destination therapy.

However, despite enormous progress in the field of MCS, there remain many obstacles to be overcome. After a VAD implantation, a prothrombotic state may develop, depending on pump design and patient characteristics. The incidence of stroke among these patients varies from 3 to 47 %. This hypercoagulable state requires antithrombotic therapy with a combination of oral anticoagulation and antiplatelet therapy. The use of warfarin (international normalized ratio [INR] target 2.5) and aspirin (100 mg/day), with point-of-care tests showing at least 70 % platelet function inhibition, seems to have the best bleeding-thrombosis trade-off. For many patients, maximum aggregation can be reduced to less than 30 % through use of small doses of aspirin (25 mg twice daily) and of clopidogrel (35 mg/day). The use of thromboelastography to monitor antithrombotic therapy in these patients may be recommended.

Two clinically important interactions occur in VAD patients. First, due to long-term treatment with heparin before and after surgery, heparin-induced thrombocytopenia (HIT) type II may develop. HIT is caused by platelet-activating antiplatelet factor 4/heparin antibodies. However, clinical HIT (thrombocytopenia or thrombosis, or both) develops in only a minority of patients who form antibodies. The incidence of heparin-induced immunization and clinical HIT II approach 65 and 10 %, respectively, with a high risk of cerebrovascular ischemia/infarction. Close monitoring of symptoms or even regular laboratory tests during heparin infusion may be necessary. In acute situations (e.g., for heart transplantation or device exchange), short-term re-exposure to heparin with concomitant use of IIb/IIIA inhibitor tirofiban is a reasonable option. Alternatively, use of bivalirudin has been successful in previous studies. The use of alternative, non-heparin agents for routine post-implant anticoagulation in VAD patients should be further evaluated.

The second major effect of continuous-flow VADs on the coagulation system is the acquired vWF deficit, which appears to be a significant contributor to bleeding episodes during support. The mechanism of this effect remains unclear. Routine monitoring of vWF multimers and their activity should be addressed.

## Antithrombotic therapy in patients with valvular and congenital heart disease: where do we stand?

### Valvular heart disease

Patients with prosthetic heart valves require chronic oral anticoagulation and face an elevated risk of thromboembolic events that depends on the type of prosthesis and its anatomical position. Patients with mechanical valves are at high risk, necessitating the use of VKAs. In North America, warfarin is the sole representative of this drug class. Phenprocoumon is widely used in South America and Europe, while fluindione, and acenocoumarol are less frequently employed.

Before the implantation of an artificial heart valve, it is crucial to estimate the individual risk of bleeding. Each type of prosthetic heart valve has its own thrombogenicity profile. The risk of thrombosis is also directly related to valve position. Valves placed in the mitral position have an increased risk of thromboembolic complications compared with those in the aortic position. Guidelines recommend that patients with mechanical valves in the aortic position should have an INR of 2.0–3.0, and patients with valves in the mitral position should have an INR of 2.5–3.5. Newer anticoagulants, such as dabigatran and apixaban, are not recommended for artificial valves, as there are no clinical data to support their use. There are reports of massive valve thrombosis when warfarin was replaced by dabigatran.

The addition of antiplatelet agents to VKAs has been shown to reduce the occurrence of embolic complications (including death). Patients deemed to be at high risk for embolic events, including those with concomitant AF, previous thromboembolism, and mitral prostheses, may derive a greater benefit from concomitant antiplatelet therapies.

Patients with bioprosthetic valves are often treated with systemic anticoagulation for a short period of time following implantation. Current evidence recommends anticoagulation for bioprosthetic valves during the first 90 postoperative days, but this still remains a point of debate among clinicians and a point of uncertainty in the guidelines. Data from the Society of Thoracic Surgeons database show that among patients aged 65 years and older, death and embolic events were relatively rare in the first 3 months after bioprosthetic aortic valve replacement. In that registry, a regimen of aspirin plus warfarin compared with aspirin only was associated with a reduced risk of death and embolic events, but at the cost of increased bleeding risk. There is no consensus on anticoagulation for valves placed endovascularly; some authors have suggested that dual antiplatelet therapy (aspirin and clopidogrel) for 6 months after the procedure may be sufficient for thromboembolism prevention.

Often, patients with mechanical valves require temporary interruption of VKA therapy for clinical or surgical reasons and will usually require some temporary anticoagulation during this time. This is referred to as a bridge therapy. Bridging is reasonable to consider for a patient with a high risk for thromboembolic events. Low-molecular-weight heparin should be used when there is a low predicted risk of bleeding. For patients with a higher bleeding risk (e.g., female, low body weight, end-stage renal failure), hospital admission and the use of unfractionated heparin is encouraged.

Emergency surgery is most reasonable for patients with a thrombosed left-sided prosthetic valve and New York Heart Association (NYHA) functional class III/IV symptoms. Fibrinolytic therapy should be considered for patients for whom surgical intervention carries a prohibitively high risk or for those with absolute contraindications to surgery. In patients with a small clot burden who are NYHA functional class I or II, treatment with short-term intravenous unfractionated heparin therapy or continuous infusion of fibrinolytic therapy may be considered. Fibrinolytic therapy is also reasonable for thrombosed right-sided prosthetic heart valves with NYHA functional class III/IV symptoms.

### Congenital heart disease

There are a few clinical situations in which anticoagulation is required for congenital heart disease. Children with a heart valve prosthesis should be managed as recommended for adults. Post-operative management after the Fontan procedure may include anticoagulation, as chronic or acute venous conduit thrombosis has been reported. But this has to be weighted individually, in a risk/benefit fashion.

Anticoagulation is not recommended as routine for patients with cyanotic heart disease, except in the presence of AF, documented pulmonary thrombosis or embolism, transient ischemic attack or stroke, deep venous thrombosis, and occasionally after placement of a right-sided device (such as a permanent pacemaker).

Atrial septal defects (patent foramen ovale [PFO], atrial septal defect [ASD], or atrial septal aneurysm [ASA]) in adults deserve special considerations regarding anticoagulation for prevention of paradoxical systemic embolism. Therapeutic options for prevention of recurrent stroke are antiplatelet agents or anticoagulants, and surgical or percutaneous closure of the defect. The choice depends on several factors, especially the type of abnormality. Existing retrospective and prospective data are conflicting with regard to the relationship between ischemic stroke and PFO, ASD, and ASA. Population-based studies suggest that a PFO, even when large, is not an independent risk factor for cryptogenic ischemic stroke. Current guidelines state that, for patients with an ischemic stroke or transient ischemic attack and a PFO, antiplatelet therapy is reasonable (class IIa), but there are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO (class IIb), and there are insufficient data to make a recommendation regarding PFO closure in patients with stroke and PFO (class IIb).

