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Personalized healthcare in clotting disorders

Haifeng M Wu[†], LiHui Xu, Daniel D Sedmak, Clay B Marsh, and Mark W Wurster

Abstract

In terms of managing thrombotic disorders, genotype-based individualized patient care emerged as early as 1994 when the association of factor V Leiden (G1691A), and later, prothrombin (G20210A), with thrombotic phenotypes were discovered. Since then, genetic tests for specific thrombophilic SNPs have been routinely incorporated into daily practices in both thrombotic risk assessment and clinical decision-making with respect to prophylactic anti-thrombotic therapy. Recently, the area of pharmacogenomics in major anti-thrombotic drugs, such as warfarin and clopidogrel, has been the principal driver for personalized therapy based on one's own individual characteristics.

Keywords

anticoagulant; antiplatelet; clopidogrel; clotting; pharmacogenomics; SNP; warfarin

Individual variability in hemostasis & personalized medicine

Hemostasis is a complex system composed of many procoagulant and regulatory pathways. Multiple pathways, such as the intrinsic pathway, platelet activation and the tissue factor pathway, can affect coagulation status. Similarly, there are many systems that control the extent of thrombosis. Examples include anti-thrombin, the protein C/thrombomodulin pathway and fibrinolysis. Under physiological conditions, hemostasis is well balanced, enabling adequate maintenance for the integrity of the circulatory system and allowing the host to respond to different stimulations such as inflammation or tissue injury [1–2]. Failure of these regulatory pathways could result in either abnormal clot formation or excessive bleeding.

One striking feature in hemostasis is that the levels and activity of coagulant and anticoagulant factors are quite variable among individuals. For instance, reference ranges for most clotting factors vary from 50% to as high as 150% [3–4]. Similarly, major anticoagulant factor levels, such as those of anti-thrombin, protein C and protein S, also span broad ranges across the population. Variability is owing to both genetic variation and acquired factors, vitamin K intake, stress responses and pregnancy. In pathological conditions, combined genetic and environmental influences eventually disrupt hemostatic balances, putting individual patients at risk of either thrombosis or bleeding. When excess thrombosis occurs in the arterial system, patients can suffer from heart attack or stroke. When thrombosis occurs in the venous system, patients may develop deep-vein thrombosis or pulmonary embolism.

[†]Author for correspondence: Clinical Coagulation Laboratory, Departments of Pathology and Internal Medicine, Ohio State University College of Medicine, 164 Hamilton Hall, 1645 Neil Avenue, Columbus, OH 43210, USA, Tel.: +1 614 292 9335, Fax: +1 614 292 3144, haifeng.wu@osumc.edu.

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Over the last 20 years, much knowledge has been gained towards advancing the understanding of human genetics and elucidating the molecular basis of common diseases. A SNP is variation in one nucleotide at a specific location in the genome that, by definition, is found in more than 1% of the population. In fact, there are over 3 million SNPs in the human genome [5]. SNPs are important genetic markers that determine an individual's susceptibility to various diseases [6]. Recent studies have begun to reveal the contribution of genetic variation to individual hemostatic status and drug responses. For instance, medically significant SNPs have been described that predict patients' drug responses to drugs such as warfarin and clopidogrel [7–8]. Furthermore, there appear to be differences in hemostatic responses among different ethnic groups [9–12]. Thus, incorporation of genetic information into medical practice will enable further understanding of an individual's health status, predilection for thrombosis and the application of genetic information for optimizing anti-thrombotic therapy.

Personalized approach in diagnosis of thrombophilia

The field of thrombosis is at the forefront of personalized healthcare. Thrombophilia refers to hereditary conditions that predispose patients to the risk of thromboembolism [13]. As early as 1994, factor V Leiden (G1691A) was among the first SNPs to be linked to a disease phenotype. In a landmark study, factor V Leiden was reported as a hereditary thrombophilic factor for venous thrombosis [6]. In 1996, it was observed that a polymorphism (G20210A) in the 3' untranslated region of the prothrombin gene was also associated with venous thrombosis [14]. Since then, SNPs associated with thrombophilia have been utilized in routine care for patients with clotting disorders. Thus, thrombosis management represents one of the earliest examples of personalized medicine.

