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Phenotyping Bleeding

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Abstract

Purpose of review—Although recorded evidence of phenotyping bleeding disorders extends back two millennia, standardization of phenotyping has only begun in the past half century. This was spurred by the need for greater precision in diagnosing disorders in order to select proper laboratory tests and treatment, and the realization that the bleeding history provides prognostic information about the future risk of bleeding with surgery or invasive procedures.

Recent findings—New bleeding assessment tools (BATs) have been developed to: 1. evaluate the relative bleeding risks associated with new anticoagulants and antiplatelet agents, 2. assess the efficacy of new thrombopoiesis stimulating agents in preventing hemorrhage in patients with immune thrombocytopenia, and 3. assess complex gene-gene and gene-environment interactions. New web-based systems allow many researchers to collaborate by sharing the same electronic phenotyping infrastructure. Major issues of validation remain, but at present, the data indicate that the new BATs have relatively high negative predictive value for excluding a significant bleeding disorder, but disappointingly low positive predictive values.

Summary—New instruments to phenotype bleeding have been developed to address a number of different important clinical and research goals. The improved standardization and opportunities for collaborative studies hold promise for maximizing diagnostic, prognostic, and scientific information.

Keywords

bleeding; phenotyping; von Willebrand disease; immune thrombocytopenia; percutaneous coronary intervention

Introduction

Written records of phenotyping bleeding extend back to the Talmudic era (200 BCE – 200 CE) when rabbis recognized that fatal bleeding following circumcision could be inherited, and thus decided that newborn males in such families should not be circumcised. (1) The 10th century Islamic surgeon Albucasis described a hemophilic-like bleeding disorder and its treatment in his major work, al-Tasrif, (2) and by the 12th century, the Hebrew physician Moses Maimonides recognized that familial bleeding tendencies were transmitted through the mother.[1] Individual cases and kindreds with the disorder ultimately termed hemophilia were reported in the medical literature starting with an anonymous report in 1793,(3) followed a decade later by Otto's landmark description in 1803.(4) Spurred by the birth of

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Conflicts of Interest
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modern genetics and the British Eugenics Movement, in 1911 Bullock and Fildes, under the auspices of the Galton Laboratory, methodically compiled all of the known hemophilia pedigrees to that time and fastidiously detailed each patient's symptoms. (3)

With the beginning of modern hematology and the introduction of effective therapy for blood clotting disorders in the second half of the 20th century, the concept of the "bleeding history" emerged to aid in the diagnosis of the disorders, along with an appreciation that considerable subtlety is required to differentiate symptoms that are most likely to indicate the presence of a bleeding disorder from those experienced by the healthy population. (5) This realization led to a series of early attempts to develop standardized methods for obtaining a bleeding history,(5) but none of these became widely accepted. Equally important to the practicing hematologist was the ability to predict the likelihood of bleeding with surgery, especially after the introduction of cardiac bypass surgery, since it poses a major hemostatic challenge. The recognition that the bleeding history probably provides as much or more information about the risk of bleeding as any single or combination of laboratory tests added additional importance to the bleeding history. (6;7) Subsequently, modified versions of bleeding questionnaires were developed to serve a variety of functions in response to new, specific medical needs, including: 1. The ability to predict the likelihood of bleeding when patients are treated chronically with warfarin and other vitamin K antagonists; 2. The ability to compare the relative hemostatic risks associated with different anticoagulant and anti-platelet regimens used in conjunction with percutaneous coronary artery interventions, including angioplasty and stent placement; 3. The ability to assess the severity of bleeding in patients with immune thrombocytopenia and the clinical efficacy of drugs designed to stimulate thrombopoiesis in preventing hemorrhagic symptoms in these patients; and 4. The ability to assess the relationship among genotype, phenotype, and environmental influences (Table 1). This review focuses on recent advances in each of these areas.

