Precision Monitoring of Antithrombotic Therapy in Cardiovascular Disease

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Abstract

Thrombosis, the process of blood clot formation in blood vessels, is an important protective mechanism for avoiding excessive blood spillage when an individual is exposed to trauma. The body has both a thrombosis inhibition and a thrombus removal system, which interact in a balanced manner. If these mechanisms become unbalanced, and too many clots form and block the lumen, thrombosis occurs. Thrombosis is currently the leading cause of death from disease in humans and is one of the most common events leading to many cardiovascular diseases. Antithrombotic drugs are an integral part of the pharmacological treatment regimens, and interventional strategies are currently recommended for thrombotic complications in patients with thrombosis. Despite major advances in these therapies, the high risk associated with thrombosis and bleeding remains, because of the complex interplay among patient comorbidities, drug combinations, multifaceted dose adjustments, and care settings. Detailed assessment of the effects of bleeding and thrombosis is necessary to establish optimal treatment plans for patients with thrombosis. This study retrospectively evaluated methods for assessing the risk of bleeding/ischemia in thrombosis and the individualized use of these methods.

Keywords: cardiovascular disease; antithrombotic therapy; individualized monitoring

Introduction

Thrombosis is a common condition that severely endangers human health [1]. This pathological condition occurs when a blood clot (embolus) forms and obstructs blood vessels, thereby impairing circulation. Thromboembolism, the detachment and movement of a thrombus within the bloodstream, may potentially cause vessel blockage and result in tissue hypoxia, necrosis, or edema. This collective process, termed thrombosis, is categorized into arterial or venous thrombosis, according to the affected vessel type [2, 3]. Arterial thrombosis can lead to life-threatening diseases, such as myocardial infarction and cerebral infarction, and venous thrombosis can lead to complications such as pulmonary embolism and deep vein thrombosis. Standard anticoagulant therapy for formed thrombi is an important tool to decrease morbidity and mortality [4]. However, because of interindividual differences in metabolic

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processes and pharmacodynamic responsiveness to anticoagulants, even with standard treatment in accordance with guidelines, some patients experience secondary complications, such as severe gastrointestinal bleeding or ischemic events. Therefore, precise individualized anticoagulation therapy is essential.

Anticoagulation effects can be monitored through the detection of indicators such as prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR) [5], and treatment plans can be adjusted to some extent. However, these indicators cannot adequately reflect interindividual differences in the status of the coagulation system. In recent years, new technologies such as thromboelastography have brought hope for individualized treatment; these methods can detect multiple dimensions, such as thrombin generation and platelet aggregation force, thus aiding in the assessment of individual coagulation function [6] and providing a basis for formulating precise anticoagulation treatment intensity. In addition, new tools such as genetic testing have shown promise [7] by enabling the identification of individual differences in patients’ prothrombin activity, platelet adhesion capability, and other relevant functions. Some studies have also sought to establish new scoring systems that include clinical factors to guide individualized medication.

However, truly accurate and individualized anticoagulation treatment protocols and guidelines remain lacking, because of the following reasons: the tests reflect only a portion of coagulation function, thus making the assessment incomplete; no operational scoring system incorporating clinical characteristics is available; and consideration of age, renal function, and other differences in the development of individualized monitoring and medication regimens is lacking. Therefore, new comprehensive and accurate testing technology must be developed and used in combination with clinical characteristics to establish personalized treatment and monitoring strategies as illustrated by Figure 1. Only in this way can anticoagulation therapy be transformed from traditional group monitoring to truly individualized monitoring, to benefit more patients with thrombosis.

In this article, we review dilemmas in the field of anticoagulation therapy for thromboembolic disease, existing progress in achieving treatment individualization, and the future outlook, to promote the development of this field, and the improvement of the effectiveness and safety of anticoagulation therapy.

**Classification, Epidemiology, and Status of Thrombosis Treatments**

According to the site of thrombus formation, thrombosis can be classified into two main categories: arterial thrombosis and venous thrombosis. Arterial thrombosis occurs primarily in the cardiovascular system, and common forms of arterial thrombosis include coronary artery thrombosis and cerebral artery thrombosis [8]. Arterial thrombosis directly blocks blood vessels and causes tissue necrosis, thereby leading to myocardial infarction, cerebral infarction, and other life-threatening diseases in severe cases [9]. Venous thrombosis, which occurs primarily in the deep veins of the lower limbs and leads to varicose veins and skin color changes, can also cause dangerous pulmonary embolism if the thrombus dislodges in the pulmonary artery [10]. According to epidemiological data, the morbidity and mortality of thrombotic diseases are high. More than 3 million venous thrombosis events occur per year in China, and more than 200,000 patients die from pulmonary embolism [11]. Arterial thrombosis
is also extremely common, and is one of the leading causes of stroke and myocardial infarction [12]. The incidence of thrombosis is also high in developed countries: each year, approximately 600,000 people in the United States experience venous thrombosis, and more than 100,000 die from pulmonary embolism [13]. Hence, thrombosis has become a major threat to human health, and in-depth research on the mechanism of thrombus formation must be strengthened, to develop effective methods for predicting thrombus formation, and design appropriate preventive measures.

Arterial thrombus formation is an extremely complex process that involves several key aspects, such as damage to vascular endothelial cells, platelet activation and aggregation, thrombin generation and activation, and coagulation protein synthesis and deposition [9]. When vascular endothelial cells are damaged by various factors, the tissue factor under the vascular endothelium is exposed and activates plasminogen, which in turn is converted into thrombin. Thrombin cleaves fibrinogen and catalyzes its polymerization, thereby producing fibrin, and promoting platelet adhesion and aggregation. Activated platelets also release large amounts of procoagulant substances, which further activate thromboplastin and accelerate thrombin production [14]. The large amount of generated thrombin can cleave more fibrinogen and activate procoagulant factors, such as coagulation factor V and coagulation factor VIII, which amplify the entire coagulation reaction and ultimately lead to large amounts of fibrin deposition, platelet aggregation, and thrombus formation [15]. Therefore, arterial thrombosis occurs through interactions among the coagulation system, platelets, and vascular endothelium.

