Highlights from the I international symposium of thrombosis and anticoagulation in internal medicine, October 23–25, 2008, Sao Paulo, Brazil

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Abstract The importance of thrombosis and anticoagulation in clinical practice is rooted firmly in several fundamental constructs that can be applied both broadly and globally. Awareness and the appropriate use of anticoagulant therapy remain the keys to prevention and treatment. However, to assure maximal efficacy and safety, the clinician must, according to the available evidence, choose the right drug, at the right dose, for the right patient, under the right indication, and for the right duration of time. The first *International Symposium of Thrombosis and Anticoagulation in Internal Medicine* was a scientific program developed by clinicians for clinicians. The primary objective of the meeting was to educate, motivate and inspire internists, cardiologists and hematologists by convening national and international visionaries, thought-leaders and dedicated clinician-scientists in Sao Paulo, Brazil. This article is a focused summary of the symposium proceedings.

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The importance of thrombosis and anticoagulation in clinical practice is rooted firmly in several fundamental constructs that can be applied both broadly and globally. First, hemostasis, representing the physiological or protective phenotype of thrombosis is life-sustaining. Second, thrombotic disorders are common and occur in patients of all ages, races, ethnicities and medical/surgical conditions. Third, in many instances, thrombosis as the proximate cause of venous thromboembolism (VTE), stroke and myocardial infarction is preventable and treatable. Awareness and the appropriate use of anticoagulant therapy remain the keys to prevention and treatment. However, to assure maximal efficacy and safety, the clinician must, according to the available evidence, choose the right drug, at the right dose, for the right patient, under the right indication, and for the right duration of time.

The opportunity to share ideas, and advance the care of patients with thrombotic disorders, is the fundamental tenet of practicing clinicians worldwide. This can only be accomplished through knowledge gained from carefully designed, meticulously conducted and honestly interpreted translational and clinical research.

True to the lasting spirit of scholarly interchange, the first *International Symposium of Thrombosis and Anticoagulation in Internal Medicine* was a scientific program developed by clinicians for clinicians. The symposium was promoted by the Federal University of Sao Paulo together with the Brazilian Society of Internal Medicine and the Duke Clinical Research Institute of Duke University School of Medicine. It was also supported by the Brazilian and Paulista Societies of Cardiology. 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. The symposium took place in Sao Paulo, Brazil from the 23–25 of October, 2008.

The primary objective for the 3 days of academic presentations and open discussions was to educate, motivate and inspire internists, cardiologists and hematologists by convening national and international visionaries, thought-leaders and dedicated clinician-scientists in Sao Paulo, Brazil. The following is a focused summary of the symposium proceedings.

Thrombosis—what is the role of the endothelium?

It is widely recognized that the endothelium is not a static barrier between the vessel lumen and the vessel wall, but rather a dynamic organ that synthesizes, secretes and regulates a wide variety of substances, including nitric oxide (NO), cytokines, chemokines, adhesion molecules and mediators that affect the function of different cells.

The endothelium is the major regulator of vascular homeostasis. Under normal conditions, the endothelium promotes vasodilation and exerts antioxidant, anti-inflammatory effects, inhibiting leukocyte adhesion and transmigration. It also inhibits smooth muscle cell proliferation and migration, platelet adhesion and aggregation, and displays both anticoagulant and profibrinolytic properties.

Several traditional risk factors for atherosclerosis (systemic arterial hypertension, diabetes mellitus, hypercholesterolemia, smoking, ageing) adversely affect endothelial cell function, even before the development of obstructive atherosclerotic plaques. The resultant "endothelial dysfunction" is characterized by a propensity toward vasoconstriction, release of inflammatory mediators and predisposition to thrombosis (Fig. 1). Endothelial dysfunction is considered a marker of early atherosclerosis, and is considered the pathophysiological foundation for atherosclerotic plaque progression, which include impaired vascular repair leading to erosion and disruption.

Oxidative stress and the free-radical-mediated neutralization of nitric oxide (NO) are closely linked to atherothrombosis. Apart from NO, endothelial cells secrete
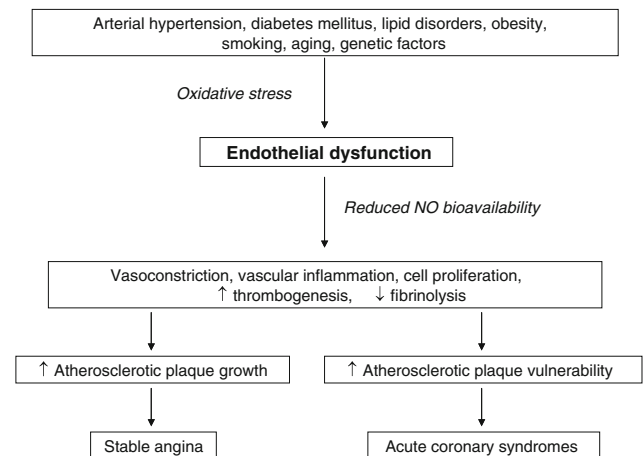
Fig. 1 Cardiovascular risk factors induce endothelial dysfunction, closely associated with oxidative stress and characterized by reduced nitric oxide (NO) bioavailability. The dysfunction of vascular endothelial cells establishes an environment characterized by a propensity toward vasoconstriction; the release of inflammatory mediators; and. a marked predisposition to thrombosis. Endothelial dysfunction is a fundamental pathophysiological alteration that governs initiation, growth and erosion/rupture of atherosclerotic plaque-the proximate cause of clinical syndromes, including stable or unstable angina and acute myocardial infarction

