

Predicting the Quality of Warfarin Therapy: Reframing the Question

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Medical treatment of venous thromboembolism (VTE) is undergoing a paradigm shift.¹ Before 2009, vitamin K antagonists (VKAs) such as warfarin were the only 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.² The same can be said for stroke prevention in patients with atrial fibrillation (AF), where DOACs have also become the first-line therapy.³

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.⁴ 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 (►Table 1).^{5,6} 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.⁷ 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.⁸ 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 3,874 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 (►Table 1).^{9,10} Of note, many risk scores based on clinical factors have *c*-indexes near or under 0.6.

This is contrast to the practice-based observational study by Kataruka et al of 1,943 patients with newly diagnosed VTE being initiated on warfarin.⁸ 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-

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Table 1 Performance of the SAME-TTR score in AF and VTE studies

Study population	Study size	Study type	Outcome measure	c-Index (95% CI)
Atrial fibrillation (derivation study) ⁴	1,019	Randomized trial	TTR < 31%	0.72 (0.64–0.79)
			TTR < 50%	0.58 (0.53–0.62)
Atrial fibrillation ⁵	911	Practice-based, observational	PINRR ≤70%	0.56 (0.52–0.60)
			PINRR ≤60%	0.53 (0.49–0.57)
Atrial fibrillation ⁶	1,524	Practice-based, observational	TTR < 65%	0.56 (0.53–0.59)
Venous thromboembolism ⁸	3,874	Randomized trial	TTR < 66%	0.58 (0.56–0.60)
Venous thromboembolism ⁹	1,943	Practice-based, observational	TTR < 65%	0.65 ^a
Venous thromboembolism ¹⁰	1,308	Practice-based, observational	TTR < 65%	0.52 (0.48–0.55)

Abbreviations: AF, atrial fibrillation; CI, confidence interval; PINRR, per cent of international normalized ratio results; TTR, time in the therapeutic range; VTE, venous thromboembolism.

^a95% confidence interval not provided.

based patients. Second, anytime a risk score is used in a different population than it was initially derived (e.g. use in VTE while developed in AF), it may need adaptation to improve its discriminatory and predictive properties. Perhaps other elements are needed to predict VKA management quality that may be more specific to the VTE population.

Nevertheless, it is not clear that testing a summative risk score to predict good versus poor quality VKA therapy is the most useful clinical question. For many patients, DOAC therapy is the first line when clinically appropriate. However, for others, use of VKA is preferable due to drug cost, availability or concerns about readily available reversal agents. For these patients, identifying modifiable characteristics that may improve the quality of VKA therapy is a worthwhile clinical and research endeavour. Some of these characteristics are likely to be included in the SAME-TT2R2 score, such as tobacco use and concurrent use of medications with drug-drug interactions. However, other elements of the SAME-TT2R2 score (e.g. age, race, sex) are not modifiable. And a direct connection between individual SAME-TT2R2 score elements and VKA control is not always apparent. For instance, it follows logically that removing an interacting drug may improve the quality of VKA therapy. However, it is not clear how much tobacco use itself influences VKA control or if tobacco use is a marker for some other patient characteristic that influences VKA control.

Future studies aiming to improve anticoagulation care for patients with VTE are needed, including:

- How can risk scores be incorporated into decision aids that promote shared decision making for patients with AF and/or VTE?
- Which modifiable clinical factors associate with good/poor VKA therapy? Which of these factors are specific to patients with AF and VTE?

- 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 implemented 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 potential to 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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Conflict of Interest

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