The mechanism of venous thrombosis is similar to that of arterial thrombosis, and involves a hypercoagulable state of the blood, platelet activation, and endothelial damage. As the venous blood flow slows, blood tends to aggregate and activate the coagulation system. When the production of thrombin and fibrinogen increases, platelet aggregation is promoted, and a white thrombus is formed. Simultaneously, activated platelets release procoagulant substances that continue to activate thrombin production and promote red blood cell thrombus formation. The poor elasticity of the venous wall makes vascular endothelial cells susceptible to damage when blood flow is stagnant, and exacerbates the coagulation response [16]. In addition, coagulation products such as D-dimers directly stimulate endothelial cells and impair endothelial anticoagulation [17]. Therefore, venous thrombosis equally involves activation of the coagulation system, platelet aggregation, and vascular endothelial damage [18].

Current clinical guidelines recommend initiating antithrombotic therapy as soon as possible after the confirmation of thrombosis. Commonly used anticoagulant or antithrombotic drugs include low-molecular-weight heparin, warfarin, aspirin, and P2Y12 inhibitors. The main mechanism of action of anticoagulant drugs involves inhibition of the generation and activation of thrombin, and decreasing the amount of fibrin generated by thrombin cleavage of fibrinogen, to inhibit de novo thrombus formation and dissolve the existing thrombus [19]. The main mechanism of action of antiplatelet drugs involves inhibition of platelet aggregation, thereby preventing adenosine diphosphate–induced platelet aggregation and increasing cyclic adenosine monophosphate levels, and consequently inhibiting platelet activation and aggregation [20].

Numerous clinical studies have demonstrated that standard anticoagulation therapy significantly decreases patient mortality rates after thrombosis and the incidence of serious thrombosis-related complications, such as pulmonary embolism and cerebral infarction [21, 22]. Therefore, anticoagulation has become the standard of care for thrombotic disorders, and guidelines recommend initiating anticoagulation therapy immediately after the diagnosis of thrombosis. Although anticoagulation therapy is recommended by the guidelines, a small number of patients with thrombosis experience severe secondary bleeding or ischemic events [23–32]. These adverse outcomes may be associated with the following factors: interindividual differences in thrombin generation and platelet adhesion and aggregation, which prevent standard-dose anticoagulation from achieving effective anticoagulation; inability of some large thrombi to be completely dissolved, and risk of dislodging residual thrombi; and insufficient monitoring of coagulation recovery during anticoagulation therapy, thus precluding timely adjustment of the therapeutic regimen (Table 1).
<table>
<thead>
<tr>
<th>Study</th>
<th>Size</th>
<th>Follow up</th>
<th>Treatment</th>
<th>Primary endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARAMIS [23]</td>
<td>163,038</td>
<td>36 hours</td>
<td>NOAC</td>
<td>Intracranial hemorrhage</td>
<td>3.7% vs 3.2%; RR −0.51 (−1.36 to 0.34)</td>
</tr>
<tr>
<td>NCDR LAAO [24]</td>
<td>31,994</td>
<td>45 days and 6 months</td>
<td>Aspirin vs warfarin vs DOAC vs DAPT</td>
<td>Incidence of major adverse events, any stroke or transient ischemic attack, and readmission events</td>
<td>36.9% vs 20.8% vs 13.5% vs 12.3%; HR 0.692 (0.569–0.841)</td>
</tr>
<tr>
<td>ACTIV-4B [25]</td>
<td>657</td>
<td>45 days</td>
<td>Aspirin vs apixaban</td>
<td>All causes of death, symptomatic venous, arterial thromboembolism, stroke, or MI</td>
<td>2.0% vs 4.5%; RR 0.2 (−0.27 to 0.68)</td>
</tr>
<tr>
<td>INSPIRATION [26]</td>
<td>562</td>
<td>30 days</td>
<td>Intermediate-dose enoxaparin vs standard enoxaparin</td>
<td>Composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days</td>
<td>45.7% vs 44.1%; OR 1.0 (0.76–1.48)</td>
</tr>
<tr>
<td>Voyager PAD [27]</td>
<td>6564</td>
<td>3 years</td>
<td>Aspirin vs levofloxacin + aspirin</td>
<td>First occurrence of acute lower limb ischemia, vascular major amputation, MI, ischemic stroke, or cardiovascular death</td>
<td>HR 0.86 (0.75–0.98)</td>
</tr>
<tr>
<td>MARINER [28]</td>
<td>4909</td>
<td>45 days</td>
<td>Rivaroxaban vs placebo</td>
<td>Symptomatic VTE, non-hemorrhagic stroke, cardiovascular death, or MI</td>
<td>1.28% vs 1.77%; RR 0.8 (0.04–0.91)</td>
</tr>
<tr>
<td>TO-ACT [29]</td>
<td>67</td>
<td>1 year</td>
<td>Heparin</td>
<td>Ratio of mRS 0–1 points</td>
<td>RR 0.99 (0.71–1.38)</td>
</tr>
<tr>
<td>Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease [30]</td>
<td>7470</td>
<td>21 months</td>
<td>Oral rivaroxaban + aspirin</td>
<td>Cardiovascular death, MI, or stroke</td>
<td>5% vs 7%; HR 0.72 (0.57–0.90)</td>
</tr>
<tr>
<td>ISAR-TRIPLE [31]</td>
<td>614</td>
<td>9 months</td>
<td>6 weeks clopidogrel vs 6 months clopidogrel</td>
<td>Composite of death, MI, definite stent thrombosis, stroke, or TIMI major bleeding</td>
<td>9.8% vs 8.8%; HR 1.14 (0.68–1.91)</td>
</tr>
<tr>
<td>PLATO [32]</td>
<td>18,624</td>
<td>1 year</td>
<td>Ticagrelor + aspirin vs Clopidogrel + aspirin</td>
<td>Composite of vascular death, MI, or stroke</td>
<td>9.8% vs 11.7%; HR (0.77–0.92)</td>
</tr>
</tbody>
</table>

CV, cardiovascular; DAPT, dual antiplatelet therapy; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; OR, odds ratio; RR, relative risk; ST, stent thrombosis; TIMI, thrombolysis in myocardial infarction.
Mechanisms Underlying Bleeding/Ischemic Events

Genetic factors are important risk factors for thrombosis. Several inherited coagulation factor defects or anticoagulation factor defects, such as defects in anticoagulant proteins C and S, the presence of anticoagulant protein antibodies, and mutations at the factor V locus [33, 34], increase thrombosis risk. These genetic defects lead to dysfunction of the coagulation system and promote excessive coagulation.