other antithrombotic substances, such as prostacyclin (PGI2), CD39, thrombomodulin, heparan sulfate, and tissue plasminogen activator (tPA).The vascular endothelium also synthesizes prothrombotic substances, such as von Willebrand factor, P-selectin, tissue factor and plasminogen activator inhibitor-1 (PAI-1). Under normal conditions, inhibitors of platelet activation and coagulalation predominate, allowing thrombin generation and fibrin formation to be tightly regulated. In contrast, when the endothelium is dysfunctional, a shift toward a prothrombotic state takes place. An increase in the expression of selectins promotes platelet adhesion to the endothelium. Adherent, activated platelets interact with and stimulate endothelial cells and monocytes, further amplifying the inflammatory environment that inherently typifies atherosclerosis.

There is ample evidence linking endothelial dysfunction and changes in NO metabolism to atherothrombosis, providing mechanistic support for an observed independent association between endothelial dysfunction and future cardiovascular events. Accordingly, treatment strategies targeting endothelium/NO pathways may promote vascular health and reduce thrombotic events. For example, risk factor control, statins, angiotensin-converting enzyme inhibitors, physical exercise, antioxidants and red wine improve endothelial performance. Cell-based therapeutics that target signaling pathways implicated in endothelial dysfunction may confer additional benefit and warrant further investigation.

Thrombosis and hemostasis

Fibrin clot formation, the basis for both protective hemostasis and pathological thrombosis, is a complex, cell-based process represented by several integrated biochemical steps designed to maintain blood fluidity and vascular integrity.

Following vascular injury, platelets tether and ultimately adhere to collagen fibers within the subendothelium-a physical event mediated by platelet membrane glycoproteins GPIaIIa, GP VI, GP 1b, GPIIbIIIa, and von Willebrand factor, which represent the predominant ligand for both transient and stable adhesion and fibrinogen that builds a "bridge" between adjacent platelets, establishing a stable aggregate.

Activated platelets expose phospholipids that, in turn, provide a surface for coagulation protein assembly. Tissue factor, in the presence of calcium ions and the exposed phospholipids on the activated platelet membrane, initiates activation of factor VII at the site of endothelial injury. Activated factor VII (VIIa) activates factor IX which, in the presence of factor VIII, forms the X-ase complex that activates factor X. Factor Xa, in the presence of factor Va forms the prothrombinase complex that cleaves the pro-thrombin molecule, forming a small amount of thrombin. Thrombin is capable of activating both factors V and VIII, thus creating a positive feedback loop that leads to additional thrombin formation.

Thrombin, by cleaving fibrinopeptides A and B from fibrinogen, generates fibrin monomers that polymerize to form the lattice of a fibrin clot. Finally, thrombin activates factor XIII, which promotes covalent binding within gamma chains of fibrin to stabilize the fibrin clot.

Several intrinsic regulatory mechanisms, such as fibrinolysis by plasmin or the inactivation of coagulation proteins by endogenous anticoagulants like antithrombin III and activated protein C provide a counterbalance that, in most instances, prevents pathologic (or unwanted) thrombosis.

Pharmacokinetics and pharmacodynamics of vitamin K antagonists

Vitamin K antagonists (VKAs) have been the only oral anticoagulants available for clinical use until now, and have been used for more than 60 years. Their effectiveness has been demonstrated for primary and secondary VTE prophylaxis, prevention of systemic embolism in patients with atrial fibrillation, prosthetic cardiac valves, or large myocardial infarctions, particularly with mural thrombosis.

VKAs exert their effect by inhibiting vitamin K oxide reductase, thus limiting the amount of reduced vitamin K available for the γ-carboxylation of the glutamate residues on the N-terminal regions of coagulation proteins II, VII, IX and X. This specific carboxylation step is an absolute prerequisite for calcium- dependent binding to cofactors on phospholipid surfaces- its absence reduces the coagulant potential of the blood. VKAs also interfere with carboxylation of the anticoagulant proteins C, S and Z and several proteins synthesized in bone.

There are two VKAs available in Brazil: warfarin, the most commonly used, with a half-life of about 35 h and phenprocoumon, a much longer-acting agent, with a half-life of 5.5 days. Both preparations are metabolized by the cytochrome P450 system in the liver.

Individual response to VKAs varies greatly depending on genetic factors, concomitant diseases and both medication and food interactions. For these reasons, close monitoring of treatment with VKAs is necessary; to include INR determinations at least every 4 weeks, clinical interview, and ascertainment of new (or changes in) medications or foods. The INR provides a reliable and evidence-based parameter for effectiveness and risk of bleeding, and must be maintained in the range between 2 and 3 for most patients. The effect of VKAs may be attenuated or fully reversed by vitamin K administration.