## Management of anticoagulant-associated bleeding

Oral anticoagulation with VKAs has served as the primary treatment for the prevention of stroke and systemic embolization in patients with AF for decades. Over the past several years, multiple novel oral anticoagulants targeting key mediators of coagulation, including thrombin and factor Xa, have been developed. Specifically, agents targeting thrombin (dabigatran) and factor Xa (apixaban and rivaroxaban) have either reached late stages of clinical development (apixaban) or received approval (dabigatran, rivaroxaban) by the FDA for use in patients with nonvalvular AF. The promising results derived from large-scale clinical trials with these agents compared with warfarin expands the available therapeutic options for the prevention of stroke and systemic embolization in this rapidly increasing patient population. However, there is an unmet clinical need—specifically, the absence of data on reversal that threatens the optimal use of a new generation of effective anticoagulants.

From a clinical perspective, the desire to attenuate or fully reverse an anticoagulant's pharmacodynamic effect arises in several relatively common scenarios—scheduled procedures associated with a risk for bleeding, unscheduled procedures associated with a risk for bleeding, moderate to severe trauma, and active bleeding that is serious or life-threatening. In each instance, the desired goal is to restore hemostatic potential without increasing the risk of thrombosis. In the absence of antidotes, management options are directed toward either removing active drug from the circulation (e.g., dialysis for dabigatran) or, more commonly, generating thrombin substrate by accelerating the synthesis of normally functioning coagulation proteins (e.g., vitamin K for warfarin), administering coagulation proteins (e.g., fresh frozen plasma, prothrombin complex concentrate, activated prothrombin complex concentrate), and/or facilitating coagulation protein assembly on activated platelet (e.g., recombinant factor VIIa).

Fundamentally, the requirements for attenuating the pharmacodynamic effects of an anticoagulant—low "free" drug plasma concentration, coagulation factor substrate (concentration/activity) given exceeds drug inhibitory capacity, short drug half-life, and ability to generate

thrombin—may depend on the pharmacological properties of the drug (anticoagulant) or require an understanding of coagulation. Clinicians must weigh the risks and benefits of anticoagulant reversal, and all institutions should develop practical guidelines for the prevention and management of bleeding.

## Bleeding in patients with ACS: importance and management

Over the last 3 decades, there have been numerous advances in the management of patients with ACS and secondary prevention of ischemic events after ACS. However, each of these therapies, including more frequent and earlier coronary angiography and intervention and the development of more potent antiplatelet and anticoagulant therapy, while improving ischemic outcomes, has increased the risk of bleeding among ACS patients. The challenge today is to balance ischemic and bleeding risk to optimize overall outcomes.

Understanding the importance of bleeding and its management is made difficult by a variety of factors. First, from clinical trials, it has become clear that bleeding is common among ACS patients, but clinical trial populations substantially underestimate the frequency of bleeding among all patients treated with modern interventional and antithrombotic therapy in the community. For example, rates of bleeding in clinical trials have ranged from 3 to 7.1 %, but according to the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) registry, bleeding among ACS patients in the community was as high as 11 %. This is largely because comorbidities (e.g., older age and renal insufficiency) that predispose to bleeding are more frequent, and women are treated in greater proportions in the community than among populations selected into clinical trials.

Second, clinical trials and registries use varying definitions of bleeding, which challenges cross-study comparisons of bleeding rates and the effect of various antithrombotic treatments on bleeding rates. For example, the rates of major bleeding across the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy), CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events), SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors), TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction), and CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trials ranged from 1.7 to 9.1 %, but each trial used a different definition of bleeding. Further, from pooled data from the PURSUIT and PARAGON-B (Platelet IIb/IIIa Antagonist for the Reduction of ACS Events in a Global Organization Network-B) trials that simultaneously reported bleeding on both the GUSTO and TIMI scales, the rates of major bleeding were nearly eightfold higher using the TIMI scale (8.2 vs. 1.2 %). In an attempt to circumvent this problem, the Academic Bleeding Consensus Working Group, an international, multidisciplinary collaboration, has developed the Bleeding Academic Research Consortium classification for bleeding with the goal of standardizing the reporting of bleeding in practice and clinical trials.

Despite the challenges of translating trial results to community populations and the widely varying definitions of bleeding (and thus the differing rates of bleeding across clinical trials and registries), one common theme remains: ACS patients who bleed have higher mortality, longer lengths of stay, and greater costs of care than those who do not bleed. The relationship with mortality is observed in short-, intermediate-, and long-term follow-up but is more apparent when a "clinical" (GUSTO) rather than laboratory-based (TIMI) definition of bleeding is used. Further, the relationship is present regardless of the source of bleeding (access site [adjusted HR for 1-year mortality 1.82; 95 % CI 1.17–2.83,] or non-access site [adjusted HR 3.94; 95 % CI 3.07–5.15]), although the association of non-access site bleeding with mortality is more than two times greater than for access site bleeding.

Finally, in an interesting observation from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) investigators, a bleeding event within the first 30 days after an ACS event was associated with an even greater risk for mortality over the ensuing year (12.5 %) than an MI during the first 30 days (8.6 %), a difference that persisted after adjustment for baseline characteristics. The 1-year mortality rate among patients with both bleeding and MI during the first 30 days was 28.9 %. Importantly, in clinical trials of novel anticoagulant agents that reduced bleeding rates compared with standard therapies, these agents also seemed to confer later mortality benefit. Whether radial access for coronary angiography and intervention can reduce access site related bleeding and improve clinical outcomes is unknown but is under study in the SAFE-PCI (Study of Access Site for Enhancing Percutaneous Coronary Intervention) trial. In the meantime, use of risk scores to guide treatment selection and careful consideration of antiplatelet and anticoagulant dosing in the setting of increased age, lighter body weight, and impaired renal function are means to minimize bleeding risk in ACS patients.