Diagnosis of an Inherited Bleeding Disorder and the Prediction of Future Bleeding

A personal history of excessive mucocutaneous bleeding is a key component in the diagnosis of a number of bleeding disorders, including von Willebrand disease (VWD), platelet function disorders (PFD), and coagulation factor deficiencies. However, the evaluation of hemorrhagic symptoms in patients with mild bleeding disorders is a well-recognized challenge for both patients and physicians because the reporting of bleeding symptoms is subjective and significant symptoms may be overlooked because they are considered normal. Further complicating the challenge, minimal or trivial symptoms may be given undue consideration, as exemplified by the high frequency of bleeding symptoms reported by the general population. (5;22) In response to these challenges, a number of attempts have been made to standardize bleeding histories in an effort to improve diagnostic accuracy and thus avoid unwarranted laboratory testing.

A set of provisional criteria for the diagnosis of VWD type 1 have been established by the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) on von Willebrand factor (VWF), including the threshold that must be met for mucocutaneous bleeding symptoms to be considered significant. (23) Building on these threshold criteria, more recent efforts have attempted to standardize quantitative assessments of bleeding. A group of Italian investigators led by Rodeghiero pioneered this work by developing and validating a Bleeding Assessment Tool (BAT) for the diagnosis of Type 1 VWD in a primarily adult population. (8) It has also been studied in obligate carriers of Type 3 VWD and patients with type 2B VWD.(9;24) Since this landmark publication, several adaptations have been developed and tested in both primary and tertiary care settings

for VWD as well as PFD and other inherited hemorrhagic disorders. (10;11;25–28) In general, the conclusions from all of these studies are similar: the sensitivity and positive predictive value of the questionnaires vary depending on the setting and patient population enrolled, but the negative predictive value of all versions in all settings is very high, meaning that a negative bleeding score nearly excludes a clinically significant inherited bleeding disorder. Additionally, the ability to predict the risk of future bleeding holds great value for the clinician. A number of studies have addressed this using BATs and in general, the higher the bleeding score the greater the risk of future bleeding. (9;24) Specifically, the mucocutaneous section of the MCMDM1-VWD Bleeding Questionnaire has been shown to predict the risk of future bleeding for both dental extractions and surgical procedures. (9)

In addition to the BATs derived from the Italian group's work, a number of other tools have been developed and published, including a comprehensive web-based system developed at Rockefeller University,(13;20**) tools designed exclusively for the assessment of menorrhagia, (29–31) and a questionnaire specific for the Quebec Platelet Disorder. (32) In order to consolidate the knowledge learned from these published studies, and to develop a consensus bleeding assessment tool, a Working Party sponsored by the VWF and Perinatal/ Pediatric Hemostasis Subcommittees of the International Society on Thrombosis and Haemostasis/Scientific Standardization Committee (ISTH/SSC) was established in 2008. This group, with input from the Women's Health Issues in Thrombosis and Haemostasis SSC, published the ISTH-BAT in 2010(12**) and studies to validate this new tool are ongoing. The ISTH-BAT was specifically designed to extend the utility of the earlier BATS, which were focused on mild bleeding disorders, to include severe bleeding disorders by incorporating information on both symptom frequency and severity. The ISTH-BAT has been mapped to a bleeding history ontology (20;33) (see Correlation Among Genotype, Phenotype, and Environment below) and is freely available to all investigators through a web-based system. (34)