Antithrombotics in acute coronary syndrome with st-segment elevation

Advances in the management of patients with STEMI have been achieved with antithrombotic pharmacotherapies. Further contributions are likely with new compounds such as oral, direct factor Xa inhibitors (otamixaban, apixaban, Du 183b, Tak 442 and rivaroxaban), platelet P2Y12 receptor blockers (cangrelor, AZD 6140, prasugrel) and platelet thrombin receptor (PAR-1) blocker. Among the approved drugs, important data has been presented in the last few years. A brief summary is presented below:

(A) *Antiplatelet drugs*: Clopidogrel was tested against placebo in two STEMI studies that included a total of nearly 49,000 patients. The primary endpoint in CLARITY was the composite of an occluded culprit coronary artery, death or reinfarction at the time of the coronary angiography or at hospital discharge. A 36% risk reduction ($P < 0.001$) in the main endpoint, in favor of clopidogrel was demonstrated. In COMMIT, the primary endpoint was a composite of death, reinfarction or stroke up to 28 days, and the results showed a 9% relative risk reduction ($P = 0.002$), also in favor of clopidogrel. In both studies, the bleeding rates were similar between clopidogrel and placebo. The ACC/AHA STEMI

guidelines recommend clopidogrel whether or not reperfusion therapy has been provided. More recently the TRITON Trial was published, and its sub-analysis for patients with STEMI was presented during the European Society of Cardiology Congress. The results were as follows: incidence of the primary endpoint (CV death, MI, stroke) at 30 days of 12.4% and 10% for clopidogrel and prasugrel, respectively ($P = 0.002$); stent thrombosis of 2.8% and 1.6%, respectively($P = 0.02$). There was no significant difference in bleeding between groups.

(B) *Antithrombin drugs*: In 2001 the HERO-2 study was published, showing that bivalirudin, in addition to streptokinase, had a similar 30-day mortality rate (primary endpoint) compared to UFH, but an increase in the incidence of bleeding. The CREATE study was published in 2005, and reported a lower incidence of death, reinfarction or stroke at 7 and 30 days (main endpoint—HR of 0.87, $P = 0.014$) for reviparin compared to placebo, but at the cost of increased major bleeds (HR $= 2.49$, $P = 0.001$). The OASIS-6 Trial, published in 2006 included 12,000 patients treated initially with either fibrinolytics or primary PCI, and then randomized to fondaparinux, placebo or UFH. The primary efficacy endpoint was the composite of death or MI at 30 days. The observed hazard-ratios were as follows: for the comparison of fondaparinux and placebo or UFH, 0.86 ($P = 0.008$); for the comparison of fondaparinux and placebo, 0.79 ($P < 0.05$); and, for the comparison of fondaparinux and UFH, 0.95 ($P = $ NS). Moreover, there was an unfavorable interaction ($P = 0.03$) between fondaparinux and primary PCI, with a hazard-ratio of 1.20 for patients undergoing PCI, and 0.88 for those without primary PCI. There were no significant differences in bleeding, between fondaparinux and UFH. A meta-analysis including 27,000 patients treated with LMWH or UFH, revealed a significant 16% net clinical benefit in favor of enoxaparin in relation to UFH.Based on the available information, the ACC/AHA guidelines recommend UFH, enoxaparin or fondaparinux for patients with STEMI, but caution that "because of the risk of catheter thrombosis, fondaparinux should not be used as the sole anticoagulant to support PCI".

Anticoagulation in acute coronary syndromse without ST-segment elevation

Platelets play a pivotal role in the transformation of a stable to an unstable atherosclerotic plaque. Disruption of an atherosclerotic plaque exposes the subendothelial matrix (e.g. collagen and tissue factor) to circulating blood.

Antiplatelet therapy, a cornerstone of therapy in NSTE-ACS, is directed at decreasing the formation of thromboxane A_2 (aspirin), inhibiting the P2Y12-mediated platelet activation (thienopyridines) and directly inhibiting platelet aggregation (GP IIb/IIIa inhibitors). In four randomized trials, the use of aspirin versus placebo was associated with a 50% reduction in death or MI. Therefore, after an initial dose of 162–325 mg, a dose of 75–100 mg daily is recommended in patients with ACS. Clopidogrel when added to aspirin, confers a 20% reduction in cardiovascular death, MI, or stroke, compared with aspirin alone, in both low- and high-risk patients with NSTE-ACS. The dose of clopidogrel for medical treatment is 300 mg, followed by 75 mg daily. The benefit of GP IIb/IIIa inhibitors is most evident when used in high-risk patients (e.g. elevated troponin, diabetes mellitus). Abciximab is currently approved only in patients undergoing PCI within 12 h of treatment initiation. Eptifibatide and tirofiban can be used in either a conservative or intervention-based strategy.

Anticoagulation, traditionally with unfractionated heparin (UFH) is another cornerstone of therapy for patients with NSTE-ACS. A meta-analysis showed a 33% reduction in death or MI comparing UFH plus aspirin versus aspirin alone. Low-molecular-weight heparins (LMWHs) combine factor IIa and Xa inhibition and thus inhibit both the action and generation of thrombin. LMWH has several potential advantages over UFH. In ESSENCE and TIMI 11B trials, enoxaparin was superior to UFH, with a statistically significant 20% reduction in events among moderate-risk patients. In the SYNERGY trial, including high-risk patients managed with an invasive strategy enoxaparin was found to be noninferior to UFH. The standard dose of enoxaparin is 1 mg/kg given subcutaneously (SC) every 12 h.