Despite the clear association of bleeding with mortality after an ACS event, the underlying mechanism through

which bleeding results in worse outcomes is uncertain. In part, this relationship is driven by the greater number of comorbidities among patients who bleed compared with those who do not. This hypothesis is supported by adjusted analyses in the studies described above, and by the FEAST (Iron [Fe] and Atherosclerosis Study) trial in which phlebotomy of healthy individuals (removing 920 mL of blood over five visits) resulted in no difference in mortality over 6 years of follow-up. Hemodynamic instability that results from bleeding, response to bleeding, including acute reversal of antiplatelet and antithrombotic therapy, and withholding of therapy at discharge also likely contribute. In one study, ACS patients who had an in-hospital bleed were approximately 55 % less likely to receive aspirin and 38 % less likely to receive clopidogrel at discharge. Not until 1 year for aspirin and 6 months for clopidogrel did use among patients with bleeding approximate that among patients who did not bleed. In another study, even nuisance bleeding resulted in withholding of clopidogrel at discharge among patients who had received a drug-eluting stent; overall, 85.7 % of patients experienced nuisance bleeding, and 11 % were discharged without clopidogrel. Importantly, other researchers showed that these interruptions in treatment correlated with worse ischemic outcomes at 6 months (adjusted HR for death, MI, or stroke 1.36; 95 % CI 1.01–1.85). Finally, it appears that transfusion itself is associated with nearly four-fold greater mortality at 30 days among ACS patients, though the mechanism, particularly what is not explained by baseline characteristics and hemodynamic status, is not well understood. Randomized trials of transfusion strategies and comparing older blood versus newer blood stores are ongoing and should provide insight into this important question.

In summary, with treatment advances, ischemic outcomes among ACS patients have improved over time, but, in parallel, bleeding has emerged as an important clinical event that is associated with increased mortality among these patients. Efforts to reduce bleeding are a priority, and strategies that reduce bleeding (anticoagulants such as bivalirudin and fondaparinux and selection and management of vascular access sites) are associated with improved survival. Attention to assessment of bleeding risk, to application of these strategies when bleeding risk is high, and to appropriately dose-adjusting medications for reduced renal function and body weight should help to minimize bleeding and its consequences in practice.

## ICH in patients treated with warfarin: where do we stand and how can we manage it?

Intravenous tissue plasminogen activator (tPA) is an effective treatment to reduce the risk of death or disability following an acute ischemic stroke; however, tPA can also cause symptomatic ICH. This treatment-related risk is presumed to be higher among patients already on home anticoagulant therapy. To date, clinicians have had little guidance on how to treat such patients. The American Heart Association/American Stroke Association guidelines permit use of intravenous tPA in warfarin-treated patients, provided that the patient's INR is below 1.7. Yet, data for these recommendations are limited. Warfarin-treated patients were uniformly excluded from major trials of tPA, and existing observational studies of tPA use in warfarin-treated patients have been small and yielded highly inconsistent findings. Recently, a large series from the American Heart Association's Get With The Guidelines stroke program has provided new insights on this topic.

## Anticoagulation in the elderly population: is there an age limit?

In recent years, use of long-term anticoagulation therapy has increased, especially in elderly patients. There are several possible reasons for this, including the fact that less intensive treatment regimens have been associated with lower rates of serious bleeding complications compared with past treatment regimens that used higher doses of medication. Also, data from randomized clinical trials have demonstrated both the safety and efficacy of long-term oral anticoagulation in elderly patients. In the setting of nonvalvular AF, older patients who were treated with warfarin experienced a 60–70 % reduction in their risk of stroke with an acceptably low rate of serious bleeding complications, which averaged only 0.1–0.6 % per year. The mean age of patients enrolled in these trials was older than 65 years, which clearly demonstrates that anticoagulants can be safely administered to elderly patients. However, there are many gaps in these studies that prevent us from generalizing these results. The risk of bleeding may be higher among patients who do not receive the regular follow-up and careful monitoring that are characteristic of these studies. The mean follow-up period of these studies was 2 years, so we do not know the longer-term risks of hemorrhage in patients who are chronically receiving oral anticoagulants.

The issue of anticoagulation in the elderly is important to address because of the high frequency of thrombotic disorders in this age group. The high prevalence of thrombotic disorders in the elderly appears to be in large part related to the frequency of underlying conditions that predispose individuals to develop thrombosis, such as congestive heart failure, malignancy, surgery, and immobility. However, there appear to be no differences in coagulation factors when individuals aged 50–80 years are compared with younger people.

Clinicians caring for elderly patients need to know which individuals are at highest risk for the development of thrombotic complications so that preventive and treatment strategies can be targeted at those who would potentially benefit most from anticoagulation. In patients with AF, risk stratification for ischemic stroke can be done with the $CHADS_2$ (congestive heart failure, hypertension, age $>$ 75 years, diabetes mellitus, stroke or transient ischemic attack [2 points]) score. The bleeding risk must also be assessed. The most recent bleeding risk stratification scheme for elderly patients (>65 years old) includes eight variables to ascertain bleeding risk. However, ischemic stroke risk and bleeding risk are predicted by overlapping factors. So, patients who profit most from stroke risk reduction also have higher bleeding risk.

Despite evidence advocating the use of oral anticoagulation in the elderly to reduce the risk of thromboembolic complications, such therapy is often underused because of the perceived increased risk of bleeding. In particular, fall risk tends to be overestimated as a contraindication to anticoagulation. Cognitive decline in combination with low socioeconomic status argue against anticoagulation as the success or failure of oral anticoagulation therapy depends partly on the patient's understanding of the benefits and risks of such medication and the maintenance of the INR within the therapeutic range.

In conclusion, the decision to start or withhold anticoagulation in the elderly patient has to be made on the basis of an assessment of stroke and bleeding risk as well as the ability to offer tighter INR control. Time in therapeutic range is a potent predictor of warfarin effectiveness and safety. New oral anticoagulants for the prevention of stroke in patients with nonvalvular AF have been available recently, among them the reversible direct thrombin inhibitor dabigatran and the factor Xa antagonists rivaroxaban and apixaban. The lack of necessity for regular monitoring is advertised as a major advantage. Although AF is a disease with increasing prevalence with higher age, these new drugs have not been extensively studied in multimorbid geriatric patients.

