Predicting the Quality of Warfarin Therapy: Reframing the Question

Geoffrey D. Barnes, MD, MSc

1 Department of Internal Medicine, Frankel Cardiovascular Center, University of Michigan, Ann Arbor, Michigan, United States

Address for correspondence Geoffrey D. Barnes, MD, MSc, Department of Internal Medicine, University of Michigan, Frankel Cardiovascular Center, Ann Arbor, MI, United States (e-mail: gbarnes@umich.edu).

Medical treatment of venous thromboembolism (VTE) is undergoing a paradigm shift. Before 2009, vitamin K antagonists (VKAs) such as warfarin were the widely available oral anticoagulants (OACs) for the acute and long-term treatment of VTE. In the decade since, four direct OACs (DOACs) have become the first-line therapy for many patients with VTE given their efficacy, favourable safety profile and ease of use. The same can be said for stroke prevention in patients with atrial fibrillation (AF), where DOACs have also become the first-line therapy.

However, with more therapeutic choices comes the challenge of selecting the best therapy for each individual patient. For some patients, the choice is easy (e.g., VKA for patients with mechanical heart valves). However, for many patients, a variety of clinical and non-clinical factors may influence the decision process. It stands to reason that predicting the quality of VKA therapy may be useful when selecting between VKA and DOAC therapy. This is particularly important given the VKAs remain very widely used globally.

Initially developed in 2013 for warfarin-treated patients with AF, the SAMe-TT2R2 score incorporates many clinical and demographics factors into a risk score for good or poor warfarin control. Using data from the Atrial Fibrillation Follow-up Investigation of Rhythm Management trial, the authors who initially developed the SAMe-TT2R2 score described good discriminatory ability (c-index of 0.70–0.72) for identifying which patients would experience extremely poor VKA control (time in the therapeutic range [TTR] of 30–35%). However, the discriminatory ability was less robust (c-index of 0.58) for a more clinically relevant TTR threshold of 50 to 55%. Similar results were seen in other validation studies of VKA-treated patients with AF. Nonetheless, use of the SAME-TT2R2 score has been recommended as a possible guide for OAC decision-making for patients with AF. Specifically, patients with a score of > 2 are less likely to achieve a good TTR. Therefore, they are recommended to receive early review, more frequent international normalized ratio checks and education or counselling to ensure safe and effective warfarin therapy. Otherwise, these patients can be considered for DOAC therapy instead of warfarin.

The study by Barco et al in this issue of *Thrombosis and Haemostasis* explores the predictive ability of the SAME-TT2R2 score for VKA control in patients with VTE. This is a reasonable question given that many of the SAME-TT2R2 elements apply to patients with AF and VTE (e.g., age, gender, race, tobacco use, co-morbidities). In their analysis of 3874 patients with VTE treated with warfarin in the control arm of a randomized clinical trial, those with a low SAME-TT2R2 score (0–1) represented a minority of patients in the cohort (24%) and had a lower TTR than patients with a SAME-TT2R2 score of ≥ 2 (64.7% vs. 70.7%, p < 0.001). However, they found that low negative (0.59) and positive predictive ability (0.52) and discriminatory characteristics (c-index 0.58) for a TTR cut-off of 66%. These findings broadly mirror those from prior validation studies in VTE populations. Of note, many risk scores based on clinical factors have c-indexes near or under 0.6.

This contrast to the practice-based observational study by Kataruka et al of 1,943 patients with newly diagnosed VTE being initiated on warfarin. In that study, patients with higher SAME-TT2R2 scores had lower mean TTR (57 ± 21% vs. 50 ± 23% for SAME-TT2R2 or 0–1 vs. > 3). The discriminatory ability to predict a TTR of 65% was 0.65, moderately higher than in the Barco et al study. This may reflect the overall lower quality of warfarin control in the practice-based cohort from Kataruka et al than the randomized trial cohort reported by Barco et al.

Certain factors may have influenced the utility of the SAME-TT2R2 score in this analysis by Barco et al. First, they used a post hoc analysis of the Hokusai-VTE study, where patients with acute VTE were randomized to warfarin or edoxaban therapy following a 5- to 10-day parenteral lead in period. Using a highly selected randomized controlled trial population with specific inclusion and exclusion criteria may introduce selection bias in favour of patients who are healthier, more compliant with medical therapy and often have closer health system monitoring than unselected practice-
patients with VTE are needed, including:

acteristic that in or if tobacco use is a marker for some other patient char-
not clear how much tobacco use itself in
instance, it follows logically that removing an interacting
elements and VKA control is not always apparent. For
- What interventions can be targeted at these modifiable
clinical factors and how much improvement in the quality
of VKA therapy can be expected?
- How can these interventions be bundled and implement-
ted for utilization?
- Will the effectiveness of these assessments and interventions
differ when performed by nurses, pharmacists or physicians?

Answers to these and other important questions have the
to potentially greatly impact care for patients with VTE. In the
meantime, clinicians and patients searching for guidance
when selecting OACs in both AF and VTE treatment must look
beyond the SAME-TT2R2 score.

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1219–1229
NOACs for treatment of venous thromboembolism in clinical
atrial fibrillation: past, present and future. Comparing the guide-
lines and practical decision-making. Thromb Haemost 2017;117
(07):1230–1239

<table>
<thead>
<tr>
<th>Study population</th>
<th>Study size</th>
<th>Study type</th>
<th>Outcome measure</th>
<th>c-Index (95% CI)</th>
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<td>Atrial fibrillation</td>
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<td>Randomized trial</td>
<td>TTR &lt; 31%</td>
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<td>(derivation study)⁴</td>
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<td>TTR &lt; 50%</td>
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<td>PINRR ≤60%</td>
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<td>Venous thromboembolism</td>
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<td>Venous thromboembolism</td>
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Abbreviations: AF, atrial fibrillation; CI, confidence interval; PINRR, per cent of international normalized ratio results; TTR, time in the therapeutic range; VTE, venous thromboembolism.

*95% confidence interval not provided.