Fondaparinux is a synthetic, indirect, specific factor Xa inhibitor that requires antithrombin III for its pharmacodynamic activity. In the OASIS-5 trial, fondaparinux at a dose of 2.5 mg SC once daily produced similar rates of death, MI or refractory ischemia to enoxaparin, but with substantially less major bleeding.

Direct thrombin inhibitors have a theoretical advantage over heparin compounds; they do not require antithrombin III and can inhibit clot-bound thrombin; they do not interact with plasma proteins, they provide a very stable level of anticoagulation and do not cause thrombocytopenia. In the ACUITY trial, patients were managed with an early invasive strategy, and randomized to receive either bivalirudin alone, enoxaparin or UFH plus a GP IIb/IIIa inhibitor or bivalirudin plus a GP IIb/IIIa inhibitor. No differences were observed between the three treatment arms for the composite of death, MI or unplanned

revascularization at 30 days, but bivalirudin caused less bleeding compared with the other two arms (3% vs. 5% vs. 7%, respectively; $P < 0,001$).

Atrial fibrillation and acute coronary syndromes

Atrial fibrillation (AF) is a common complication of myocardial infarction (MI) with a reported incidence ranging from 5% to 23%. It is associated with worse in-hospital and long-term outcomes.

Although antithrombotic therapy is important in the treatment of patients with both AF and MI, the combined administration of aspirin, thienopyridines, and a vitamin K antagonist (triple therapy) increases the risk of bleeding. The current AF guidelines recommend VKA anticoagulant therapy for patients with a $CHADS_2$ score ≥ 2 as a class IA recommendation. Guidelines also recommend low dose aspirin (81 mg/day), clopidogrel, and warfarin (with target INR 2.0–2.5) after stenting for patients with acute coronary syndromes and a concomitant indication for oral anticoagulation. The available literature on the subject of "triple therapy" shows that patients with AF and ACS are not discharged from the hospital on a VKA. Paradoxically, patients deemed to be at highest risk of stroke ($CHADS_2$ score ≥ 2) are least likely to be treated due to physician concerns over the potential risk of bleeding.

New onset AF that develops in the setting of ACS continues to be a marker of poor short and long-term prognosis. There appears to be a "treatment-risk paradox" concerning VKA use, highlighting the need for additional investigation to better understand risk-benefit relationships and optimal management strategies.

Atrial fibrillation

The prevalence of atrial fibrillation (AF) is increasing worldwide. Older age, hypertension, heart failure, and obesity all increase the risk of developing AF. Atrial fibrillation is a potent risk factor for stroke raising the risk on average 5-fold. The seminal trials in nonvalvular AF demonstrated the remarkable efficacy of warfarin in stroke prevention with a risk reduction of 68%. Current guidelines recommend warfarin for patients with stroke, transient ischemic attack, or systemic embolism and for patients with two or more of the following risk factors: age 75 years and greater, hypertension, heart failure, diabetes mellitus. Aspirin or warfarin is recommended if only one of these risk factors is present, depending on patient preference. Despite the efficacy of warfarin, numerous studies have shown that only about one-half of patients are treated. Older age and perceived bleeding risk are the most often-cited negative predictive factors. Difficulty with warfarin monitoring is also a major obstacle to its use.

Recent randomized trials have focused on maintenance of sinus rhythm and the potential role of antiplatelet therapy in stroke prevention in AF. These studies have illustrated that prolonged maintenance of sinus rhythm remains elusive and antiplatelet agents, either as monotherapy or in combination (aspirin plus clopidogrel), is less efficacious than anticoagulant treatment in AF. Because the 30-day mortality of AF-related stroke is 24%, use of less efficacious agents mandates careful consideration. Current trials in AF will explore the efficacy of novel anticoagulant drugs as potential replacements for warfarin.

Hemorrhage is a serious adverse effect of antithrombotic therapy. The clinical dilemma in atrial fibrillation is that both risk of stroke and risk of hemorrhage increase with age. Older age is also associated with lower warfarin dose requirements and a slower return to therapeutic levels following an episode of excessive anticoagulation. Concomitant antiplatelet therapy also increases the risk of extracranial and intracranial hemorrhage. Strategies to minimize these risks include vigilant monitoring of the International Normalized Ratio (INR) with a target INR of 2.5, maintaining blood pressure less than 130/80 mmHg, and minimizing concomitant aspirin use. It is important to emphasize that the frequency and severity of stroke in AF outweigh the risk of warfarin-related hemorrhage for most patients.

New studies on atrial fibrillation

There are several ongoing phase II and phase III trials of antithrombotic therapy for stroke prevention in atrial fibrillation. They are summarized in Figs. 2, 3 and 4. The trials of warfarin (versus placebo) for stroke prevention in atrial fibrillation included approximately 3,800 patients. Recently completed and ongoing trials will include a total of 71,600 patients. The results of these trials are eagerly awaited and will be important to better understand this common disease and to improve patient care.