## New oral anticoagulants and risk scores for patients with AF

Despite the advances in our understanding of AF and stroke, many gaps still exist that challenge the optimal care of patients with AF. As an example, our ability to discriminate risk of stroke remains limited. Although recent models that incorporate cardiac biomarkers have improved discriminatory power, the c-statistics of these models are still less than 0.7, a score traditionally interpreted as having limited clinical value. The utility of bleeding risk scores is also uncertain. These scores predict aggregate bleeding that includes all major forms of hemorrhage, ranging from severe epistaxis to intracranial bleeding. Given the severity of strokes in AF, bleeding scores should be used to identify and address mutable risk factors such as blood pressure or concomitant antiplatelet therapy to minimize risk of hemorrhage. In addition, there is significant overlap among the risk factors for stroke and risk factors for hemorrhage, particularly age, hypertension, renal dysfunction, and prior stroke, which further compromises their utility in routine practice.

Bleeding is the most often cited reason for discontinuation of anticoagulant therapy. Although the novel anticoagulants—dabigatran, rivaroxaban, and apixaban—significantly reduced the risk of ICH in clinical trials, the more frequent complication, gastrointestinal hemorrhage, was increased with rivaroxaban and the 150-mg dose of dabigatran. Further research is needed to elucidate the mechanism of gastrointestinal tract bleeding and identify factors (e.g., proton pump inhibitors) that might mitigate this risk.

Distinct from oral VKAs, all of the novel anticoagulants depend to some degree on renal elimination pathways. Recent analyses from clinical trial data have been reassuring regarding their overall safety among individuals with moderate renal impairment. However, baseline renal function does not necessarily inform fluctuations in renal function over time, and more data are needed for this important subgroup. Other areas of intense investigation include defining the burden of AF that warrants lifelong anticoagulant treatment and the role of subclinical AF. A recent study highlighted the stroke risk among individuals with brief bouts of atrial tachyarrhythmias detected by pacemaker.

## How to manage anticoagulation in AF patients undergoing cardioversion

AF patients have a 5 % annual risk of embolic events. Patients undergoing cardioversion (CV) of AF longer than 48 hours without anticoagulation have the same risk in less than a 1-month period. All types of AF longer than 48 hours (paroxysmal, persistent, permanent, and lone) have increased risk of embolism after CV, and the thromboembolic risk is about the same in all types of CV: electrical, pharmacological, overdrive suppression, spontaneous, and ablation.

Fibrillating atria have all the components of Virchow's triad: hypercoagulability, endothelium dysfunction, and circulatory stasis. Although these components persist after CV, the circulatory stasis becomes even more pronounced immediately after resumption of sinus rhythm, a phenomenon

known as atrial stunning. The stunning is evidenced by the reduction of emptying velocities in the left atrium and appendage immediately after reversion to sinus rhythm. Interestingly, this phenomenon does not occur if sinus rhythm is not achieved, or if CV is performed in arrhythmias other than AF or flutter. Thromboembolism occurs because of migration of a previous thrombus or, most importantly, due to a de novo formation of thrombus after reversion to sinus rhythm. Mechanical atrial function usually resumes after 1–4 weeks. Therefore, patients have to be on a very rigorous antithrombotic therapy for at least 3–4 weeks before and after CV. The antithrombotic regimens include warfarin at a dose adjusted to a target INR of 2.0–3.0 for 3 weeks before and at least 4 weeks after CV; if CV must be performed earlier, after effective anticoagulation either with warfarin, unfractionated heparin, or low-molecular-weight heparin (enoxaparin), a transesophageal echocardiography is performed to exclude the presence of atrial or appendage thrombus. If there is no thrombus, CV is performed, and anticoagulation is maintained for a minimum of 4 weeks. Recently, the new direct antithrombin inhibitor dabigatran was shown to be as effective as warfarin for prevention of thromboembolism after CV, since it is administered for the same time period. If patients have a $CHADS_2$-VASc score $\geq 1$, anticoagulation must be maintained indefinitely, since all antiarrhythmic treatments of AF are not curative. The same consideration can be applied to catheter ablation.

## AF and heart failure: what's new?

Atrial fibrillation and heart failure commonly coexist, and management of the combination requires specific considerations. Heart failure is a risk factor for stroke in AF, and AF increases risk of adverse outcomes in chronic as well as in hospitalized heart failure populations. The novel oral anticoagulants have consistent benefits for AF in patients with and without heart failure. Biomarkers provide insight into risk in AF, and B-type natriuretic peptide (BNP) is a powerful predictor of stroke. BNP is also a predictor of which patients who have "cryptogenic" stroke also have underlying AF. Subclinical AF, including in patients with heart failure, is associated with risk of stroke and provides an important opportunity to study whether oral anticoagulation may improve clinical outcomes.

Between 17 and 28 % of the populations in recent clinical registries and trials had heart failure or left ventricular dysfunction (left ventricular ejection fraction $\leq$40 %). In patients with heart failure, there is a relationship between more severe heart failure and greater prevalence of AF, with <10 % in the SOLVD (Studies of Left Ventricular Dysfunction Prevention) trial having left ventricular dysfunction without heart failure and 50 % in the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) trial of NYHA class IV patients. In the Framingham Study, over 30 % of heart failure patients without AF at baseline developed it within 4 years. Moreover, the development of AF was independently associated with higher risk of death.

Can AF be prevented in patients with heart failure? Yes, there are modest reductions in development of new AF with effective heart failure treatments, such as with angiotensin receptor blockers and eplerenone. This provides yet another rationale for use of these life-saving treatments.

The role of rate versus rhythm control is largely driven by symptoms, since trials that tested a routine rhythm control strategy, such the AFFIRM (AF Follow-up Investigation of Rhythm Management) trial, have shown no benefit. Thus, rhythm control can generally be reserved for patients with refractory symptoms. It was suspected that rhythm control might be beneficial in a heart failure population for which optimizing left ventricular filling and cardiac performance would be especially important. However, the AF-CHF (AF and Congestive Heart Failure) trial showed no benefit from rhythm control, mainly with amiodarone, in a heart failure population. While lenient versus strict rate control (to <80 beats/min) has not been well tested in the heart failure population, strict control had no benefit on hard outcomes or quality of life in the RACE II (Rate Control Efficacy in Permanent AF: A Comparison Between Lenient versus Strict Rate Control II) trial in a general population with AF.