Thromboembolism is associated with significant morbidity and mortality. The most common predisposing clinical factors for clotting disorders include advanced age, immobilization, pregnancy, hormonal manipulation and cancer. In many cases, clotting disorders occur at a younger age or at an unusual site, without apparent contributing clinical factors. These cases of clotting events are often associated with underlying genetic predisposition(s). One type of genetic predisposition is due to rare DNA mutations that result in a deficiency of anticoagulant factors such as protein C, protein S or anti-thrombin [15–16]. In turn, insufficient endogenous anticoagulant function leads to a prothrombotic state. Because protein C, protein S and anti-thrombin deficiency may each involve as many as 100 different types of DNA aberrations, including point mutations, deletions or insertions, a genetic test for diagnosis is not feasible. For these types of uncommon genetic abnormalities, functional assays have been the standard practice for clinical diagnosis of anticoagulation factor deficiency.

The second type of hereditary influence is due to high-frequency SNPs in the general population. The most commonly indicated SNPs for the diagnosis of hereditary thrombophilia are factor V Leiden (G1691A) and prothrombin G20210A [17]. Initial studies suggested a role for the SNP methylenetetrahydrofolate reductase (*MTHFR* C677T) in contributing to both arterial and venous thrombosis [18–19]. However, more recent publications have raised uncertainty regarding its clinical utility [20–21]. The SNPs that predispose to thrombosis are found in more than a half of all cases of idiopathic thrombo-embolism. At the present time, genotyping these SNPs along with conducting functional studies for protein C, protein S and anti-thrombin is recommended for individuals at a high risk of clotting disorders [22]. The information on genetic risk factors for thrombosis enables clinicians to more accurately diagnose and manage patients [23].

The factor V Leiden mutation, which is the most common genetic risk factor of thrombosis known to date, is associated with the condition known as activated protein C (APC) resistance. The mutation in factor V Leiden results in a change of one amino acid from arginine to

glutamine at the cleavage site of APC. This, in turn, causes ineffective inactivation of factor Va, leading to a prothrombotic state. In fact, when APC is added to plasma from a patient with factor V Leiden, it cannot effectively remove factor Va. Therefore, the patient's plasma is resistant to APC-induced prolongation of clotting time, a phenomenon of APC resistance. Analyses of APC resistance and factor V Leiden have made their way into clinical medicine and are now routinely performed around the world. The SNP G20210A, present in the promoter region of the prothrombin gene, results in an increased plasma level of prothrombin that in turn may be an underlying mechanism for an increased risk of venous thrombosis [17]. The prevalence of this abnormality is approximately 2% in the general population, with approximately 3% of southern Europeans being affected; it is less commonly seen in Asian and African populations [24].

Under current medical practice, genetic testing for factor V Leiden (G1691A), prothrombin G20210A and *MTHFR* C677T has been routinely performed for patients at a higher risk of thrombotic disorders, along with functional assays for deficiencies in protein C, protein S and anti-thrombin. These include patients who present with unexplained or 'idiopathic' thromboembolism, patients with thromboembolism that is unusually extensive or in an unusual location (e.g., portal vein thrombosis) or patients with a striking family history of venous thromboembolism. When testing is positive, it is recommended that healthcare providers counsel patients regarding the enhanced risk of thrombosis for themselves and family members, the importance of early recognition of venous thromboembolism signs and symptoms, and the risks and benefits of thromboprophylaxis.

SNPs currently under study as genetic risk factors for thrombosis

Success in the identification of factor V Leiden and prothrombin mutation (G20210A) as genetic risk factors led to the exploration of other genetic factors that may contribute to thrombotic disorders. Bezemer *et al.* performed a large-scale population study involving more than 4000 study subjects. A total of 19,682 candidate SNPs were evaluated with respect to their association with deep vein thrombosis (DVT). The study confirmed contributory roles for factor V Leiden and prothrombin G20210A. In addition, the study revealed several new SNPs that are associated with DVT, including SNPs in the genes coding for CYP4V2, SERPINC1 and GP6. While the study revealed possible new genetic risk factors for DVT, the significance of their clinical impact requires further clarification [13,25].

In another population-based study involving more than 3000 subjects in each of the DVT or control groups (Leiden Thrombophilia Study and Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis [MEGA]) [26], investigators examined two SNPs (rs2289252 and rs2036914) in factor XI. They concluded that these two SNPs, which are associated with increased plasma factor XI levels, are independent risk factors for DVT [26]. In a follow-up study, Li *et al.* confirmed the association of factor XI SNPs (rs2289252 and rs2036914) with DVT [26].

Siegerink *et al.* demonstrated that the polymorphic SNP 455G/A in the β -chain of fibrinogen is associated with increased plasma fibrinogen levels. Interestingly, SNP 455G/A is an independent risk factor for stroke but not for myocardial infarction, suggesting a unique role of plasma fibrinogen in the prediction of specific vascular events [27].