VTE prophylaxis in Brazil—a global perspective

VTE, as a public health problem, frequently affects hospitalized patients at risk for thromboembolic events and represents a major field for prophylaxis interventions. Guideline-recommended thromboprophylaxis reduces the burden of VTE, both in at-risk surgical and medical patients. However, multinational, prospective registries such as the IMPROVE show that risk factors are very common in medical patients (93% have at least one risk
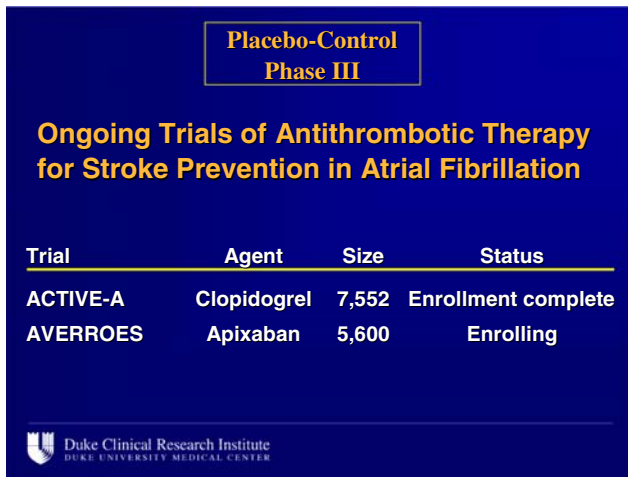
Fig. 2 Ongoing Placebo-control phase III trials of antithrombotic therapy for stroke prevention in atrial fibrillation
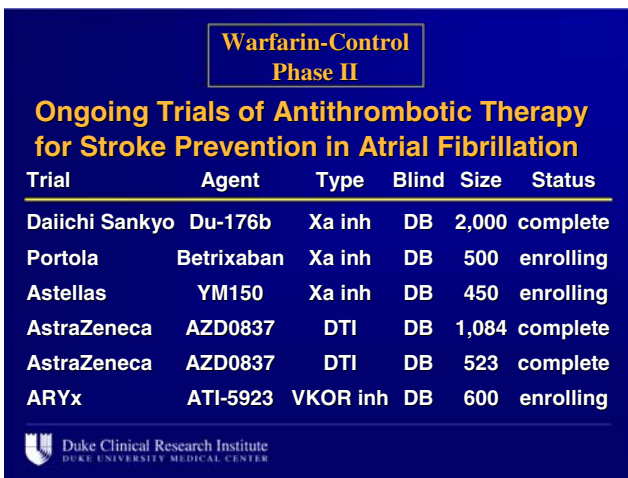

Fig. 3 Ongoing Warfarin-control phase II trials of antithrombotic therapy for stroke prevention in atrial fibrillation
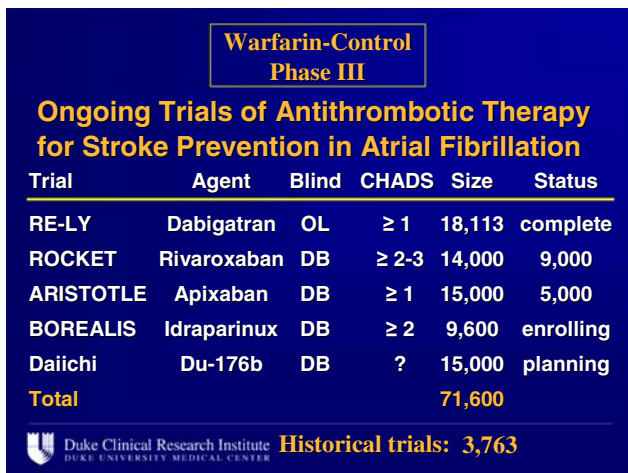

Fig. 4 Ongoing Warfarin-control phase III trials of antithrombotic therapy for stroke prevention in atrial fibrillation

factor), but that VTE prophylaxis is underutilized in the participating countries. In Brazil, the utilization of prophylaxis was significantly less than "rest of world" (36% vs. 51%), particularly among the public hospitals. The ENDORSE study, a large, global observational study of VTE prophylaxis in medical and surgical patients, included 32 countries, 358 hospitals and 68,183 patients. Using a cross-sectional design, the study showed that more than half of the hospitalized patients were at-risk of VTE and that prophylaxis was underutilized in both surgical and medical patients (59% and 40%, respectively). Therefore, there is a clear gap between guidelines and clinical practice, observed across many countries.

VTE prophylaxis in special patient populations

Given the coexisting risk of thrombosis and bleeding associated with acute CVA, the PREVAIL study evaluated the efficacy and safety of enoxaparin (40 mg SC daily) versus unfractionated heparin (5,000 IU SC 12–12 h) for the prevention of VTE. The study showed that enoxaparin was superior to UFH for the prevention of VTE and proximal deep vein thrombosis, reducing the overall incidence by 43% without increasing the risk of major bleeding. The EXCLAIM study investigated the potential benefit of prolonged VTE prophylaxis in acutely ill medical patients with recent reduced mobility. Hospitalized medical patients were randomized to enoxaparin (40 mg daily) or placebo for an additional 28 days after initial 10 day-prophylaxis with enoxaparin. The study showed a significant reduction in VTE (4.9% vs. 2.8%). Major bleeding was significantly more frequent in the enoxaparin group (0.6% vs. 0.1%). One could conclude that highly selected, acutely ill medical patients, including those with reduced mobility, age >75 years, malignancy or previous history of VTE, might benefit from extended prophylaxis beyond the recommended 10 ± 4 days, but at a cost of increased bleeding.