Assessing Treatment Efficacy in Immune Thrombocytopenia

The diagnosis of immune thrombocytopenia (ITP) is based on the clinical presentation of the patient (ecchymoses, petechiae, and/or mucocutaneous bleeding ranging from mild to severe) and isolated thrombocytopenia without an obvious underlying cause. The quantification of bleeding in patients with ITP, however, is more difficult, and this measurement is particularly important in assessing the efficacy of new treatments. A number of tools to quantify bleeding in chronic ITP have been developed (14–16*), but there is no currently available accepted standard. Many clinical trials have relied on longitudinal measurements of platelet counts as the clinical endpoint as opposed to patient symptoms, which can vary between individuals with the same platelet count. (35–40) In January 2012, the performance of the WHO Bleeding Scale was evaluated in two large clinical trials of eltrombopag, a thrombopoietin receptor agonist. (41**) The WHO Bleeding Scale rates bleeding severity on a five-point scale (0=no bleeding, 4=debilitating blood loss), and although originally developed to assess patients undergoing cancer treatment,(17) it has been applied in other situations to assess thrombocytopenic bleeding. (42–45) Although the conclusion was that WHO Bleeding Scale was potentially useful in ITP patients, there were limitations making widespread adoption of this tool difficult. To address the need for a standardized BAT for assessing bleeding associated with ITP, an ISTH Working Group has been established to develop one and then validate it.

Bleeding Associated with Percutaneous Coronary Interventions

Bleeding associated with percutaneous coronary interventions (PCI) can have important clinical consequences, including increasing the risk of thrombotic events in response to the

cessation of antiplatelet and/or anticoagulant therapy. Factors that can contribute to the risk of bleeding include the anticoagulant(s) and antiplatelet agent(s) employed and the access route, with the radial route associated with much less access site bleeding than the femoral route. (46) Thus, a quantitative assessment of bleeding associated with PCI is an important factor in assessing new therapeutic agents.

The Bleeding Academic Research Consortium (BARC), composed of representatives from academic research organizations, the FDA, the National institutes of Health, pharmaceutical and cardiovascular device manufacturers, and independent physician thought leaders in cardiovascular medicine, published a report in which they reviewed the different definitions that have been used to assess bleeding in association with cardiovascular interventions. (18**)They emphasized the clinical significance of hemorrhage on clinical outcomes, the heterogeneity of bleeding definitions across trials, and the challenges of creating a universal bleeding definition, including the definition of bleeding associated with coronary artery bypass graft surgery. They proposed a new definition broken down into 5 types, with several subtypes, based on objective criteria. A subsequent retrospective patient level pooled analysis of 12,459 patients from 6 randomized trials indicated that 9.9% of patients had excessive bleeding according to BARC criteria and that there was an increase in one-year mortality in patients with BARC Class ≥2 or Class ≥3 bleeding. (47) Other bleeding grading systems also correlated with one-year mortality, however, and so it is not clear that the BARC scale improves clinical prediction.

Several groups have merged both efficacy data (that is, protection from ischemic complications) and safety data (that is, hemorrhage) into a “net” clinical benefit assessment, but equating bleeding and thrombotic events is problematic. Moreover, since bleeding is known to have an impact on efficacy, combining the data may double count the impact of bleeding. Finally, the use of a radial artery approach vs. a femoral artery approach consistently reduces the risk of access site bleeding.

Bleeding Associated with Chronic Oral Anticoagulation

The pioneering studies by Landefeld and his colleagues in the 1980s to systematically identify risk factors for hemorrhage associated with oral anticoagulant use opened a new era in risk assessment of hemorrhage. (48) Since then many studies have been performed to identify predictors of hemorrhage associated with these agents, one of the most common adverse drug effects. (49–51) Recently, Loewen and Dahri (19) analyzed the predictive performance of the mOBRI, “RIETE,” and HAS-BLED clinical prediction rules (CPRs) for major bleeding (using the International Society on Thrombosis and Haemostasis definition) associated with warfarin or ximelagatran therapy in four published studies. They used likelihood ratios (LR) rather than the *c* statistic because they judged the LR the most directly applicable measure of diagnostic test performance. Individual trial and pooled analysis showed that the mOBRI and HAS-BLED CPRs had weak predictive accuracy at all levels of risk. A low RIETE score was moderately predictive for the absence of bleeding, but higher scores lacked clinically meaningful predictive value. They concluded that prospective validation and evidence that a CPR improves patient outcomes is required before any of the CPRs could be recommended for routine use in clinical practice.