Protein C is an important inhibitor of blood coagulation. There are two polymorphisms within the promoter region of the protein C gene (C/T at position 2405 and A/G at position 2418). Pomp *et al.* demonstrated that the CC/GG genotype is associated with lower levels of protein C and thus, carries an elevated risk of venous thrombosis compared with the TT/AA genotype [28].

Several studies support the role of inflammation in the development of thrombotic disorders. For instance, tissue-factor expression is upregulated by inflammatory cytokines such as IL-1, TNF- α and IL-6. In addition, IL-1 also enhances blood coagulation by downregulating the anticoagulant activity of thrombomodulin and the endothelial cell protein C receptor. Furthermore, IL-1 influences fibrinolysis by increasing the production of plasminogen activator inhibitor and decreasing the production of tissue-type plasminogen activator. These findings have led to the exploration of SNPs in the genes coding for IL-1 receptors, as they are potential genetic risk factors for venous thrombosis. A recent case-control study by van Minkelen *et al.* demonstrated that homozygous carriage of haplotype 5 in IL-1 receptor antagonist (IL-1RN) (H5, tagged by SNP 13888T/G, rs2232354) increases the risk of venous thrombosis [29].

Large-scale genotype-phenotype association studies have discovered many genotypes, other than factor V Leiden and prothrombin G20210A, that may contribute to thrombophilia. However, in general, these newly discovered SNPs are not strong predictors of the disease, with odds ratios of usually less than 2. This suggests that thrombotic disorders are multifactorial, perhaps involving many genetic traits and clinical factors that interact together, collectively causing a disease phenotype. Perhaps most genetic traits only marginally contribute to the disease phenotype. To date, the SNPs factor V Leiden and prothrombin G20210 carry the strongest predictive power. There may be another strong genotype(s) that is yet to be discovered, particularly in minority ethnic groups. Predictive medicine is likely to change the practice of medicine from being reactive to being proactive and has the potential to significantly decrease the incidence and prevalence of many diseases. This new paradigm is well demonstrated in the field of thrombosis, where genetic factors are routinely used for the surveillance, diagnosis and prophylaxis of clotting disorders.

Personalized strategy in anti-thrombotic therapy

Thrombotic disorders are divided into two groups based on the location of thrombus formation: arterial and venous thrombosis. Arterial thrombotic disorders differ from venous thrombosis disorders in a number of ways. First, the incidence of arterial thrombosis is much higher. Second, the pathological process of arterial thrombosis is complex and involves pre-existing atherosclerotic lesions, inflammatory processes and hemostatic abnormalities. By contrast, venous thrombosis is often associated with stasis and the formation of a large fibrin clot.

There are three classes of anti-thrombotic drugs used to treat patients with clotting disorders. These different types of medication are used for both arterial and venous thrombosis but target different pathways. Anticoagulant agents, such as warfarin, heparin or thrombin inhibitors, are frequently used to treat patients with venous thrombosis and are sometimes used for arterial thrombosis such as acute myocardial infarction (AMI) or stroke. Antiplatelet drugs are primarily used for patients with arterial thrombosis. Thrombolytic agents are mainly used for AMI, in particular within a few hours of an acute event in order to reduce the extent of ischemic myocardial injury secondary to the AMI. Variability in the clinical efficacy of anti-thrombotic therapy has been known about for many years; however, only recently have we begun to understand the genetic determinants that influence each individual's level of drug efficacy and drug safety.

Anticoagulant therapy

Warfarin and heparin have formed the mainstay in the prophylaxis of DVT, prevention of stroke in atrial fibrillation and treatment of thromboembolic disease. Other alternatives are becoming available such as antifactor Xa (anti-Xa) inhibitors and direct thrombin inhibitors. Warfarin is a unique anticoagulant since it exhibits a very narrow therapeutic window. Failure to achieve the target therapeutic range carries a high risk of serious adverse events. Patients

who are subtherapeutic are still at risk of thrombosis while patients who are overdosed are susceptible to bleeding events that are sometimes fatal. Thus, the clinical need for precision warfarin therapy has led to substantial progress in the area of warfarin pharmacogenomics.