Infections, another common thrombotic trigger, can cause inflammatory responses, cytokine release, activation of the coagulation system and platelets, and damage to the vascular endothelium. Severe infections can also cause dehydration and impaired venous reflux, and further increase thrombosis risk [27]. Moreover, certain pathogens directly affect the coagulation system and induce thrombosis [35]. Novel coronaviruses directly invade the vascular endothelium and activate platelets and coagulation factors, thereby leading to virus-associated thrombosis. In addition, viral infections can initiate the body’s immune-mediated coagulation response and even the development of antibodies against anticoagulant proteins, thus resulting in immune-associated thrombosis [36]. These findings provide new perspectives regarding the mechanism of viral infection–associated thrombosis. In recent years, new mechanisms through which viral infections regulate the balance of the coagulation system have received extensive research attention. In infections caused by novel coronaviruses, viral proteins activate platelets and endothelial cells, and lead to abnormal release of cytokines, which in turn activate thrombin generation [37]. In addition, novel coronaviruses can directly induce local thrombosis by destroying the endothelial cells of pulmonary microvessels [38]. Potential mechanisms underlying the occurrence of hemorrhagic events include excessive inhibition of the coagulation system by anticoagulant drugs, which disrupt the normal connection between the thrombus and the vessel wall, and consequently lead to dislodgement of the thrombus and hemorrhage. Ischemic events are associated with mechanisms such as dislodgement of residual thrombus and vessel embolization, as well as insufficient recovery of platelet function after discontinuation of anticoagulant drugs, thus leading to re-aggregation of emboli [39]. Therefore, monitoring the recovery of embolic lesions and coagulation function while performing anticoagulation therapy is important to guide the adjustment of anticoagulation therapy and decrease the risk of secondary adverse events.

For different types of thrombosis, individualized monitoring strategies are required, depending on the characteristics of the condition, to prevent secondary bleeding and ischemic events to the greatest extent possible. Moreover, for myocardial infarction or cerebral infarction caused by acute arterial thrombosis, given the rapid thrombus formation and the high risk of bleeding transformation, the intensity of anticoagulation must be monitored to avoid excessive anticoagulation, and prevent thrombus rupture and bleeding. Simultaneously, cardiac enzymes, electroencephalograms, and other indicators should be monitored, and timely adjustment of treatment plans is necessary if ischemia worsens. For deep vein thrombosis of the lower extremities, residual thrombus size changes and D-dimer levels should be monitored to determine the effects of thrombolysis, to avoid large residual thrombus dislodgement and subsequent pulmonary artery embolism. Simultaneously, recovery of coagulation function should be monitored, and the intensity of anticoagulation should be individualized accordingly.

For postoperative venous thrombosis, in addition to standard anticoagulation therapy, monitoring of the mobility of the affected limbs, promoting physical activity, and avoiding prolonged bed rest are necessary. For patients with underlying hypercoagulable states, long-term monitoring is needed to prevent new thrombus formation after anticoagulation is discontinued. Personalized monitoring of different types of thrombotic lesions can effectively predict and prevent secondary serious adverse events, and guide the adjustment of anticoagulant therapy, to ensure therapeutic efficacy.

Updated Approaches for Predicting Thrombosis/Bleeding-Related Events in Venous Thromboembolism

Definition of the Disease, Epidemiology, and Guideline-Recommended Treatment

Deep venous thrombosis is a venous return disorder characterized by the formation of abnormal blood
clots in the deep veins, typically in the lower extremities. Dislodgement of these thrombi can lead to pulmonary embolism (PE). Together, deep venous thrombosis and pulmonary embolism are referred to as venous thromboembolism (VTE) [40]. VTE manifests at a rate of 1–2 incidents per 1000 person-years, and has a higher prevalence in men than women. Notably, its incidence escalates to 1 event per 100 person-years in individuals over 55 years of age [41]. The prevalence of VTE is lower in Asia than in Europe and the United States. Alarmingly, approximately 20% of patients with VTE die within 1 year of diagnosis. Current guidelines advocate the use of novel anticoagulants, such as direct oral anticoagulants (DOACs), which inhibit thrombin generation and activation, thereby decreasing fibrin formation [42].

Subsequent Bleeding/Ischemic Events after Antithrombotic Therapy and Risk Stratification Tools for Patients with VTE

Olaf and colleagues have demonstrated that the incidence of pulmonary embolism can be significantly decreased, from 20% with no treatment to 3% with standard anticoagulation therapy. Hisada et al. [43] have reported post-anticoagulation complications, such as severe gastrointestinal bleeding, in 1.5% of patients. Despite standard anticoagulation treatment, a small proportion of patients experience secondary adverse events [44], such as ischemic incidents or gastrointestinal bleeding. Therefore, personalized risk assessment and tailored anticoagulation strategies are needed to minimize the likelihood of such adverse events.

The risk of adverse events after venous thrombosis is influenced by patient-specific risk factors, such as age over 70 years, hepatic and renal insufficiency, hypoproteinemia, and a history of acid-suppressing drug use. Older patients and those with renal insufficiency face a particularly elevated risk of gastrointestinal bleeding, because of diminished clearance of anticoagulants [45, 46]. Concurrent conditions such as ulcerative colitis further increase this risk. Therefore, anticoagulation therapy must be individualized according to a comprehensive risk assessment in high-risk patients, such as older people, or those with hepatic or renal insufficiency. Using decreased doses of anticoagulants and closely monitoring coagulation parameters are critical to avoid excessive anticoagulation and subsequent bleeding. For patients with lower bleeding risk, standard dosing can be applied, with continuous monitoring to balance the risk of ischemia and serious bleeding [47]. This approach ensures a more personalized, safer anticoagulation strategy.

Limitations of Existing Methods and the Dilemma of Detection

Traditional prothrombin time assays indicate thrombin generation, and the APTT evaluates both endogenous and exogenous thrombin activation. However, neither assay directly measures changes in fibrin levels. In contrast, iProspect technology directly quantifies fibrin D-dimer levels, thus enabling more dynamic assessment of fibrin production and lysis [48]. Accurately determining anticoagulation intensity and overall coagulation status requires more than a single index; instead, multiple test results must be integrated with the clinical picture. Current models, such as the Padua prediction in ACCP guidelines, use primarily prothrombin time and D-dimer, but fall short in incorporating crucial individual factors such as age and liver or renal function, which are essential for assessing bleeding risk [49].