Chen et al. studied the association between $CHADS_2$ risk factors (chronic heart failure, hypertension, advanced age, diabetes, and prior stroke/transient ischemic attack) and the risk of bleeding in patients on warfarin. (52) Based on data from 41 separate studies they concluded that none of the $CHADS_2$ covariates had a high strength of evidence for association with any bleeding type. Advanced age was the only covariate with moderate strength of evidence. In contrast, Oldgren et al. analyzed the rate of major bleeding and

intracranial bleeding in 18,112 patients with atrial fibrillation treated with warfarin or dabigatran in the RE-LY trial and found both to be associated with the composite $CHADS_2$ score, going from 2.26% to 4.42% for major bleeding with $CHADS_2$ scores of 0 vs. 3–6 and from 0.31% to 0.61% for intracranial bleeding, respectively. (53)

Bleeding Associated with Cardiac Surgery

A team of clinicians and operational researchers with experience in clinical risk models reviewed 11,592 consecutive records at Papworth Hospital, split into 6,906 used to form a prediction model and 4,686 to assess the performance of the model. (21*) They identified 5 factors as correlating best with the risk of post-operative hemorrhage: emergency or urgent surgery priority; surgery other than coronary artery bypass or single valve surgery; aortic regurgitation, stenosis, or both; body mass index <25; and age greater than 75 years. It was unclear whether data on the patient's bleeding history were included in the analysis. Further adjustments were made for use of aprotinin and tranexamic acid. Under all conditions the model correlated well with the outcome data, with the low risk group having less than 5% risk of excessive blood loss compared to ~20% or more in the high risk group. Thus, while the score had a high negative predictive value, its positive predictive value was relatively low.

Correlation Among Genotype, Phenotype, and Environment

To obtain the maximum scientific and clinical benefit from the new genomic and related data requires that their correlation with high quality and high granularity clinical phenotypes go beyond the data usually collected for medical care. This is especially important for identifying subtle and/or complex gene-gene and gene-environment interactions. For example, if just 3 genes interact to affect a phenotype in a binary fashion, then one would expect as many as 8 separate clinical phenotypes. To identify these different phenotypes requires detailed standardized descriptions of bleeding manifestations from large numbers of patients and healthy controls. Registries of patients with inherited disorders of bleeding supported by the International Society on Thrombosis and Haemostasis have variably included data on patient bleeding phenotypes,(54) but the data are limited because they were not collected in a standardized manner and reporting is incomplete. To address the need for improved standardization, Mauer et al. developed a formal bleeding history ontology to comprehensively define all bleeding history symptoms and the relationship among the different signs, symptoms, and treatments. (20;34) They then developed a freely available web-based comprehensive questionnaire to standardize the collection of phenotypic, genotypic, and laboratory data, with the goal of encouraging investigators from all over the world to enter their de-identified patient data into an ever-growing database. They also published the results of their first use of the system in 500 healthy adults across broad racial and ethnic groups. (13**)

Conclusions

The ability to characterize, classify, and predict bleeding is of great value in many different clinical settings, including the diagnosis and assessment of patients with inherited or acquired bleeding disorders and for understanding the risk of treating patients with anticoagulants and/or antiplatelet agents. Different tools have been developed for these purposes and their performance has been variably validated. One common theme that emerges, however, is that while the ability to predict who will bleed remains at a disappointing low level, a number of tools are able to predict which individuals are unlikely to bleed with considerable precision.