Warfarin is an anticoagulant that disrupts vitamin K recycling. Vitamin K is an essential cofactor for the post-translational modification of several clotting factors including factors II, VII, IX and X, and the anticoagulant proteins C and S. Patients on therapeutic warfarin exhibit low clotting factor activity and therefore show less propensity for thrombotic disorders [30]. There are two major pathways that determine warfarin drug efficacy. First, warfarin inhibits the function of vitamin K epoxide reductase (VKORC1) that is responsible for the regeneration and recycling of vitamin K [31]. Suppression of VKORC1 results in decreased reutilization of endogenous vitamin K and a subsequent reduction of vitamin K-dependent clotting factors. It has been demonstrated that *VKORC1* variants exhibit different sensitivities to the drug. Patients who are found to have the sensitive genotype (*VKORC1* 3673G>A in the promoter region) may have a decreased amount of VKORC1, and therefore typically require a lower warfarin dose than average. Conversely, patients found to be resistant to warfarin are referred to as having the GG genotype and typically require a larger dose of the drug to achieve the desired therapeutic effect. Other patients could carry a heterozygous AG genotype. It was also demonstrated that a *VKORC1* polymorphism, SNP1639G>A, also influences warfarin dose requirement [11]. Importantly, the studies by Reider and Wang *et al.* provided functional data demonstrating that expression levels of VKORC1 are determined by *VKORC1* haplotypes [11,32]. The elimination of warfarin is almost entirely controlled by metabolism. The warfarin drug effect is primarily removed when it is converted to a hydroxylated metabolite by hepatic microsomal enzymes (cytochrome P450 [CYP]). The CYP2C9 isozyme appears to be the principal form of human liver P450, which controls the metabolism of the *S* isomer protein, a more potent isoform of drug warfarin. The variant alleles, particularly variant *CYP2C9**2 and *CYP2C9**3, result in decreased hydroxylation of warfarin, therefore reducing the rate of warfarin clearance [33–35].

It is known that interindividual variation in warfarin-dose requirements to achieve effective clinical anticoagulation can be as high as 20-fold [36,37]. Clinical studies so far have concluded that 30–50% of this variability is due to the SNPs found in *VKORC1* and *CYP2C9* [31,38–40]. However, there are no definitive data yet, based on prospective and randomized clinical trials, suggesting that DNA-guided warfarin therapy indeed provides improved clinical efficacy, fewer adverse events and better cost-effectiveness. Klein *et al.* evaluated the algorithms for estimating the appropriate warfarin dose based on both clinical and genetic data from 4043 study patients. They concluded that the warfarin dose algorithm based on genotypes and clinical variables produced significantly better dose estimates than a fixed-dose approach, and was better than a clinical algorithm alone [7]. The greatest benefit of the genotype-guided dose algorithm can be seen in the patients ultimately requiring 21 mg or less of warfarin per week and in those requiring 49 mg or more per week [7]. Several pilot prospective trials have also demonstrated the feasibility and promises of incorporating pharmacogenomics into the determination of appropriate doses for warfarin therapy [41–44]. Presently, the NIH has an ongoing multicenter trial named ‘A Randomized Trial of Genotype-Guided Dosing of Warfarin Therapy’ (GGDWT). Hopefully, this trial will ultimately clarify whether genotype-guided warfarin therapy will significantly improve the efficacy and safety profiles of long-term warfarin therapy.

Antiplatelet therapy

Antiplatelet therapies are most useful in clinical conditions caused by clot formation in arteries. Antiplatelet agents block platelet aggregation and plug formation at the site of the lesion. The most widely used and inexpensive agent is aspirin. Platelet ADP receptor antagonists such as

clopidogrel are popular, especially for patients with aspirin intolerance or who have failed aspirin therapy. In some clinical conditions, such as percutaneous coronary intervention (PCI), aspirin and clopidogrel have demonstrated a synergistic effect and are recommended as a combined therapy to provide better cardiovascular protection. More recently, a newer derivative of ADP receptor antagonist, prasugrel, has been evaluated in clinical trials. In comparison with clopidogrel, prasugrel appears to offer a better clinical efficacy in PCI with a more predictable pharmacological action, although a higher incidence of bleeding complications has been reported [45].