Recommendations for normal values of existing monitoring indicators are too general, and significant differences exist among types and stages of venous thrombosis; however, refined and clearly defined guideline thresholds are lacking [33]. The current limitations in the clinical applicability of monitoring results are evident, particularly because most indicators detect primarily overt hemorrhage without predicting concealed chronic blood loss. Enhancing clinical utility requires establishing clearer and more stringent risk value intervals tailored to different disease types and stages. This approach would enable the conversion of monitoring results into clinically actionable recommendations for adjusting treatment protocols – a crucial step toward achieving personalized anticoagulation therapy. In patients with high-risk venous thrombosis with multiple comorbidities, such as heart failure or malignant tumors, the coagulation status is notably complex and variable. The evident dysfunction in the blood circulation and
coagulation systems significantly affects the efficacy and outcomes of anticoagulation therapy [50]. However, the current monitoring system does not consider these key influencing factors in developing targeted testing protocols and medication strategy recommendations. Therefore, the establishment of a new comprehensive assessment model and the development of novel testing indicators, to optimize individualized monitoring and treatment regimen selection for patients with such complex venous thrombosis, will be an important direction of development for increasing the precision of anticoagulation therapy.

Current monitoring models have notable limitations in facilitating individualized anticoagulation therapy, and often cannot support precise assessment and interpretation of the coagulation status and anticoagulation response in specific patient groups. A clear need exists for a more scientific and rational scoring system incorporating patients’ individual characteristics alongside existing testing indices. Moreover, therapeutic objectives and risk criteria tailored to different types of venous thrombosis and stages of disease progression must crucially be defined. This approach would enable the development of truly personalized anticoagulation treatment plans, thus enhancing the effectiveness and safety of medications for patients with venous thrombosis. Achieving this goal will necessitate close collaboration between clinicians and laboratory personnel, and fostering a patient-centered approach in the treatment of venous thrombosis.

Updated Approaches for Predicting Thrombosis/Bleeding-Related Events in Acute Coronary Syndrome and Chronic Coronary Syndrome

Definition of the Disease, Epidemiology, and Guideline-Recommended Treatment

Acute coronary syndrome (ACS) is a group of clinical syndromes in which myocardial ischemia and hypoxia are caused by decreased or interrupted coronary blood flow due to coronary thrombosis. Its main manifestations include acute angina pectoris, ST-segment changes, and elevated cardiac enzymes [51]. Chronic coronary syndrome (CCS) refers to chronic stenotic lesions of the coronary arteries that result in myocardial ischemia and hypoxia, which manifest as stable angina [52]. The incidence rates of ACS and CCS are high; notably, the incidence of CCS is two times higher than that of myocardial infarction, and CCS is projected to affect 18% of the adult population by the year 2030 [53]. Percutaneous coronary intervention (PCI) is recommended for ACS to restore perfusion; PCI or coronary artery bypass graft surgery is recommended for CCS, to increase blood flow according to the severity of the lesion; and antithrombotic therapy with antiplatelet and anticoagulant drugs is recommended to prevent de novo thrombosis [54].

Bleeding/Ischemic Events after Antithrombotic Therapy and Risk Stratification Tools for Patients with ACS and CCS