The role of oral anticoagulation in heart failure with reduced left ventricular ejection fraction has been the subject of a series of trials. The most recent and most relevant trial, WARCEF (Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction), found no benefit to warfarin compared with 325 mg a day of aspirin on the primary outcome of ischemic stroke, ICH, or death. There was a modest reduction in ischemic stroke itself that was counterbalanced by more bleeding. This trial leaves open the possibility that there could be a role for a safe and effective oral anticoagulant in chronic heart failure, in the right population.

To what extent heart failure itself, with or without left ventricular dysfunction, is a risk factor for stroke and a reason for oral anticoagulation in AF has been debated. Heart failure with decreased left ventricular ejection fraction may be a more important risk factor than with preserved function. The Danish registry showed that heart failure as a single factor identifies risk of stroke in AF, with a similar increased risk as for hypertension, diabetes, vascular disease, and older age.

A relevant question is whether the new oral anticoagulants—dabigatran, rivaroxaban, and apixaban—have

similar effectiveness compared with warfarin among patients with versus without heart failure or left ventricular dysfunction. The answer is yes: each of the drugs seems to have consistent benefits in this population.

Blood protein biomarkers have been shown to be independently associated with risk in the AF population. In particular, N-terminal pro-BNP (NT-proBNP) is a powerful predictor of stroke and of vascular death in the RE-LY trial database, and the relationship with outcomes appears to be additive to the clinical factors in the $CHADS_2$ score. In the ARISTOTLE trial, NT-proBNP was a powerful predictor of stroke, of death, and even of bleeding, including after adjustment for renal function. BNP has also been shown to differentiate patients with ischemic stroke into those who do and those who do not have AF subsequently recognized. Thus, BNP has promise as a biomarker to understand the likelihood of subclinical AF in certain populations as well as to stratify risk of stroke and other outcomes in patients with known AF. How this can be used to refine our patient selection and use of oral anticoagulants is an important area of ongoing investigation.

In summary, the intersection of AF and heart failure is an important and common clinical scenario. There is an opportunity to improve the use of medical therapies for each condition as well as to prevent each condition and its consequences. In years to come, this high-risk combination will be an area ripe for further study to search for better treatments.

## How do I decide who should receive DVT prophylaxis in clinical practice?

Pulmonary embolism remains the most common preventable cause of hospital death. The prevention of VTE is the priority strategy to improve patient safety in hospitals. There is strong evidence from a vast number of randomized trials that appropriately employed thromboprophylaxis is cost effective and has a desirable benefit-to-risk ratio. Thus, selecting who should receive DVT prophylaxis is very important. All physicians should be encouraged to increase the use of early ambulation and shorter lengths of hospitalization for all patients, whenever possible, to diminish the risk of VTE.

In hospitalized medical patients, there are many models to assess risk for VTE (e.g., IMPROVE [International Medical Prevention Registry on VTE] and Padua risk scores) and risk for bleeding (e.g., IMPROVE risk score), although none have been validated in prospective trials. In general, prophylactic anticoagulation is recommended for most patients who are hospitalized with an acute medical illness, who do not have an increased risk of bleeding and who have at least one risk factor for VTE (e.g., congestive failure, acute exacerbations of chronic pulmonary disease, stroke with paralysis, sepsis, inflammatory bowel disease, a high degree of immobility, age more than 75 years, and presence of cancer or a previous episode of VTE) and limited mobility for more than 3 days.

The risk of postoperative VTE is usually higher and depends on the surgical procedure (e.g., degree of invasiveness, type and duration of anesthesia, duration of immobilization), as well as patient-related variables (e.g., increasing age, prior VTE, presence of malignancy or obesity, presence of an inherited or acquired hypercoagulable state). Patients are divided into low-, moderate-, and high-risk categories in many perioperative care guidelines. For patients undergoing low-risk general surgery procedures that do not have other additional risk factors for VTE, the only recommendation is early and frequent ambulation. Most other surgical patients will require some kind of DVT prophylaxis.

A recent randomized trial, Apixaban Dosing to Optimize Protection from Thrombosis (ADOPT), assessed the efficacy and safety of prolonging prophylaxis for VTE in medically ill patients beyond hospital discharge. This double-blind, double-dummy, placebo-controlled trial included acutely ill patients who had congestive heart failure or respiratory failure or other medical disorders and at least one additional risk factor for VTE and who were hospitalized for at least 3 days. A total of 6,528 patients were randomized in a concealed fashion to receive apixaban administered orally at a dose of 2.5 mg twice daily for 30 days or enoxaparin administered subcutaneously at a dose of 40 mg once daily for 6–14 days. The primary efficacy outcome was the 30-day composite of death related to VTE, pulmonary embolism, symptomatic DVT, or asymptomatic proximal-leg DVT, as detected with the use of systematic bilateral compression ultrasonography on day 30. The primary safety outcome was bleeding. Among the patients who could be evaluated, 2.71 % in the apixaban group (60 patients) and 3.06 % in the enoxaparin group (70 patients) met the criteria for the primary efficacy outcome (relative risk = 0.87; 95 % CI 0.62–1.23; $P = 0.44$). By day 30, major bleeding had occurred in 0.47 % of the patients in the apixaban group (15 patients) and in 0.19 % of the patients in the enoxaparin group (6 patients) (relative risk = 2.58; 95 % CI 1.02–7.24; $P = 0.04$).

The MAGELLAN (Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of VTE in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban With Enoxaparin) trial, not yet published, was presented at ACC 2011. In this double-blind, double-dummy, placebo-controlled randomized trial, 8,101 patients were randomized to receive 10 mg of rivaroxaban once daily for 35 days or 40 mg of enoxaparin once daily by subcutaneous injection for 10 days, as the standard

recommendation. Patients included had one or more acute medical conditions, including infectious disease, heart failure, respiratory insufficiency, ischemic stroke, active cancer, or inflammatory/rheumatic diseases. Patients had an average age of 71 years, and 60 % had renal impairment. They were in the hospital for an average of 11 days. The study's primary efficacy outcome was a composite of asymptomatic proximal DVT, symptomatic DVT, symptomatic nonfatal pulmonary embolism, and VTE-related death. The aim of the trial was to show noninferiority of rivaroxaban at 10 days and superiority at 35 days. The primary safety outcome was a composite of treatment-related major bleeding (International Society on Thrombosis and Haemostasis definition) and clinically relevant nonmajor bleeding. The composite primary efficacy endpoint occurred in 2.7 % in each group at day 10 ($P$ for noninferiority was 0.0025) and was reduced by 23 % in the rivaroxaban group at day 35 ($P = 0.02$ for superiority). Because of the higher bleeding rates with rivaroxaban (increased by 130 % [$P < 0.0001$] in days 1–10 and by 200 % [$P < 0.0001$] in days 11–35), the net clinical benefit favored enoxaparin, although the number of deaths favored rivaroxaban—there were six extra fatal bleeds and 11 fewer pulmonary embolism deaths in the rivaroxaban group. The publication is awaited, where a deeper analysis of the subgroup results will be provided.