Aspirin has been used for centuries, first as an antipyretic/analgesic, and more recently as an antiplatelet agent [46,47]. The use of aspirin reduces fatal vascular events by approximately 15–20% and nonfatal vascular events by as much as 30% [48,49]. Aspirin primarily inhibits platelet cyclooxygenase (COX)-1, the enzyme that converts arachidonic acid into the potent platelet activator thromboxane A₂. Inhibition of COX-1 activity by aspirin suppresses platelet aggregation, thus preventing arterial thrombotic events. However, aspirin is known for its variety of pharmacological effects that suppress platelet function. Studies have demonstrated that more than 30% of patients on standard doses of aspirin do not achieve adequate pharmacological efficacy [50]. Insufficient suppression of platelet function in these resistant individuals is associated with an increased risk of cardiovascular events. Many investigators believe that the variability in platelet response to aspirin is, in part, genetically determined. Pharmacogenetic studies have been primarily focused on polymorphisms in several aspirin drug-target proteins, including the genes coding for COX-1 and platelet glycoprotein (GP) receptors such as GP-IIIa [51–53]. However, the mechanism underlying the action of aspirin is complex, possibly involving many different gene products. In addition, genetic variations exist in different races that influence aspirin responses [54]. Thus far, the studies on aspirin pharmacogenomics are not conclusive. A better understanding of the relationship between genotypes, acquired factors and clinical outcome is essential to personalize aspirin therapy in order to maximize anti-thrombotic benefit while minimizing the risk of bleeding for each individual patient. Clopidogrel is a thienopyridine derivative. Most of the clopidogrel is converted by esterases into inactive metabolites *in vivo*. A small percentage of clopidogrel is transformed into its active metabolite in a two-step process involving several CYP isozymes. Upon transformation, the active metabolite exerts its pharmacological effect by inhibiting the platelet P2Y₁₂ receptor that is normally activated by the platelet activator ADP [55]. However, clinically, approximately 25% of patients treated with standard loading and maintenance doses display poor responsiveness, characterized by the insufficient inhibition of platelet aggregation when assessed *in vitro* [8,56,57].

Many studies performed in the past decade have aimed to identify specific gene polymorphisms that are responsible for treatment failure of clopidogrel. Candidate polymorphic genes include CYP isoforms (*CYP2C9*, *CYP3A4* or *CYP3A5* and *CYP2C19*), *ABCB1*, *GP-Iba*, *GP-Ia/-IIa*, *GP-IIb/-IIIa* and *P2Y₁₂* [58–61]. One simple approach is to evaluate how each candidate genetic variant is associated with reduced inhibition of platelet activation *in vitro* during clopidogrel treatment. In this scenario, patients are treated with clopidogrel until the therapeutic level is achieved. Afterwards, blood is drawn to measure platelet function in response to ADP stimulation. When a patient's platelets exhibit more than the expected response to ADP stimulation in a platelet aggregation study, they are considered poor responders to clopidogrel treatment. Such a study is less time consuming and does not require a longitudinal patient cohort. However, the major limitation is the lack of direct evidence suggesting that measured on-treatment platelet activity truly represents the *in vivo* status of platelet function. Using this approach, Mega *et al.* recruited 162 healthy donors and treated them with clopidogrel. They demonstrated that a specific loss-of-function genotype (*CYP2C19*2*) was associated with reduced inhibition of platelet activity measured by platelet aggregation [62]. Although the study of platelet aggregation in response to ADP has been considered the gold standard method

for assessing platelet function, it is a labor-intensive and technically challenging test. Thus, the *in vitro* pharmacodynamic response to clopidogrel can be highly variable depending on the procedures and operators.

An ideal approach is to examine whether genotype is related to clinical outcomes of cardiovascular disease that are secondary to clopidogrel treatment in a longitudinal clinical cohort [58,63]. Such a study is expensive and time consuming, but with sufficient sample sizes, candidate genes in clopidogrel treatment failure can be defined. In a published study by Collet *et al.*, 259 young patients (aged < 45 years) who survived their first myocardial infarction were treated with clopidogrel and were followed longitudinally. The results showed that death, myocardial infarction and urgent coronary revascularization occurred during treatment with clopidogrel. After multivariable analysis, the *CYP2C19**2 genetic variant was demonstrated to be the independent predictor of cardiovascular events [64]. A recent report by Simon *et al.* used a much larger cohort [56] with 2208 patients being followed for 1 year post-AMI. The relationships between genotype variants and risk of death or recurrent cardiovascular events were evaluated. The results showed that those carrying any two *CYP2C19* loss-of-function alleles (*2, *3, *4 or *5) had a higher rate of developing subsequent cardiovascular events than those who did not. This effect was particularly striking among the patients undergoing PCI after AMI. Another study by Mega *et al.* treated 1477 acute coronary syndrome patients with clopidogrel and then determined the relationship between *CYP2C19* variants and the clinical outcomes of cardiac death. They concluded that among individuals treated with clopidogrel, carriers of a reduced-function *CYP2C19* allele had significantly higher rates of major adverse cardiovascular events, including stent thrombosis, than noncarriers. Sibbing *et al.* examined the effect of the *CYP2C19* 681G>A loss-of-function polymorphism on stent thrombosis in 2485 consecutive patients undergoing coronary stent placement following pretreatment with 600 mg of clopidogrel. The authors concluded that *CYP2C19**2 carrier status is significantly associated with an increased risk of stent thrombosis [65]. Giusti *et al.* studied 772 patients who were on dual antiplatelet treatment and were followed longitudinally after PCI. They demonstrated that the *CYP2C19**2 allele was associated with the occurrence of stent thrombosis and cardiac mortality in high-risk vascular patients [66].