According to the expert consensus report published by the American Heart Association, approximately 5% of patients with ACS who have undergone dual antithrombotic therapy with anticoagulation and antiplatelets experience various degrees of hemorrhagic adverse events, including severe gastrointestinal bleeding and cerebral hemorrhage; moreover, approximately 2% of these patients experience new ischemic cardiovascular events, such as myocardial infarction extension and angina aggravation [55]. In contrast, patients with CCS who have received the same treatment have a 3% incidence of bleeding events and a 7% incidence of new ischemic events [55]. The difference in the incidence of secondary adverse events after treatment is associated with the pathophysiological characteristics of both ACS and CCS [56]. In addition to the traditional CRUSADE, Syntax, and GRACE scores [57], the PRECISE DAPT score and the PRAISE score are useful in the assessment of adverse clinical events after hemodialysis in patients with ACS [58]. The efficacy of anticoagulants can also be determined by measuring plasma concentrations of anticoagulant drugs; e.g., the efficacy of ticagrelor can be assessed by measuring the plasma concentration of its main active metabolite (AR-C124910XX) [59]. Traditional platelet function assays, such as
VerifyNow, light transmission aggregometry, multi-electrode platelet aggregometry (MEA), and vasodilator-stimulated phosphoprotein (VASP), have been used to assess adverse clinical events in patients with ACS [60]. Introduced in 2005, VerifyNow is a mass spectrometry-based system that measures platelet aggregation. A blood sample is mixed with a carrier containing a specific activator to stimulate platelet activation. The system evaluates the efficacy of antiplatelet drugs by monitoring changes in optical signals after platelet aggregation, thereby providing a precise method for assessing the effects of antiplatelet therapy [61]. This method is used in clinical applications to help assess patients’ responses to medications, guide treatment adjustments, prevent the risk of bleeding during surgery, and assess patients’ risk of thrombosis, thus providing rapid and accurate results. Although the VerifyNow assay has emerged as a novel test of platelet function assessing platelet aggregation capability, its relevance to ischemic events in patients with cardiovascular disease has not been validated in several clinical trials conducted in recent years [62–64]. First introduced in the early 1970s, light transmission aggregometry remains a frequently used method for assessing platelet function. On the basis of the Lorentz-Boltzmann law, optical turbidimetry is used to evaluate platelet function by measuring the extent of platelet aggregation in a solution. This method activates platelets and quantifies aggregation by measuring changes in light transmission through the sample before and after activation. Optical turbidimetry is widely used in various clinical domains and is instrumental in hematology, monitoring of anticoagulant therapy, and assessing cardiovascular diseases; it also plays a major role in drug development and clinical trials. This enduring method exemplifies the integration of classic principles with modern medical practices [65], and serves as an important tool for assessing platelet function, diagnosing blood clots and platelet dysfunction, and monitoring antiplatelet therapy. However, the requirement for large samples, poor reproducibility, and long assay times can lead to a decrease in platelet activity [64, 65]. VASP research began around 1994, and initially focused on its role in cell signaling, but VASP gained widespread attention in the early 2000s for its utility in monitoring platelet function. VASP assessment involves measuring its phosphorylation levels in activated platelets, which indicates platelet inhibition and is particularly valuable in evaluating the effects of antiplatelet drugs, such as P2Y12 antagonists. VASP has become a critical tool in clinical practice for assessing the efficacy of antiplatelet drugs and platelet function. This method aids in crafting personalized therapeutic strategies and in risk assessment for thrombosis-related disorders, thus advancing patient-specific medical care [66, 67]. The limitations of VASP, such as differences in technical standardization, complexity, and uncertainty in the interpretation of the results, have limited its widespread use as an indicator of platelet function [68, 69]. Developed between the late 2000s and 2010, MEA is a key method for assessing platelet function and the effects of antiplatelet therapy. MEA replicates the platelet aggregation process after vascular injury and uses multiple electrodes to monitor platelet aggregation dynamics simultaneously. This technique is crucial in evaluating the effectiveness of antiplatelet drugs, predicting surgical risk, diagnosing platelet dysfunction, and preventing cardiovascular and cerebrovascular diseases in clinical settings. MEA’s comprehensive approach enhances the understanding of platelet behavior; therefore, this method is integral to modern thrombosis-associated medical practice [70–72]. Thromboelastography (TEG), an advanced technology for dynamically monitoring coagulation function, simulates the in vivo clotting process and records changes in blood samples placed in a specially designed cup. TEG measures various parameters, including clotting time, thrombus formation rate, clot strength, stability, and thrombolysis rate. These parameters collectively offer insights into coagulation and fibrinolytic functions, and provide a more comprehensive assessment than traditional coagulation tests. The results are depicted graphically or in chart form, thus enhancing the interpretability and utility of the data in clinical settings. Therefore, TEG is a valuable tool in the detailed evaluation of hemostatic processes [73], and can be used to comprehensively and continuously assess the overall effects of anticoagulants and antiplatelet agents on the coagulation system, dynamically predict bleeding and ischemic risk, provide a basis for individualized drug adjustment, help physicians assess
patient coagulation status and function, and guide blood management during treatment or surgery [74]. In one clinical trial, triple antiplatelet therapy (clopidogrel + aspirin + cilostazol) for patients in the clopidogrel low-responder group, identified on the basis of TEG metrics, has been found to improve the clinical prognosis of high-risk patients undergoing elective PCI [75]. Overall, TEG can detect changes in coagulation function holistically and dynamically, and may predict the risk of complications of antithrombotic therapy; therefore, its application prospects are promising. Promoting the clinical application of TEG in patients with ACS and CCS may help achieve precision and individualization of antithrombotic therapy, minimize the occurrence of bleeding and ischemic events, and improve the efficacy of medication. In addition, new individualized assessment methods based on genetic and metabolomic technologies have broad application prospects. The above methods for assessing ischaemic imbalance are summarized in Figure 2. The detection of genes associated with the metabolism of antithrombotic drugs, such as CYP2C19 and VKORC1, can be used to identify drug metabolism function in patients and guide the selection of individualized drug regimens, and can also detect changes in vasoactive substances, such as NO and cGMP, and assess the effects of antithrombotic therapy on vascular endothelial function [76]. The use of metabolomic technology to detect changes in metabolite composition in patients can determine the effects of the target actions of anticoagulation and antiplatelet therapy, predict bleeding or ischemia risk, and provide a basis for treatment [77]. The application of these new technological tools may help achieve truly precise antithrombotic therapy based on the individual characteristics of patients with ACS and CCS, and has substantial clinical dissemination value.

For the same type of thrombosis, individual differences exist in the responsiveness to anticoagulant and antiplatelet drugs [78]. Patients who exhibit high platelet reactivity and anticoagulant resistance can be assessed with several specific tests to guide individualized dosing regimens. Detection of genotypes associated with drug metabolism, such as CYP2C19, can be applied to predict the effect of clopidogrel on antiplatelet aggregation [79]. Detection of polymorphisms of coagulation factor genes, such as F5, can be used to assess the anticoagulant responsiveness of warfarin [80]. In addition, the pharmacokinetics of antithrombotic drugs varies among individuals. Patients with, rather than without, single-nucleotide polymorphisms in the coding region of CYP3A4/5 have a 30%–40% lower ability to metabolize warfarin, and require adjustment of the anticoagulant dose [4]. In patients with combined hepatic and renal insufficiency, which directly affects metabolic processes and the excretion rates of anticoagulant and antiplatelet drugs, blood levels of plasma-drug concentration must be monitored and individualized to mitigate the risk of excessive accumulation, thereby preventing potential side effect such as bleeding disorders or toxicity [81]. Patient age is another factor influencing the sensitivity to antithrombotic drugs. Only 50% of patients older than 75 years achieve the desired INR value with standard doses of warfarin, as compared with 80% of younger patients [82]. Therefore, anticoagulation lower doses are necessary in older patients to avoid bleeding. In
addition, thrombin generation and platelet aggregation in pediatric and adolescent patients also differ significantly from those in adults, and require the establishment of a specific antithrombotic regimen [83]. Finally, female patients also have specific individual characteristics. In pregnant women and those who use hormonal contraceptives, the blood is in a hypercoagulable state, which may affect antithrombotic therapy [84]. Therefore, individualized antithrombotic medication and monitoring should be directed to different patients through assessment of their individual characteristics and clinical background information. Consequently, physicians must develop a specific treatment strategy for each patient to achieve truly individualized and precise medication. Various monitoring indicators for anticoagulant therapy in patients with ACS are compiled in Table 2.

