Predicting the Quality of Anticoagulation During Warfarin Therapy

The Basis for an Individualized Approach

“Prediction is very difficult, especially about the future.”

A quote attributed, although with some controversy, to the Danish physicist Niels Bohr, 1885-1962

In medicine, there is an emerging tendency toward individualized medicine, that is, an approach to medicine based on available evidence, but enriched by the awareness of the inherent limitations of any “one size fits all” approach. As a matter of fact, diseases show individual differences with regard to onset and course, and individuals show different responses to drugs and interventions, thus suggesting the rationale for an individualized approach to disease treatments, able to predict individual responses. The most sophisticated approach to individualization and tailoring of medicine is personalized medicine, a broad and rapidly advancing field of health care that is informed by each person’s unique clinical, genetic, genomic, and environmental information.1 Treatment with vitamin K antagonists (VKAs) has been one of the traditional settings for individualization of treatment. The concept of personalized medicine specifically applies to warfarin dosing, a setting where knowledge of the complex polymorphic variants in the gene encoding cytochrome 2C9 (CYP2C9) and of the genetic variants in the gene encoding vitamin K epoxide reductase complex 1 (VKORC1) may help to predict the interindividual variability in warfarin pharmacokinetics and pharmacodynamics, as well as warfarin-associated events and costs.2 However, it is still uncertain and unproven whether management of warfarin dosing guided by pharmacogenetics may improve patient outcomes.3

The article by Apostolakis et al4 in this issue of CHEST (see page 1555) is an interesting contribution in the field because it reports on the validation of a simple, user-friendly score (SAME-TT2R2 [sex female, age <60 years, medical history [more than two comorbidities], treatment (interacting drugs, eg, amiodarone for rhythm control], tobacco use (doubled), race (doubled)]) for predicting the likelihood of poor control of international normalized ratio (INR) in patients with atrial fibrillation (AF) on warfarin therapy, that is, a low value of time in therapeutic range (TTR). This score can be considered when making therapeutic decisions, including the choice of novel oral anticoagulants (NOACs) as an alternative to warfarin, with the advantage of using simple patient-related clinical parameters (SAME-TT2R2). This score appears to be of special value in an era of limited resources because it may provide useful information for improving the safety and effectiveness of antithrombotic prophylaxis, without the need for previously proposed sophisticated genotype-phenotype characterizations.1-3

The study included 1,061 patients from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, randomly divided into derivation and internal validation cohorts, and a subsequent cohort of anticoagulated patients followed in Birmingham for external validation.4 The authors show that the SAME-TT2R2 score can predict poor control of INR and aid decision-making by identifying those patients with AF who would do well on warfarin (SAME-TT2R2 score = 0-1) or, conversely, those (ie, with SAME-TT2R2 score ≥ 2) who require improved care, additional interventions, or other approaches. The clinical relevance of this article is enhanced, at this time, by the availability of NOACs that are effective and safe, but costly. In this perspective, identification of those patients who are unlikely (or likely) to maintain INR at range during treatment with VKAs could better recognize the patients to be candidates for NOACs as first priority. This approach can be justified because prediction of a poor TTR has clinically important implications, such as increased risk of bleeding, stroke, and mortality during warfarin treatment5-6 and an improved cost-effectiveness profile of NOACs.7

It is well known that there are important variations in the quality of managing warfarin prescription, as measured by TTR among different centers dedicated to anticoagulation monitoring, as well as among different geographical contexts.5,8 However, the authors did not consider specific TTR cutoff points but percentiles of TTR values, thus still allowing identification of the patients with the worst control of warfarin treatment, within the general quality level of locally available anticoagulation services and independently of the mean TTR of the specific center. This makes it possible to facilitate the selection of prioritized candidates to NOACs, within the specific context of the local anticoagulation clinic. Because age < 60 years is included in the SAME-TT2R2 calculation, we can expect that adoption of this score will facilitate the selection of younger patients with an increased tendency to low TTR as ideal candidates for NOAC, a well-motivated choice in view of the expectations, usual preferences, and lifestyle of younger and more active patients.8

Even at this time of emerging NOACs, there is a need for studies focused on the quality of warfarin treatment and on its prediction. This is justified by the fact that appropriate implementation of NOACs, as recently reported, is relatively slow even in the United States.8 Moreover, patients with severe kidney
disease are not candidates for currently available NOACs and those at risk for progression to severe kidney disease or with coronary artery disease undergoing percutaneous revascularization are not the most attractive candidates for NOACs at the present time. AF is an emerging “global” epidemic and in view of its prevalence in developing countries, it is expected that the cost of NOACs will be unaffordable in low-income to middle-income countries. If warfarin could be prescribed in these countries with some infrastructure for checking INR, then a selection of potential candidates for warfarin, based on predicted TTR, vs potential candidates for NOACs can be considered.

Apart from suggesting an alternative option to warfarin, predicting a poor TTR before starting treatment with a VKA may be the basis for a more focused follow-up and more comprehensive control of patient compliance and education. This is an important implication and can be applied to both valvular and nonvalvular AF. As a matter of fact, 11% to 12% of the patients in the derivation and internal validation cohort of this study had valvular AF. For patients with AF in the setting of a valvular disease, whose prevalence is even higher (up to 22%) in a global perspective, VKAs will remain the appropriate treatment of AF for many years because NOACs have not been favorably tested in this clinical context. As a matter of fact, current sponsored symposia at medical meetings, and articles in the media, may give the wrong impression that “warfarin is dead,” while this is not true in most countries and surely is not true for valvular patients.

In summary, in the era of evidence-based medicine, the evidence derived from randomized controlled trials is the basis for recommendations of consensus guidelines. However, decision-making in individual patients would benefit from tailoring, based on prediction of individual responses to treatment, as well as assessment of individual preferences and values. In a context with a challenging risk-benefit ratio, such as anticoagulant treatment, Apostolakis and colleagues should be commended for their valuable contribution to individualization of therapeutic choices in the setting of anticoagulation for AF. Because the quality of anticoagulation in individual patients during warfarin therapy is not always the SAMe, improved prediction through the SAMe-TT<sub>R</sub><sup>2</sup> score may help us in the difficult decision-making of daily “real world” practice.

Giuseppe Boriani, MD, PhD
Bologna, Italy

Affiliations: From the Institute of Cardiology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna.

References


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Correspondence to: Giuseppe Boriani, MD, PhD, Institute of Cardiology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy; e-mail: giuseppe.boriani@unibo.it

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