Brazilian guidelines for VTE prophylaxis in medical patients

VTE refers to deep vein thrombosis (DVT) and pulmonary embolism (PE), frequent complications responsible for 10% of deaths in the hospital. Although classically related to surgical procedures, fatal PE can occur in high-risk medical patients as well. VTE prophylaxis among hospitalized patients remains low, partially due to the lack of readily available risk assessment tools and widely implemented "triggers" for ordering prophylactic measures upon hospital admission.

In 2006, 12 Brazilian Medical Societies published the "Brazilian Guideline for VTE Prophylaxis in Medical

Patients" as part of the Guidelines Project of the Brazilian Medical Association (http://www.projetodiretrizes.org.br/volume_4.php). A systematic review was performed, with the objective to identify diseases and conditions associated with VTE and the optimal strategy for its prevention. An algorithm was subsequently developed to assist physicians in day-to-day clinical practice.

Risk assessment

Every medical patient admitted must have his/her VTE risk evaluated. Patients 40 years of age or older, with reduced mobility and at least one additional risk factor for VTE must be considered at risk. In the absence of contraindications, prophylaxis should be provided. Patients younger than 40 years, but having one or more risk factors for VTE may also benefit from prophylaxis.

Prophylaxis

For prophylaxis, once a day SC low molecular weight heparin (enoxaparin 40 mg, dalteparin 5.000 IU, or nadroparin 3,800 and 5,700 IU, respectively for patients weighing 70 kg or more), or SC unfractionated heparin, 5.000 IU three times a day, may be used. Prophylaxis should continue for 6–14 days, even if the patient resumes ambulation.

Improving VTE prophylaxis in medical patients

There are several barriers for implementation of an effective VTE prophylaxis program, beginning with lack of awareness of the recommendations, resistance to change, fear of inducing bleeding, absence of institutional policies, economical barriers, and lack of an adequate risk assessment tool. It is widely recognized that continuing medical education (CME) initiatives, including lectures and dissemination of guidelines are not effective. Multifaceted interventions, targeting specific barriers are more effective than single-strategy interventions. A combined approach must include formal presentations of the guidelines to hospital physicians; distribution of the printed guidelines; creation of a working group to identify local barriers to change; use of printed or electronic reminders, and constant evaluation of physician and institution performance.

VTE prophylaxis programs

Identification of interested personnel is an important first step in the development of a VTE prophylaxis program. The hospital administration must also be engaged and committed to the process and support the establishment of a Commission for VTE Prophylaxis (CVTEP) that should be multidisciplinary, with participation of physicians, nurses, pharmacists, physiotherapists, and hospital quality control personnel. The CVTEP should be proactive, performing a daily evaluation of prophylaxis utilization to include patient selection and dosing in every area of the hospital. The CVTEP should also be responsible for providing physician feedback and establishing mechanisms for continued quality improvement. Additional strategies for success include staff presentations emphasizing VTE prophylaxis in medical, surgical, and subspecialties areas, distribution of educational material, decision-support systems, risk assessment tools, and electronic alerts. An active, integrated, and multifaceted approach may be the key to achieving and maintaining long term compliance with VTE risk evaluation and prophylaxis.

Orthopedics surgery—How to prevent thromboembolic events?

Patients undergoing orthopedic surgery are at increased risk of venous thromboembolic events; proven prophylactic measures are available but are generally underused. The incidence of deep venous thrombosis (DVT) in patients undergoing orthopedic surgery is reported to range from 40% to 60% in patients who did not receive thromboprophylaxis.

Several studies provide evidence of a significant reduction in venous thromboembolic events using low-molecular-weight heparin (LMWH), unfractionated heparin, warfarin, or fondaparinux. A new class of oral anticoagulants, direct factor Xa inhibitors, appears particularly promising.

The RECORD program included several phase III trials that compared the efficacy and safety of rivaroxaban to enoxaparin in patients undergoing major orthopedic surgery. The RECORD 1 investigated VTE thromboprophylaxis in patients undergoing total hip arthroplasty. It was randomized, double-blind study that assigned 4,541 patients to receive either 10 mg of oral rivaroxaban once daily, beginning after surgery, or 40 mg of enoxaparin subcutaneously once daily, beginning the evening before surgery, plus a placebo tablet or injection. A total of 3,153 patients were included in the superiority analysis and 4,433 were included in the safety analysis. There was a highly statistically significant reduction in total VTE favoring rivaroxaban (absolute risk reduction, 2.6%; 95% confidence interval [CI], 1.5–3.7; $P < 0.001$). Major VTE was 0.2% in the rivaroxaban group and 2.0% in the enoxaparin group (absolute risk reduction, 1.7%; 95% CI, 1.0–2.5; $P < 0.001$).

The RECORD 2 study compared the use of rivaroxaban for extended thromboprophylaxis with short-term thromboprophylaxis with enoxaparin. 2,509 patients scheduled to

undergo elective total hip arthroplasty were randomly assigned, stratified according to centre to receive oral rivaroxaban 10 mg once daily for a total of 31–39 days or enoxaparin 40 mg given subcutaneously once daily for 10–14 days (with a placebo tablet given for 31–39 days). Analyses were done using a modified intention-to-treat population. The primary outcome occurred in 2.0% patients in the rivaroxaban group, compared with 9.3% in the enoxaparin group (absolute risk reduction 7.3%; 95% CI 5.2–9.4; $P < 0.0001$). The incidence of any on-treatment bleeding was similar in both groups (6.6% events in the rivaroxaban safety population vs. 5.5% in the enoxaparin safety population; $P = 0.25$).