### Limitations of Existing Methods and the Dilemma of Detection

Current coagulation function testing and antithrombotic therapy monitoring systems have several shortcomings. First, inconsistencies exist among testing methods, and the interpretation of the results must be comprehensive. Among platelet aggregation function tests, the VerifyNow test and VASP test reflect only the inhibition effect of the adenosine diphosphate pathway and P2Y12 receptor, whereas TEG can detect the alteration of platelet aggregation function in multiple pathways. The results of these assays are not completely consistent and must be interpreted comprehensively [86]. For each test indicator, the critical value should be set at different thresholds for different types of thrombotic diseases. However, the current risk intervals of the monitoring indicators have not been fully integrated with specific disease types, thereby decreasing the clinical operability of the monitoring results [87]. No specific guidelines have been established for patients with multiple risk factors and those undergoing complex surgical treatments. The changes in coagulation function in these patients are complex, and the use of standard monitoring protocols does not fully reflect the effectiveness of their antithrombotic therapy; however, no monitoring strategy has been developed specifically for this group of high-risk patients, thus further limiting the development of individualized therapy [88]. Monitoring protocols must also be optimized for older patients, patients with systemic disease comorbidities, and patients with other comorbidities, because of differences in drug metabolism. Owing to differences in the pharmacokinetic and pharmacodynamic processes in these patients, the monitoring protocol must be adjusted to guide individualized medication. However, the applicability of the existing monitoring indexes to this patient group must be further verified [89]. The DAPT score and the PRECISE-DAPT score rely excessively on clinical characteristics and do not sufficiently consider coagulation indexes; consequently, their value in guiding of individualized medication administration is limited. The DAPT score includes clinical factors such as age, smoking, and diabetes, and the PRECISE-DAPT score includes laboratory indexes such as hemoglobin and white blood cell count, but neither includes coagulation function indicators such as thrombin generation and platelet aggregation force in the assessment. Thus, these scores are not comprehensive or sufficiently accurate in reflecting patient coagulation status. The design of individualized monitoring protocols, including coagulation kinetics, platelet aggregation function, and drug

<table>
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<tr>
<th>Monitoring indicators</th>
<th>Normal range</th>
<th>Change direction</th>
<th>Clinical significance</th>
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</thead>
<tbody>
<tr>
<td>Prothrombin time (s) [83]</td>
<td>11–13</td>
<td>Extend</td>
<td>Indication of increased anticoagulation strength</td>
</tr>
<tr>
<td>APTT (s) [83]</td>
<td>25–40</td>
<td>Extend</td>
<td>Indication of inhibition of endogenous and exogenous thrombin production</td>
</tr>
<tr>
<td>Fibrinogen (g/L) [85]</td>
<td>2–4</td>
<td>Decrease</td>
<td>Indication of decreased fibrinogen formation</td>
</tr>
<tr>
<td>D-dimer (mg/L) [85]</td>
<td>&lt;0.5</td>
<td>Increase</td>
<td>Indication of old thrombolysis</td>
</tr>
<tr>
<td>Platelet count (10^9/L) [85]</td>
<td>100–300</td>
<td>Decrease</td>
<td>Indication of antiplatelet drugs to take effect</td>
</tr>
</tbody>
</table>
metabolism indexes of antithrombotic drugs, and the development of actionable monitoring values in different clinical scenarios, remains topics worthy of in-depth study. A combination of basic and clinical research will be required to establish a truly reliable and applicable new antithrombotic therapy monitoring system to achieve precise individualized medication and management, and comparison among various methods and evaluations.

In anticoagulation and antiplatelet therapy for thrombotic diseases, such as coronary artery disease, determining how to achieve accurate prediction of bleeding and ischemia risks based on individual patient characteristics and conditions is key to improving the safety and effectiveness of medication. First, tools such as genetic testing can be used to identify biological features such as high thrombin generation and platelet aggregation hyperfunction in some individuals; the findings can suggest poor antithrombotic drug sensitivity, and enable targeting of the dosages of anticoagulant or antiplatelet drugs. In addition, the establishment of new operable coagulation kinetic monitoring protocols, such as TEG testing, and the determination of critical values for TEG parameters at different disease stages, can enable dynamic assessment of patient coagulation and fibrinolytic function, and guide adjustment of the intensity of antithrombotic therapy. Second, individual patients’ clinical background, such as ACS and CCS disease types, surgical modalities, and comorbidities, should be fully integrated into the assessment of monitoring indicator findings and the optimization of the antithrombotic treatment protocols in various clinical scenarios. Large-sample clinical studies are also necessary to establish reliable bleeding and ischemia risk assessment models to guide the selection and use of antithrombotic drugs.

In summary, only by organically combining advanced testing technologies with extensive clinical experience, and developing personalized treatment and monitoring strategies for different patients, can the safety and efficacy of antithrombotic therapy be improved while maximizing the prevention of bleeding and ischemic events. Cooperation among all medical specialties will be necessary to achieve precise individualized medication.

Updated Approaches for Thrombosis/Bleeding-Related Events in Atrial Fibrillation

Definition of the Disease, Epidemiology, and Guideline-Recommended Treatment

Atrial fibrillation (AF) is a cardiac arrhythmia characterized by rapid irregular beating of the atria [90]. According to epidemiological studies, in 2019, approximately 59.7 million cases of AF (including atrial flutter) occurred worldwide, and the prevalence of AF in China was 2.3%. The prevalence and incidence of AF increase gradually with age, and are higher in men than women across all age groups. Most AF cases (80–90%) are nonvalvular AF (NVAF), which is also the most common form of AF in China. NVAF guidelines recommend medications, electrophysiological therapy, and DOACs to decrease the risk of stroke [85, 91].

Subsequent Bleeding/Ischemic Events after Antithrombotic Therapy and Risk Stratification Tools for Patients with AF

Clinical guidelines advise maintaining an INR between 2.0 and 3.0 for patients with AF who lack additional risk factors. Tailoring anticoagulation or antiplatelet therapy is crucial for these patients, given their stroke risk. Particularly for individuals with multiple stroke risk factors, such as heart failure, a history of hypertension, and age over 75 years, guidelines strongly advocate for the use of oral vitamin K antagonists. These anticoagulants, aimed at achieving an INR of 2.5 to 3.0 or higher, have potent anticoagulant properties and high efficacy in decreasing thrombosis risk. This targeted approach underscores the importance of individualized therapy in optimizing patient outcomes in AF management [91].