One conundrum that has important semantic, nosological, research, and clinical implications is whether to require a history of excessive bleeding in order to diagnose a hemorrhagic disorder. (22;55) For example, there are benefits in requiring evidence of excessive bleeding as a diagnostic criterion for VWD from a clinical standpoint, namely that it focuses attention on those patients most likely to have clinically meaningful bleeding and avoids the potential stigma associated with carrying the diagnosis of a bleeding disorder. (55) From a research standpoint, however, this requirement may act as an impediment to identifying important gene-gene and gene-environment interactions. For example, a patient may have a genetic mutation leading to an abnormality of VWF, but may simultaneously have a compensating genetic abnormality, such as Factor V Leiden, that ameliorates or even completely compensates for what would otherwise produce an increased risk of hemorrhage. Similarly, since many individuals with modest reductions in VWF activity do not have hemorrhage symptoms, those who do may harbor one or more genetic or environmental factors that predispose them to hemorrhage. Identifying such individuals is crucial for understanding better such gene-gene interactions and, in fact, may also have clinical significance since, for example, in the former case a person's offspring may inherit the VWF mutation but not the Factor V Leiden mutation. Therefore, we support efforts to develop a consensus about disease nomenclature that achieves the clinical goals without risking the loss of potentially important scientific information. (55)

A critical consideration for both diagnostic and predictive purposes is whether the individual has previously been exposed to a hemostatic challenge that is likely to make a bleeding disorder manifest. Since it is reasonable to expect that one's ability to predict the risk of future bleeding will be more accurate when the individual has had a previous hemostatic challenge, it may be necessary to stratify patients accordingly and to judge the value of a BAT for each stratum separately. Similarly, the optimal questions to predict the risk of bleeding may differ according to the type of surgery or intervention and/or the organ involved. To achieve these levels of refinement, however, will likely require the development and implementation of bioinformatics strategies to aggregate and analyze both newly obtained and legacy data from many investigators.

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KEY POINTS

- Although phenotyping bleeding disorders started about 2 millennia ago, standardization of instruments to collect the data is a relatively recent phenomenon, spurred by the need for greater precision in diagnosis and the desire to extract prognostic and drug safety and efficacy information.
- Validation of phenotyping instruments remains an ongoing challenge with few instruments unequivocally connected to medically meaningful outcomes.
- In general, phenotyping instruments are more valuable in excluding the likelihood of a significant bleeding disorder than in predicting the occurrence of a future bleeding event.

Table 1

Alignment of Bleeding Assessment Instruments and Their Major Goal(s)

Instruments	Goals
• **Vicenza Bleeding Questionnaire and Modifications** (8–11) • **ISTH/SSC Bleeding Assessment Tool** (12) • **Rockefeller Bleeding History Questionnaire** (13)	To Diagnose Inherited or Acquired Bleeding Disorders and to Predict the Risk of Future Bleeding
• **Buchanan Grading System** (14) • **UK Clinical Severity Classification System** (15) • **ITP Bleeding Scale** (16) • **WHO Bleeding Scale** (17) • **ISTH ITP Working Group Bleeding Assessment Tool (publication in preparation)**	To Assess Bleeding Associated with Immune Thrombocytopenia and Thrombopoietic Stimulating Agents in Preventing Bleeding
• **Thrombolysis In Myocardial Infarction (TIMI) criteria** • **Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) scale** • **Bleeding Academic Research Consortium (BARC)** • **CURE criteria** • **ACUITY, HORIZONS criteria** • **CURRENT-OASIS7** • **STEEPLE criteria** • **PLATO criteria** • **GRACE criteria** • **REPLACE-2/ISAR-REACT-3 criteria** • **ESSENCE criteria** • **Amiani et al. criteria**	To Assess Bleeding Associated with Percutaneous Coronary Interventions [Reviewed in reference (18)]
• **mOBRI** • **RIETE** • **HAS-BLED** • **CHA_2DS_2-VASc** • **$HEMOR_2RHAGES$**	To Predict the Risk of Bleeding Associated with Chronic Oral Anticoagulant Therapy [Reviewed in reference (19)]
• **Papworth Bleeding Risk Score (BriSC)**(13;20)	To Predict the Risk of Bleeding with Cardiac Bypass Surgery (21)
• **Rockefeller Bleeding History Questionnaire** (13)	To Correlate Phenotypic, Genotypic, and Environment Information