## Anticoagulation in women: where do we stand?

Venous thromboembolism is a major cause of female morbidity and mortality. Risk factors for VTE include advancing age, the presence of inherited or acquired thrombophilias, hypofibrinolysis, surgery, hormone use (combined contraceptives or hormone replacement therapy), immobilization, being overweight, pregnancy, and malignancy.

The factors that affect coagulation change as women age, so anticoagulation treatment differs for the young woman, the pregnant woman, and the elderly woman. The key factor appears to be sex hormones, which alter procoagulant protein expression and the function of blood and vascular cells. Sex hormones have complicated effects on the vessel wall, coagulation proteins, and platelets that may alter thrombosis.

A pregnant woman has a two-fold to five-fold higher risk of VTE than a nonpregnant woman of the same age; in developed countries, a pregnant woman is more likely to die from fatal pulmonary embolism than from obstetric hemorrhage. The increased VTE risk is mediated through normal physiological changes of pregnancy, including alterations in hemostasis that favor coagulation, reduced fibrinolysis, and pooling and stasis of blood in the lower limbs.

Women with AF are at higher risk of stroke compared with men. Reasons for this remain unclear; strong evidence exists demonstrating gender differences in bleeding risk associated with antithrombotic treatment, mostly related to lower values of body mass, organ size, and renal function in women than men. Warfarin is the most commonly used anticoagulant in clinical practice, but new drugs are appearing. The newer anticoagulants are the direct and indirect factor Xa inhibitors and the direct thrombin inhibitors. These new agents (dabigatran, rivaroxaban, apixaban) tend to have more predictable pharmacokinetic properties and superior efficacy and safety.

## Diagnosis and management of heparin-induced thrombocytopenia: an update

Heparin-induced thrombocytopenia is a syndrome characterized by low platelet count and, paradoxically, thromboembolic events in patients who receive heparin. HIT is caused by IgG antibodies that bind to platelet factor 4, which in turn becomes immunogenic when conjugated with heparin, leading to the generation of thrombin through the activation of platelets, endothelial cells, and monocytes.

The diagnosis is often challenging because there may be an overlap of clinical situations that lead to thrombocytopenia. Sepsis, hemodilution after surgery, transfusion purple, drug-induced thrombocytopenia, and disseminated intravascular coagulation are just some of the differential diagnoses. Laboratory tests are often very specific or not widely available, and it is important to consider the pretest according to the result.

There is another form of HIT, typically characterized by a minor fall in platelet count, which occurs in the first 2 days of administration of heparin and usually returns to normal, even with prolonged use of heparin. This type of nonimmune thrombocytopenia appears to be due to a direct effect of heparin on the platelet membrane. It is usually self-limited and does not require specific treatment.

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## Recommended Reading

1. ACTIVE Writing Group (2006) Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the atrial fibrillation

Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomized controlled trial. Lancet 367:1903–1912
2. Adams HP Jr, del Zoppo G, Alberts MJ et al (2007) Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association. Stroke 38:1655–1711
3. Ainsworth CD, Blake CC, Tamayo A et al (2005) 3D ultrasound measurement of change in carotid plaque volume: a tool for rapid evaluation of new therapies. Stroke 36:1904–1909
4. Alexander KP, Chen AY, Roe MT et al (2005) Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. JAMA 294: 3108–3116
5. Alexander KP, Peterson ED (2010) Minimizing the risks of anticoagulants and platelet inhibitors. Circulation 121:1960–1970
6. Anderson JL, Adams CD, Antman EM et al (2007) ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 50: e1–e157
7. Avgil Tsadok M (2012) Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. JAMA 307:1952–1958
8. Bailey AL, Scantlebury DC, Smyth SS (2009) Thrombosis and antithrombotic therapy in women. Arterioscler Thromb Vasc Biol 29:284–288
9. Barbar S, Noventa F, Rossetto V et al (2010) A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost 8:2450–2457
10. Berwanger O, Guimarães HP, Laranjeira LN et al (2012) Effect of a multifaceted intervention on use of evidence-based therapies in patients with acute coronary syndromes in Brazil: the BRIDGE-ACS randomized trial. JAMA 307:2041–2049
11. Boersma E, Harrington RA, Moliterno DJ et al (2002) Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet 359:189–198
12. Bonow RO, Carabello BA, Chatterjee K et al (2008) 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 118:e523–e661
13. Brennan JM, Edwards FH, Zhao Y et al (2012) Early anticoagulation of bioprosthetic aortic valves in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. J Am Coll Cardiol 60:971–977
14. Camm AJ, Kirchhof P, Lip GY et al (2010) Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 23:2369–2429
15. Capodanno D, Angiolillo DJ (2010) Impact of race and gender on antithrombotic therapy. Thromb Haemost 104:471–484
16. Chan MY, Sun JL, Wang TY et al (2010) Patterns of discharge antiplatelet therapy and late outcomes among 8,582 patients with bleeding during acute coronary syndrome: a pooled analysis from PURSUIT, PARAGON-A, PARAGON-B, and SYNERGY. Am Heart J 160:1056–1064
17. Cohen M, Demers C, Gurfinkel EP et al (1997) A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. N Engl J Med 337:447–452
18. The CONSENSUS Trial Study Group (1987) Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 316:1429–1435
19. Cooper HA, Rao SV, Greenberg MD et al (2011) Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). Am J Cardiol 108: 1108–1111
20. Costa GL, Ferreira DC, Valacio RA, Vieira Moreira Mda C (2011) Quality of management of oral anticoagulation as assessed by time in therapeutic INR range in elderly and younger patients with low mean years of formal education: a prospective cohort study. Age Ageing 40:375–381
21. Ducharme A, Swedberg K, Pfeffer MA et al (2006) Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: assessment of Reduction in Mortality and morbidity (CHARM) program. Am Heart J 151:985–991
22. Eikelboom JW, Wallentin L, Connolly SJ et al (2011) Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation. Circulation 123:2363–2372
23. Ensor CR, Cahoon WD, Crouch MA et al (2010) Antithrombotic therapy for the CardioWest temporary total artificial heart. Texas Heart Inst J 37:149–158
24. Ezekowitz MD, Wallentin L, Connolly SJ et al (2010) Dabigatran and warfarin in vitamin K antagonist-naive and -experienced cohorts with atrial fibrillation. Circulation 122:2246–2253
25. Feinstein SB (2006) Contrast ultrasound imaging of the carotid artery vasa vasorum and atherosclerotic plaque neovascularization. J Am Coll Cardiol 48:236–243
26. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf S, Mehta SR et al (2006) Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 354:1464–1476
27. Fox KAA, Piccini JP, Wojdyla D et al (2011) Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J 32:2387–2394
28. Furie KL, Goldistein LB, Albers GW et al (2012) Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 43:3442–3453
29. Furie KL, Kasner SE, Adams RJ et al (2011) Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 42:227–276
30. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ (2001) Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 285:2864–2870
31. Goldhaber SZ, Leizorovicz A, Kakkar AK et al (2011) Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med 365:2167–2177
32. Granger CB, Alexander JH, McMurray JJ et al (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 365:981–992
33. Gualandro DM, Yu PC, Calderaro D et al (2011) II guidelines for perioperative evaluation. Arq Bras Cardiol 96(3 Suppl 1):1
34. Healey JS, Connolly SJ, Gold MR et al (2012) Subclinical atrial fibrillation and the risk of stroke. N Engl J Med 366:120–129