Among patients with AF with low stroke risk, antiplatelet drugs such as aspirin – which do not act directly on the coagulation system – may be considered, and their relatively low anticoagulant effects can decrease the risk of bleeding [92]. The CHA2DS2-VASc score is a guideline-recommended tool for assessing the risk of stroke in patients with AF. The score considers a range of
risk factors such as age, sex, hypertension, diabetes mellitus, heart failure, stroke/transient ischemic attack, and vascular disease. On the basis of the total score, patients can be classified into stroke risk groups, which indicate the need for anticoagulant therapy [93]. The CHA2DS2 score is similar to the CHA2DS2-VASc score and has also been shown to be useful for assessing the risk of stroke in patients with AF in clinical trials [94]. The HAS-BLED score is used to assess the risk of bleeding in patients with AF during anticoagulant therapy, and considers factors such as hypertension, abnormal liver function, stroke, history of bleeding, coagulation abnormalities, age, and drug or alcohol use. This score is used to determine whether patients are suitable for anticoagulant therapy and how best to manage the bleeding risk [95]. Routine tests such as cardiac ultrasound (echocardiography) can determine the presence of blood clots within the heart in patients with AF, to help assess the risk of stroke and guide anticoagulant therapy [96]. Blood tests, such as INR and PT, can test coagulation function, to assess the effectiveness of anticoagulant therapy and the risk of bleeding [97]. Continuous cardiac monitoring, such as Holter monitoring or event recording, can help identify changes in the heart rhythm in patients with AF and assess their risk of bleeding/ischemia [98].

Because of individual differences in drug metabolism rates and sensitivity, patients with NVAF have varying degrees of risk of thrombosis and gastrointestinal bleeding after treatment with DOACs [99]. Special attention should be paid to patients with AF with moderate-to-severe renal insufficiency. These patients are susceptible to drug accumulation due to diminished glomerular filtration rate, and excretion and clearance of anticoagulants, which may lead to severe gastrointestinal hemorrhage and other adverse effects. Thus, anticoagulation therapy in this group of patients is highly challenging, and individualized dosing and monitoring measures are necessary to decrease the risk of severe hemorrhage [100]. Many cohort studies have reported the incidence of gastrointestinal bleeding and ischemic stroke after anticoagulation in patients with NVAF. Lip et al. analyzed 17,633 patients with NVAF and showed that 4.9% developed gastrointestinal hemorrhage, and 1.8% developed ischemic stroke [99]. Pokorney et al. examined 1820 patients with AF combined with moderate-to-severe renal insufficiency and found that the risk of gastrointestinal hemorrhage during standard anticoagulation therapy was 1.7 times higher than that in patients without renal impairment [101].

The main indicators routinely used to monitor the effectiveness of anticoagulation therapy and the risk of bleeding in patients with NVAF include PT, APTT, and INR. These indicators can be used to assess the level of thrombosis and the efficacy of anticoagulation therapy. In addition to the CHA2DS2-VASc score and the HAS-BLED score, the R2CHADS2 score [102] adds renal impairment and an age range of 65–74 years to the CHA2DS2-VASc score. The scoring system categorizes patients with NVAF into four levels (low, moderate, high, and very high risk), thereby contributing to a more nuanced assessment of the stroke risk.

Assessing levels of thrombosis and the efficacy of anticoagulation therapy in patients with AF by monitoring coagulation pathology indexes such as PT, D-dimer, and APTT to guide the subsequent adjustment of anticoagulation intensity can be applied to predict the occurrence of adverse events such as ischemic stroke. However, in patients with renal impairment leading to anticoagulant accumulation, the changes in the routine coagulation indexes do not fully reflect the precise effects of anticoagulants and therefore cannot provide reliable personalized medication guidance for this high-risk group; this aspect is one limitation of the current monitoring system. For individuals with renal impairment, the interpretation of all coagulation indexes is difficult, and actionable recommendations that can be directly translated into medication and monitoring protocols are lacking. These issues constrain safe and effective personalized anticoagulation in this group of patients with complex AF with high stroke risk and renal impairment.

To achieve personalized and precise anticoagulation for patients with NVAF with renal impairment, while decreasing the risk of stroke and controlling the risk of gastrointestinal bleeding, the optimal range of anticoagulant concentrations must be defined on the basis of advanced testing techniques. Moreover, establishing personalized medication and monitoring protocols for these
patients through prospective cohort studies, and translating them into specific clinical protocols, will be important. The optimal range of anticoagulant concentrations for this group of patients can be clearly defined on the basis of advanced testing technology. Only by combining monitoring technology with the individual clinical characteristics of patients and formulating individualized therapeutic strategies can the efficacy and safety of anticoagulation be improved in patients with NV AF combined with renal insufficiency. Close collaboration among medical specialties will be necessary to continually optimize patient anticoagulation and monitoring.

**Updated Approaches for Bleeding/Ischemic Events in Valvular Disease**

**Definition, Prevalence, and Guideline-Recommended Treatment of Valvular Disease**

Valvular disease is a heart disease involving a structural or functional abnormality of the heart valves. According to the EURO II Survey results, the prevalence of valve disease is 2.5% in the overall population and increases significantly with age; in the population over 75 years of age, the incidence rate for all valves combined reaches nearly 14% [103]. The most common valve diseases are mitral valve closure insufficiency and aortic stenosis [104], and the treatment options include pharmacological management, surgical repair, or valve replacement.

**Subsequent Bleeding/Ischemic Events after Antithrombotic Therapy and Risk Stratification Tools for Patients with Valve Disease**

Patients undergoing heart valve replacement surgery require long-term oral anticoagulation therapy. Current clinical guidelines generally recommend that patients undergoing mechanical valve replacement surgery start taking vitamin K antagonist anticoagulants such as warfarin orally in the immediate postoperative period, to maintain a high anticoagulation intensity with an INR value of 2.5–3.5, and minimize the probability of perivalvular thrombosis to the greatest extent possible [105]. In contrast, a lower anticoagulation intensity regimen (INR 2.0–3.0) may be chosen for patients at low stroke risk with tissue or biologic valves [106]. Numerous cohort studies have reported the incidence of gastrointestinal bleeding and thrombotic events due to anticoagulation therapy after heart valve replacement.