Finally, in RECORD 3 the efficacy and safety of rivaroxaban in preventing venous thrombosis after total knee arthroplasty was studied. In this randomized, double-blind trial, 2,531 patients who were to undergo total knee arthroplasty received either oral rivaroxaban, 10 mg once daily, beginning 6–8 h after surgery, or subcutaneous enoxaparin, 40 mg once daily, beginning 12 h before surgery. The primary efficacy outcome occurred in 9.6% of rivaroxaban-treated patients and 18.9% of enoxaparin-treated patients (absolute risk reduction, 9.2%; 95% confidence interval [CI], 5.9–12.4; $P < 0.001$). Major VTE occurred in 1.0% and 2.6% of patients, respectively (absolute risk reduction, 1.6%; 95% CI, 0.4–2.8; $P = 0.01$). Major bleeding occurred in 0.6% of patients in the rivaroxaban group and 0.5% of patients in the enoxaparin group ($P = NS$).

Bridging (perioperative) anticoagulation: risks and benefits

Patients taking VKA anticoagulant therapy may require interruption of treatment to undergo either surgery or an invasive procedure. During temporary discontinuations, the physician (and patient) must weigh the risks and benefits of administering "bridging" (short-acting) anticoagulants such as unfractionated heparin or low molecular weight heparin. Although there is a lack of evidence from randomized controlled trials that defines an optimal perioperative anticoagulation strategy, several prospective cohort studies suggest that, even for patients at high risk of thromboembolism (e.g. a recent pulmonary embolism or a prosthetic mechanical heart valve), peri-procedural LMWH is associated with a low rate of thromboembolic events. The major challenge for clinicians is an even greater paucity of information on the risk of thromboembolism without bridging therapy. Indeed two recently published studies suggest that, for many patients with atrial fibrillation, the risk of simple warfarin interruption may be quite low. The results of these observational studies especially

when considered cumulatively with cost, inconvenience and bleeding risk conferred by peri-operative anticoagulants, highlight the need for a randomized, controlled trial of bridging therapy. Such a trial-the Bridge study, funded by the United States National, Heart, Lung and Blood Institute—is ongoing.

Oral anticoagulation in valvular heart disease

Valvular heart disease is associated with a risk of thromboembolism and resulting morbidity and mortality. Warfarin and Phenprocoumon are available in Brazil, decreasing blood levels of vitamin K dependent coagulation factors by 50–75% and biological activity of new factors being synthesized by 20–30%. Patient education is a critical component of treatment, with emphasis on what to do if bleeding occurs, when to perform blood tests, target INR, drug-drug interactions, food-drug interactions and the impact of exercise on warfarin response.

Our approach to patients requiring warfarin is as follows: we begin with a dose of 5 mg and perform an INR measurement on the third and seventh day, adjusting the dose accordingly to achieve the chosen INR. In the setting of acute thrombotic disorders, heparin is maintained until the target INR is achieved. We prefer that our patients continue their regular diet, rather than changing to a diet restricted in vitamin K-containing foods. The optimal INR varies by indication, but typically ranges from 2.0 to 4.0, with values less than 2.0 being associated with thrombosis risk, and those >4.0 posing a risk for serious bleeding. Increased bleeding episodes occur most often within the first 90 days of treatment initiation among patients with uncontrolled hypertension, INR > 4.0, previous bleeding episodes, occult malignancies and in those with medication noncompliance and poor follow-up for coagulation monitoring. Anticoagulants should be avoided in patients unable to understand all aspects of treatment; have inadequate resources;or in whom the potential risk of bleeding outweighs the benefit of treatment.

New anticoagulants

A brief overview of anticoagulants and platelet-directed therapies under development, and their respective targets of inhibition is summarized in Figs. 5 and 6.

Anticoagulation in patients with malignancy

The association between thrombosis and cancer was established by the French physician Armand Trousseau in
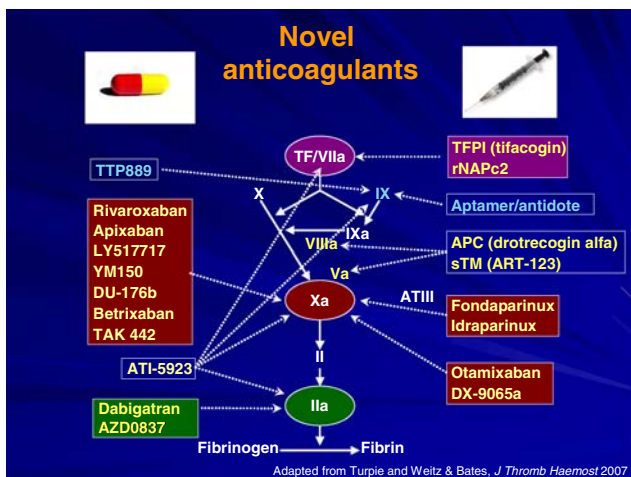
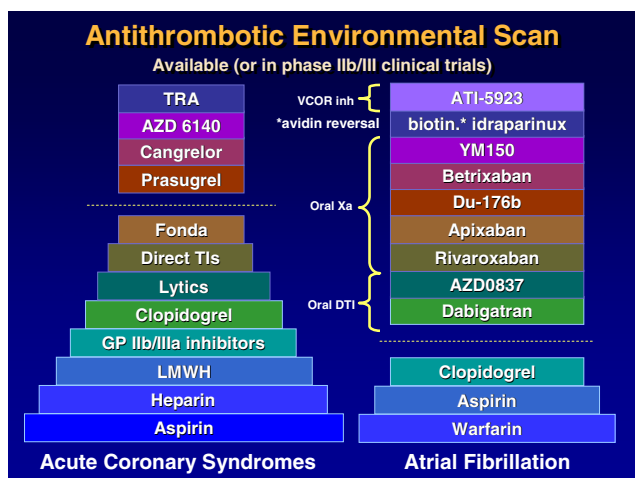Fig. 5 Novel anticoagulants and targets of inhibition