Recent clinical trials have demonstrated that the pharmacodynamic response to prasugrel, a different thienopyridine derivative, is less variable in individual drug responses. Prasugrel is less affected by variability in *CYP2C19* iso-enzymes [67] and the individuals with a poor response to clopidogrel appear to respond well to prasugrel. Thus, the alternative anti-platelet therapy of prasugrel is available for those patients who are resistant to clopidogrel. There is now sufficient literature to enable the stratification of patients with respect to genotype profiles related to clopidogrel pharmacogenomics [68]. The next step is to demonstrate the clinical utility of genotype-guided anti-platelet therapy in a prospective cohort. Such a study will establish whether genotyping will ultimately improve drug efficacy, drug safety and select the correct type and optimal dose of therapeutic agents.

Platelets are major players in arterial thrombosis. Antiplatelet therapy has a clear clinical benefit in the treatment and prevention of cardiovascular events. Aspirin remains the primary antiplatelet therapy; however, it only reduces recurrence rate of ischemia by 25% and protects only a sixth of patients against cardiovascular-related death. Combination therapy of aspirin and clopidogrel has been increasingly used in the treatment of patients with cardiac events, but there is considerable variability in the inhibition of platelet reactivity. Prasugrel offers a promising alternative therapy in standard clinical practice. Despite many existing options for antiplatelet therapy, cardiovascular events remain an important cause of morbidity and mortality in a substantial proportion of patients under treatment. Newer drug candidates, such as protease-activated receptor antagonists [69,70], are currently being evaluated in clinical trials. With the choices of antiplatelet drugs increasing, one can foresee the importance of

personalized medicine whereby drug selection and therapy can be tailored to each individual patient based on their own characteristics.

Future perspective

Abnormal clotting is the number one killer of mankind as it causes heart attack, stroke and pulmonary embolism. The underlying mechanism of thrombosis involves multiple pathways and varies among individuals. Therefore, personalized healthcare is particularly pertinent for risk stratification, diagnosis and the treatment of clotting disorders. It is anticipated that, in the next 5–10 years, increasingly more anti-thrombotic drugs will become available for the prevention and treatment of clotting disorders. Physicians will have to make treatment decisions considering patients' clinical and genetic profiles as well as cost-effectiveness for the healthcare system. In addition, more genetic polymorphisms that significantly impact patient susceptibility to clotting disorders and patient responses to therapy will be discovered in the future. Thus, an effective incorporation of genetic information into daily practice will be vital in understanding an individual's health status, risks for thrombosis and selection of optimal anti-thrombotic therapy.

Executive summary

Individual variability in hemostasis & personalized medicine

- Blood clotting is characterized by complex pathways and individual variability.
- Incorporation of genetic information into the care of thrombotic disorders has shown promise.

Personalized approach in the diagnosis of thrombophilia

- Individualized healthcare in clotting disorders has been, and will continue to be, at the forefront in the movement of personalized medicine.
- Genetic tests for common risk factors of clotting disorders have been routinely implemented in clinical practice for a decade, providing a foundation for the application of personalized medicine.

SNPs currently under study as genetic risk factors for thrombosis

- Additional research will likely identify new genetic risk factors for clotting disorders, particularly for the minority ethnic groups.

Personalized strategy in anti-thrombotic therapy

- Major therapies for clotting disorders – warfarin and clopidogrel – are currently at the forefront of clinical studies for evaluation of personalized therapy.
- Blood clotting disorders account for major mortality and morbidity in the world. The pathobiology for clotting disorders varies individually depending on one's own genetic background and clinical risk factors. Likewise, the therapy for a clotting disorder may be best given when it is tailored to one's individual characteristics. With increasing drug options for anti-thrombotic treatment that target different disease pathways, individualized therapy will likely offer the best clinical outcome with optimal therapeutic efficacy and minimal drug complications.

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