35. Hijazi Z, Oldgren J, Andersson U et al (2012) Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. Circulation 125:1605–1616
36. Hohnloser SH, Hijazi Z, Thomas L et al (2012) Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J 33:2821–2830
37. Homma S, Thompson JL, Pullicino PM et al (2012) Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med 366:1859–1869
38. Khan IA (2003) Atrial stunning: basics and clinical consideration. Int J Cardiol 2003(92):113–128
39. Klein AL, Grimm RA, Murray RD et al (2001) Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. N Engl J Med 344:1411–1420
40. Lazar RM, Shapiro PA, Jaski BE et al (2004) Neurological events during long-term mechanical circulatory support for heart failure: the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) experience. Circulation 109:2423–2427
41. Leiria TL, Pellanda L, Miglioranza MH et al (2010) Warfarin and phenprocoumon: experience of an outpatient anticoagulation clinic. Arq Bras Cardiol 94:40–43
42. Leon MB, Smith CR, Mack M et al (2010) Transcatheter aortic valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 363:1597–1607
43. Lindqvist PG, Epstein E, Olsson H (2008) The relationship between lifestyle factors and venous thromboembolism among women: a report from the MISS study. Br J Haematol 144: 234–240
44. Lip GYH, Ponikowski P, Andreotti F et al (2012) Thromboembolism and antithrombotic therapy for heart failure in sinus rhythm. A Joint Consensus Document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis. Eur J Heart Fail 14:681–695
45. Little SH, Massel DR (2003) Antiplatelet and anticoagulation for patients with prosthetic heart valves. Cochrane Database Syst Rev 4:CD003464
46. Lopes RD, Peterson ED, Chen AY et al (2010) Antithrombotic strategy in non-ST-segment elevation myocardial infarction patients undergoing percutaneous coronary intervention: insights from the ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry. J Am Coll Cardiol Intv 3:669–677
47. Lopes RD, Subherwal S, Holmes DN et al (2012) The association of in-hospital major bleeding with short-, intermediate-, and long-term mortality among older patients with non-ST-segment elevation myocardial infarction. Eur Heart J 33: 2044–2053
48. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M (2007) Prediction of clinical cardiovascular events with carotid intima-media thickness—a systematic review and meta-analysis. Circulation 115:459–467
49. Lorenz MW, Polak JF, Kavousi M et al (2012) Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. Lancet 379: 2053–2062
50. Lubenow N, Hinz P, Thomaschewski S et al (2010) The severity of trauma determines the immune response to PF4/heparin and the frequency of heparin-induced thrombocytopenia. Blood 115:1797–1803
51. Maggioni A, Latini R, Carson PE et al (2005) Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J 149:548–557
52. Mehran R, Pocock SJ, Nikolsky E et al (2010) A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol 55:2556–2566
53. Mehran R, Pocock SJ, Stone GW et al (2009) Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUITY trial. Eur Heart J 30:1457–1466
54. Mehran R, Rao SV, Bhatt DL et al (2011) Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 123:2736–2747
55. Mehta SK, Frutkin AD, Lindsey JB et al (2009) Bleeding in patients undergoing percutaneous coronary intervention: the development of a clinical risk algorithm from the National Cardiovascular Data Registry. Circ Cardiovasc Intv 2:222–229
56. Miedema I, Luijckx GJ, De Keyser J, Koch M, Uyttenboogaart M (2012) Thrombolytic therapy for ischaemic stroke in patients using warfarin: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 83:537–540
57. Morrow DA, Braunwald E, Bonaca MP et al (2012) Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med 366:1404–1413
58. Mountantonakis SE, Grau-Sepulveda MV, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC (2012) Presence of atrial fibrillation is independently associated with adverse outcomes in patients hospitalized with heart failure: an analysis of Get With The Guidelines-Heart Failure. Circ Heart Fail 5:191–201
59. Olesen J, Lip GY, Hansen ML et al (2011) Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 342:d124
60. Olsson SG, Swedberg K, Ducharme A et al (2006) Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. J Am Coll Cardiol 47:1997–2004
61. Patel MR, Mahaffey KW, Garg J et al (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 365:883–891
62. Petersen JL, Mahaffey KW, Hasselblad V et al (2004) Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes: a systematic overview. JAMA 29289–29296
63. Potapov EV, Krabatsch T, Ventura HO, Hetzer R (2011) Advances in mechanical circulatory support: year in review. J Heart Lung Transplant 30:487–493
64. Price J, Hynes M, Labinaz M, Ruel M, Boodhwani M (2012) Mechanical valve thrombosis with dabigatran. J Am Coll Cardiol 60:1710–1711
65. The PURSUIT Trial Investigators (1998) Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 339:436–443
66. Rao SV, Eikelboom J, Steg PG et al (2009) Standardized reporting of bleeding complications for clinical investigations in acute coronary syndromes: a proposal from the academic bleeding consensus (ABC) multidisciplinary working group. Am Heart J 158(881–886):e1
67. Rao SV, Jollis JG, Harrington RA et al (2004) Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 292:1555–1562