Fig. 6 Antithrombotic therapy for acute coronary syndrome and atrial fibrillation

1865, when he described thrombophlebitis or phlegmasia as a presenting sign of visceral malignancy. It is well established that tumor cells can secrete factors that initiate coagulation, including tissue factor and cancer procoagulant protein, which directly activates factor X. It has also been shown that "cryptic proteins" in the coagulation system, in the fibrinolytic system and secreted by platelets can affect angiogenesis, an essential process for tumor growth and metastasis.

VTE is a major complication of cancer and an important cause of morbidity and mortality. It has been estimated that VTE occurs in 4–20% of patients with cancer, and 14.3% of hospitalized cancer patients die as a direct result of pulmonary embolism (EP). Chemotherapy and hormonal treatment, particularly tamoxifen, increase the risk of VTE as does surgery.

Anticoagulant therapy is used in two classic conditions in cancer patients: for treatment of VTE episodes and as a prophylactic measure for hospitalized patients, particularly those who undergo surgery lasting more than 30 min. Although the American Society of Clinical Oncology does not recommend VTE prophylaxis for ambulatory cancer patients, several recent reports suggest that high-risk patients may in fact benefit from this approach.

Cancer patients frequently have long-term indwelling central venous catheters for administration of blood products, chemotherapy and parenteral nutrition. Catheter-related venous thrombosis is one of the most common complications, but routine antithrombotic prophylaxis is not recommended.

How to diagnose and treat heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a limb-and life-threatening immune-based disorder characterized by the formation of IgG antibodies against an antigenic complex consisting of heparin—a negatively-charged mucopolysaccharide and platelet factor 4 (PF4). Asymptomatic thrombocytopenia, defined as a platelet count either 50% or more below baseline or less than $150 \times 10^9/l$ develops in 30–50% of patients who develop heparin-PF4 antibodies, In turn, thrombosis involving the arterial, venous and less often microcirculatory system occurs in 30–50% of patients with thrombocytopenia. In most instances, antibody production requires 3–5 days of daily heparin exposure; however, antibodies can develop within hours of exposure, particularly in patients with recent heparin treatment or weeks later—a condition known as delayed HIT.

Clinical suspicion is the key to diagnosis, with confirmation subsequently provided by documentation of heparin-PF4 antibodies using either a functional, ELISA-based or platelet serotonin release-determined assay.

The management of HIT must begin with complete cessation of all heparin products, followed by infusion of a direct thrombin inhibitor—lepirudin, argatroban or bivalirudin (for patients undergoing percutaneous coronary intervention). A vitamin K antagonist should *not* be instituted until a direct thrombin inhibitor is started and the platelet count has increased to baseline or to a level above $150 \times 10^9/l$. The recommended duration of vitamin K antagonist treatment is, at a minimum, 6 weeks and longer if a thrombotic condition dictates.

Future directions: pharmacogenomics

The majority of common diseases arise from interactions between innate and acquired genetic alterations, exposure

to varying environmental factors and life style. Accordingly, they are referred to as complex diseases. Common diseases such as cancer, cardiovascular disease and diabetes are examples of complex diseases. Variations in DNA sequence and gene expression, influenced by environmental factors, determine individual differences in susceptibility or protection to common diseases, as well as in the response to therapy. The development of drugs tailored specifically to the patient's genetic profile or "signature", minimizing adverse effects and maximizing treatment response, constitutes the overarching theme of pharmacogenomics.

The hereditary basis of individual variability for disease susceptibility and drug response were, for a long time, studied within the classic genetic paradigm, i.e. investigating polymorphisms or mutations in a particular gene and the co-segregation of these genes and the phenotype of interest along several generations. The sequencing and mapping of the human genome expanded the possibilities for studying genetic variability: 3 million genomic sites where individuals can differ by only one DNA nucleotide were identified and these variations, called single nucleotide polymorphisms or SNPs, have subsequently been associated to risk for or protection from several diseases. Through SNP analysis it was shown that polymorphisms in the genes CYP2C9 e VKORC1, which have an essential role in warfarin's metabolism and pharmacological profile, determine a patients' response to this oral anticoagulant. Whether knowledge of a patient's genotype will allow clinicians to reduce the rate of adverse events such as bleeding remains to be established through carefully designed clinical trials.

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