Oral anticoagulants have shown excellent anticoagulant efficacy and a relatively favorable safety profile in clinical trials and practical clinical applications. However, serious bleeding events occur in approximately 2–3.5% of patients receiving oral anticoagulation each year [107]. These patients may be at risk of thrombosis if anticoagulation is discontinued. Sulman et al. have reported thromboembolic events in 16% of patients undergoing bioprosthetic valve implantation and coronary artery bypass grafting [107]. In patients with bioprosthetic valves, the risk of gastrointestinal bleeding due to overaccumulation of anticoagulants should not be ignored, and a dynamic balance between bleeding risk and thrombosis risk must be ensured through regular monitoring.

Currently, for the monitoring of anticoagulation therapy in patients after heart valve replacement, conventional indicators such as PT and INR are primarily used [108]. The cardiac renal hepatic (CRH) score, a new score combining multiple biomarkers of cardiac, renal, and hepatic function (NT-proBNP, creatinine, and albumin, respectively), based on data from the CHINA-VHD study, has been identified as the key predictor of mortality in patients with valvular heart disease [109]. Cardiac ultrasound, which indicates valve activity, ventricular function, chamber size, and possible complications, can be used to assess cardiac function and valve function after valve replacement. The overall pumping function of the heart can also be assessed by measuring cardiac function indexes such as the cardiac index and left ventricular ejection fraction [110].

Among mitral valve diseases, mitral valve closure insufficiency is the most common condition, and TMVR is a common interventional treatment for mitral valve closure insufficiency. However, complications such as thrombosis and hemorrhage persist in the postoperative period. The incidence
of stroke within 30 days of surgery ranges from 0.7% to 2.6%, and hemorrhagic complications occur in approximately 13% of cases [110]. Among aortic valve diseases, aortic stenosis is the most common. In a Danish study, ischemic stroke has been found in 8% of 873,373 patients [111]. Patients with mitral valve insufficiency and aortic stenosis often have a combination of bleeding risk factors, such as congestive heart failure, hypertension, advanced age, renal insufficiency, and diabetes mellitus. The ESC/EACTS 2017 and the ACC/American Heart Association 2020 guidelines do not provide a clear antithrombotic protocol, and current policies are largely dependent on clinician experience. Therefore, an urgent need exists for effective protocols to individualize patient treatment. In a study published by the JACC, a simple and practical risk score was developed through the COAPT research database, which consisted of four clinical variables (New York Heart Association functional class, chronic obstructive pulmonary disease, AF or atrial flutter, and chronic kidney disease) and four echocardiographic variables (left ventricular ejection fraction, left ventricular end-systolic internal diameter, right ventricular systolic pressure, and tricuspid regurgitation). The COAPT risk score is useful in predicting the risk of death or hospitalization for heart failure in patients with severe mitral regurgitation [112]. Elevated NT-proBNP has been associated with elevated mortality in patients with moderate aortic stenosis, but no studies have demonstrated whether early intervention affects prognosis. In a population of patients with moderate or severe aortic stenosis, high-sensitivity troponin I has been associated with increased left ventricular mass and fibrosis on CMR imaging, and with aortic valve replacement and death [112]. Echocardiography can be used to assess the extent of valvular disease in patients with mitral valve closure insufficiency or aortic stenosis, to assess prognosis [113].

Although interventional and antithrombotic therapy in patients with valvular disease can effectively improve prognosis, it cannot quantitatively guide individualized medication use, because of the lack of a clear definition of the optimal range of anticoagulant intensity or blood concentration targets for different populations. In addition, specifically formulated monitoring strategies and medication recommendations are lacking for high-risk groups, such as individuals with impaired liver and kidney function or older individuals. These issues limit the precision of anticoagulation in specific patients.

Long-term anticoagulation is essential for patients undergoing heart valve surgery but must be balanced against thrombosis and bleeding risk, to ensure the maximum efficacy and safety of the therapy. Therefore, advanced testing techniques and clinical experience must be combined to clearly define the optimal range of anticoagulant strengths for different patient groups, particularly those at high risk. Individualized treatment and monitoring plans must be developed to ensure that each patient attains maximum therapeutic benefit. To achieve this goal, all relevant areas of medicine must work closely together to provide precise and individualized anticoagulation for patients with heart valve disease.

Conclusion and Outlook

This review summarized current dilemmas in antithrombotic therapy, as well as strategies for individualizing antithrombotic therapy by comparing risk stratification tools for various thrombotic diseases.

The primary challenge in current antithrombotic therapy is balancing the risks of bleeding and ischemia. Individual variability and uncertain drug response hinder the ability to achieve consistent and balanced therapeutic effects. Recently, TEG has emerged as a promising solution offering insights into thrombin generation and platelet aggregation force. This method enables accurate assessment of anticoagulant intensity and paves the way to precision anticoagulation therapy. In the future, TEG, particularly when integrated with individual patient characteristics, is poised to become an essential tool in monitoring anticoagulation therapy.

In the future, with the development and in-depth application of high-throughput detection technology and information technology, antithrombotic therapy monitoring systems could lead to a shift from traditional group monitoring to truly
individualized monitoring. The high throughput and high precision of various testing technologies may provide the best and safest precise antithrombotic treatment plans tailored to different patients. Hence, all relevant medical specialties must unite in joint efforts to further improve the diagnosis and treatment of thromboembolic diseases, as well as the efficacy and safety of antithrombotic therapy.

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Conflict of interest
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REFERENCES


44. Hisada Y, Mackman N. Cancer-associated pathways and biomarkers
46. Timp JF, Braekkan SK, Versteeg HH, Kannegieter SC. Epidemiology of cancer-associated venous thrombo-
47. van der Steen W, van de Graaf Tan R, Daneshmand A, Parys Timp JF, Braekkan SK, Versteeg HH,
48. van der Steen W, van de Graaf Tan R, Daneshmand A, Parys Timp JF, Braekkan SK, Versteeg HH,
49. van der Steen W, van de Graaf Tan R, Daneshmand A, Parys Timp JF, Braekkan SK, Versteeg HH,
50. van der Steen W, van de Graaf Tan R, Daneshmand A, Parys Timp JF, Braekkan SK, Versteeg HH,
51. van der Steen W, van de Graaf Tan R, Daneshmand A, Parys Timp JF, Braekkan SK, Versteeg HH,
52. van der Steen W, van de Graaf Tan R, Daneshmand A, Parys Timp JF, Braekkan SK, Versteeg HH,
95. Lane DA, Lip GY. Use of the CHA(2)DS(2)-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. Circulation 2012;126(7):860–5.