68. Rao SV, Kaul PR, Liao L et al (2008) Association between bleeding, blood transfusion, and costs among patients with non-ST-segment elevation acute coronary syndromes. Am Heart J 155:369–374
69. Rao SV, O'Grady K, Pieper KS et al (2005) Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. Am J Cardiol 96:1200–1206
70. Rao SV, O'Grady K, Pieper KS et al (2006) A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. J Am Coll Cardiol 47:809–816
71. Rossi M, Serraino GF, Jiritano F, Renzulli A (2012) What is the optimal anticoagulation in patients with a left ventricular assist device? Interact Cardiovasc Thorac Surg 15:733–740
72. Roy D, Talajic M, Nattel S et al (2008) Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 358:2667–2677
73. Roy P, Bonello L, Torguson R et al (2008) Impact of "nuisance" bleeding on clopidogrel compliance in patients undergoing intracoronary drug-eluting stent implantation. Am J Cardiol 102:1614–1617
74. Scirica BM, Bonaca MP, Braunwald E et al (2012) Vorapaxar for secondary prevention of thrombotic events for patients with previous myocardial infarction: a prespecified subgroup analysis of the TRA 2°P-TIMI 50 trial. Lancet 380:1317–1324
75. Shantsila E, Lip GY, Chong BH (2009) Heparin-induced thrombocytopenia: a contemporary clinical approach to diagnosis and management. Chest 135:1651–1664
76. Shibazaki K, Kimura K, Fujii S, Sakai K, Iguchi Y (2012) Brain natriuretic peptide levels as a predictor for new atrial fibrillation during hospitalization in patients with acute ischemic stroke. Am J Cardiol 109:1303–1307
77. The SOLVD Investigators (1992) Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 327:685–691
78. Spyropoulos AC, Anderson FA Jr, Fitzgerald G et al (2011) Predictive and associative models to identify hospitalized medical patients at risk for VTE. Chest 140:706–714
79. Stein JH, Korcarz CE, Hurst RT et al (2008) Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 21:93–111
80. Stein PD, Henry JW (1995) Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. Chest 108:978–981
81. Subherwal S, Bach RG, Chen AY et al (2009) Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. Circulation 119:1873–1882
82. Suissa L, Bresch S, Lachaud S, Mahagne MH (2012) Brain natriuretic peptide: a relevant marker to rule out delayed atrial fibrillation in stroke patient. J Stroke Cerebrovasc Dis. doi:10.1016/j.jstrokecerebrovasdis.2012.08.010
83. Sun JC, Davidson MJ, Lamy A, Eikelboom JW (2009) Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. Lancet 374:565–576
84. Swedberg K, Zannad F, McMurray JJ et al (2012) Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. J Am Coll Cardiol 59:1598–1603
85. Taylor D, Stehlik J, Edwards LB et al (2009) Registry of the International Society for Heart and Lung Transplantation: twenty-sixth official adult heart transplant report: 2009. J Heart Lung Transplant 28:1007–1022
86. Tricoci P, Peterson ED, Mulgund J et al (2006) Temporal trends in the use of early cardiac catheterization in patients with non-ST-segment elevation acute coronary syndromes (results from CRUSADE). Am J Cardiol 98:1172–1176
87. Vahanian A, Baumgartner H, Bax J et al (2007) Guidelines on the management of valvular heart disease: the task force on the management of valvular heart disease of the European Society of Cardiology. Eur Heart J 28:230–268
88. Van Gelder IC, Groenveld HF, Crijns HJ et al (2010) Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 362:1363–1373
89. van Walraven C, Oake N, Wells PS, Forster AJ (2007) Burden of potentially avoidable anticoagulant-associated hemorrhagic and thromobembolic events in the elderly. Chest 131:1508–1515
90. Verheugt FW, Steinhubl SR, Hamon M et al (2011) Incidence, prognostic impact, and influence of antithrombotic therapy on access and nonaccess site bleeding in percutaneous coronary intervention. J Am Coll Cardiol Interv 4:191–197
91. Wang TJ, Larson MG, Levy D et al (2003) Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 107:2920–2925
92. Wang TY, Xiao L, Alexander KP et al (2008) Antiplatelet therapy use after discharge among acute myocardial infarction patients with in-hospital bleeding. Circulation 118:2139–2145
93. Warkentin TE (2005) New approaches to the diagnosis of heparin-induced thrombocitopenia. Chest 127(2 Suppl):35S–45S
94. Warkentin TE, Sheppard JA, Horsewood P, Simpson PJ, Moore JC, Kelton JG (2000) Impact of the patient population on the risk for heparin-induced thrombocytopenia. Blood 96:1703–1708
95. Weitz JI, Eikelboom JW, Samama MM (2012) New antithrombotic drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141(2 suppl):e120S–e151S
96. Wieloch M, Sjalander A, Frykman V, Rosenqvist M, Eriksson N, Svensson PJ (2011) Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. Eur Heart J 32:2282–2289
97. Wiviott SD, Braunwald E, McCabe CH et al (2007) Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 357:2001–2015
98. Xian Y, Liang L, Smith EE et al (2012) Risks of intracranial hemorrhage among patients with acute ischemic stroke receiving warfarin and treated with intravenous tissue plasminogen activator. JAMA 307:2600–2608
99. You JJ, Singer DE, Howard PA et al (2012) Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians. Evidence-based Clinical Practice Guidelines. Chest 141(2 suppl):e531S–e575S
100. Zacharski LR, Chow BK, Howes PS et al (2007) Reduction of iron stores and cardiovascular outcomes in patients with peripheral arterial disease: a randomized controlled trial. JAMA 297:603–610