Improving the Management of Warfarin May Be Easier than We Think

Running title: Rose; Warfarin dosing by algorithm

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Performance variation is easy to find - all one needs to do is to look for it. We have long known that some nations achieve better control of hypertension than others,¹ some hospitals have shorter door-to-balloon times than others,² and some cardiac surgeons have better risk-adjusted mortality after coronary artery bypass graft surgery than others.³ In fact, it is difficult to recall an instance where performance was found not to vary. Given that performance variation is ubiquitous, it is no longer shocking to find it; the more interesting question is why performance varies so much. The answer to this question would likely be a key step along the pathway to improving performance.

It is rather uncommon to find a single answer to the question of why performance variation exists. However, in the current issue of Circulation, Van Spall and colleagues have found an unusually straightforward explanation for performance variation, at least in the context of the management of warfarin.⁴ The authors found that site-level adherence to a relatively simple algorithm regarding when to change the dose of warfarin and when not to change the dose predicted fully 87% of between-center variance. Adding patient-level clinical variables (i.e. risk-adjustment), center-level variables, and country-level variables only increased the amount of explained variation to 89%. In short, management of warfarin doses appeared to be almost deterministic regarding the anticoagulation control that was achieved. Remarkably, the authors also found that greater adherence to the algorithm also predicted a reduced rate of the combined primary endpoint of stroke, major hemorrhage, or death at the site level. For each 10% increase in algorithm-consistent dosing at the center level, the annual rate of the combined endpoint was 8% lower, even after adjusting for a host of patient-level predictors. The algorithm has additional attractive features as well, not least of which is that it does not require a computer or proprietary software to use. In fact, it would be equally suitable to use in developing countries.
The authors deftly used a feature of their dataset to demonstrate that percent time in therapeutic range (TTR) really is in the causal pathway to adverse events. Because their dataset was drawn from a randomized trial of dabigatran vs. warfarin, they were able to show that while sites with more algorithm-consistent warfarin dosing had lower rates of adverse events among patients receiving warfarin, they did not have lower rates of adverse events among patients receiving dabigatran. Some have expressed doubts about whether TTR really is in the causal pathway to outcomes, suggesting that instead, sites with higher TTR also might be delivering high-quality care in other ways. If this were true, then quality improvement efforts aimed at increasing TTR might not achieve the desired benefits in terms of preventing adverse events. The finding by Van Spall and colleagues serves as a strong refutation for this line of reasoning, because if high-TTR sites were truly delivering other interventions responsible for preventing adverse events, we would have seen a similar reduction in adverse events among patients receiving dabigatran. The present study therefore serves as a strong endorsement of efforts to improve TTR at the site level and thereby prevent adverse events.

The algorithm studied by Van Spall and colleagues was similar to others that are in widespread use. The algorithm suggested no dose change for an in-range INR value, a 10% dose change when the INR was somewhat out-of-range (1.51-1.99 or 3.01-4.00), and a 15% dose change for greater deviations from the target range. The authors note that while they distributed this algorithm, they cannot know to what extent the sites of care actually used it - in essence, their study examined the difference between care that would have been algorithm-concordant, as the authors put it, "whether intentionally or not". In a study by Kim, et al., a very similar (but not completely identical) dosing algorithm was shown to improve TTR. The Kim study complements the current study in that it shows that the introduction of a standardized dosing
algorithm improved TTR considerably using a before-after design.\textsuperscript{6} While Van Spall and colleagues were able to show that algorithm-concordant care was important, they were unable to examine whether the introduction of the algorithm had actually increased the likelihood that such care would be delivered. Also, in the Kim study, algorithm-consistent dosing was highly correlated with patient-level TTR, which complements the site-level findings of the current study. Taken together, the two studies suggest that the algorithm is both valid (in the sense of predicting important outcomes)\textsuperscript{4} and feasible (in the sense that it can successfully be introduced and change clinical practice).\textsuperscript{6}

Any algorithm for warfarin dose management, whether paper-based or computer based, needs to be introduced with a caveat, namely that the clinician must always have the power to override the algorithm. Any decision about warfarin dose changes must occur in the context of the visit, and some information which is divulged by the patient (for example, recent dietary intake) may well prompt a decision that is discordant with the algorithm.\textsuperscript{7} However, both the Van Spall and Kim studies strongly suggest that clinicians managing warfarin should ask themselves whether they really have a compelling reason to deviate from the algorithm and then ask again for good measure.

The present study also adds to a growing discussion about how to manage warfarin doses when the INR is only slightly out of range. In the past, several studies have suggested that dose changes are not necessary for mildly deranged INR, and in fact may begin a cycle of overcorrection and rebound that may worsen control.\textsuperscript{8,9} Based on this limited evidence, the latest consensus guidelines for managing warfarin suggest not changing the dose when the INR deviates by \( \leq 0.5 \) from the target range, and instead merely rechecking in 1-2 weeks.\textsuperscript{10} Notably, a deviation of up to 0.5 is an even wider "tolerance range" than would be suggested by either of
the previous studies.\textsuperscript{8-9} With this issue in mind, Van Spall and colleagues examined whether their findings would also be true when the tolerance range was widened from 2.0-3.0 to 1.9-3.1, 1.8-3.2, 1.7-3.3, and 1.6-3.4. They found that TTR was higher with increased adherence to any of these ranges, but was best with the strict construction of the target range (i.e., 2.0-3.0). In addition, only the strict construction predicted the primary combined endpoint in a statistically significant fashion. Thus, the findings of the present study cast at least some doubt on the idea of a widened tolerance range, within which slightly deranged INR values do not prompt a dose change. Ideally, a well-designed prospective study could address this issue more definitively.

For now, while some clinicians may still opt to have a tolerance range, it may be prudent not to extend it beyond approximately 1.8-3.2,\textsuperscript{8-9} as opposed to the much wider range of 1.5-3.5 recommended by the most recent guidelines.\textsuperscript{10}

One noteworthy limitation of the present study stems from its origins in a clinical trial.\textsuperscript{11} The patients represented in this study may have been unusually adherent to their medication, and gaps in INR monitoring were likely minimal. In a real-world setting, dose management may not predict 87\% of site variation, and other issues, like gaps in INR monitoring, also may play an important role. Our group has shown that nonstandard target ranges, gaps in INR monitoring, and failure to recheck INR promptly after an out-of-range value are also strong predictors of site-level TTR.\textsuperscript{12-14} Together, these three measures predicted 48\% of TTR variation among sites of care in the Veterans Health Administration (our unpublished finding). It is likely, therefore, that while adherence to the algorithm examined by Van Spall and colleagues may be the single most important determinant of site-level TTR, it is not the only performance measure worth addressing. In fact, improving TTR is likely to require a multi-factorial approach, as there are many related issues that contribute to TTR (\textbf{Table 1}).
Another limitation, mentioned above, is that the present study was not an attempt to actually implement the algorithm under study. Kim and colleagues successfully implemented a similar algorithm, but they did so at a single site of care, which may not be representative of other sites. An important next step would be a prospective test of this algorithm in a real-world setting, preferably across an integrated health system. Such an effort would require great attention to the principles of implementation science in order to promote successful adoption of the algorithm. In fact, we have recently begun such a study in the New England region of the Veterans Health Administration. One challenge for our effort, and for any effort occurring in the real world, is that automated data may not reliably identify dose changes in warfarin, which is usually prescribed "use as directed". A need to rely upon chart review to track adherence to the algorithm may hamper efforts to measure its uptake.

In summary, Van Spall and colleagues have added several important new pieces of information to the literature. First, in combination with other studies, the present study convincingly demonstrates that managing warfarin according to a standard algorithm can improve patient outcomes. Second, the present study should lay to rest any lingering doubts about whether TTR is truly in the causal pathway to adverse events. Finally, the present study suggests that changing the dose of warfarin for any out-of-range INR may in fact be best, although other studies have found differently and further evidence is needed. The study by Van Spall and colleagues certainly provides a powerful argument for greater adoption of any sort of system to promote standardized dose management for warfarin – either computer support when it is available, or paper-based algorithms if not. Improving outcomes for patients receiving warfarin will not be easy, but it may be easier than we think.
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References:


**Table 1.** Some key challenges to improving anticoagulation control.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Issue</th>
<th>Challenge or Knowledge Gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin dose management</td>
<td>Limited use of computerized dose support or paper-based algorithms, both of which are shown to improve control</td>
<td>Promoting wider adoption of computerized dose support or paper-based algorithms</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>Lack of functioning systems to track patients and detect loss to follow-up</td>
<td>Need to develop such systems, particularly for sites without proprietary anticoagulation management software</td>
</tr>
<tr>
<td>Use of non-standard target INR ranges</td>
<td>Lower target INR ranges such as 1.5-2.0 remain in use, despite having been shown to produce harms without additional benefit</td>
<td>Finding effective ways to promote the use of standard rather than non-standard target ranges</td>
</tr>
<tr>
<td>Timely follow up after deranged INR values</td>
<td>Prompt follow-up after high (&gt;4) or low (≤1.5) INR improves control</td>
<td>Clinicians may resist changing practice; patients may resist frequent follow-up</td>
</tr>
<tr>
<td>Patient education</td>
<td>Patient education may lack standardization and may have limited effectiveness.</td>
<td>Developing new and innovative ways to educate and re-educate patients about warfarin therapy</td>
</tr>
<tr>
<td>Patient adherence to therapy</td>
<td>Limited adherence to pill-taking, dietary consistency, on-time follow-up, and other matters</td>
<td>Need to identify and address various patient-level barriers to improved adherence</td>
</tr>
<tr>
<td>Anticoagulation clinic leadership</td>
<td>Each clinic needs strong leadership to ensure continuous quality improvement</td>
<td>Individuals may not feel empowered to identify and implement strategies to improve outcomes</td>
</tr>
<tr>
<td>Performance measurement</td>
<td>Anticoagulation therapy is clearly important enough to deserve a program of performance measurement</td>
<td>Performance measures have been developed, but still need to be used more widely, and may need to be amended over time in response to feedback</td>
</tr>
</tbody>
</table>
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