


Is Warfarin-Induced Rapid Rise in INR Post-Cardiac Surgery Associated With Increased Bleeding Risk?

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We read with great interest the recently published article by Olson et al¹ in which they reported the results of the assessment of warfarin-related rapid rise in the international normalized ratio (INR) in post-cardiac surgery patients. The authors found a correlation between rapid rise in INR and hospital length of stay, but not bleeding events. Because of the considerable importance of the results, we think several points regarding the article are worth noting.


Olson et al¹ defined bleeding end points based on BARC (Bleeding Academic Research Consortium) criteria and included perioperative intracranial bleeding, reoperation after closure to control bleeding, chest tube output of ≥ 2 L within 24 hours, or transfusion of ≥ 5 units of whole or packed red blood cells within 48 hours, all of which are classified among the type 4 as coronary artery bypass grafting (CABG)-related bleeding in BARC criteria. However, patients in the study were not undergoing CABG. Additionally, in studies on patients who were not undergoing CABG, the BARC type 4 was not included among the bleeding assessments.² Moreover, there are several other scales that can be potentially used for the classification of bleeding such as ISTH (International Society on Thrombosis and Haemostasis), which was developed for major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. So the elaborations regarding the justification of using this type of bleeding among other types in BARC or selecting BARC over other classifications are very helpful.

In the study, some potential causes of bleeding, such as the method of surgery (minimally invasive vs conventional) or concomitant medications that can be associated with bleeding resulting from pharmacodynamic drug interactions (such as heparin, nonsteroidal anti-inflammatory drugs, antiplatelet agents, etc), were not addressed. It would have been quite valuable if the authors had utilized a probability scale for bleeding events as adverse reactions caused by warfarin. Additionally, there is a growing interest regarding the role of genetics in bleeding following cardiac surgery. For example, 5 SNPs (single nucleotide polymorphisms) that were found to be related to bleeding after cardiac surgery and located on genes associated with coagulation and platelet function have been specified.³ The possibility of different genetic backgrounds among patients with and without rapid INR rise could be mentioned as a limitation of the study.

We would like to discuss several issues regarding the interpretation of the results as well. First, dosing of warfarin

during the study was based on the pharmacist-to-dose practice model. This approach was somehow individualized based on the presence of risk factors for sensitivity to warfarin. Any increase in INR was managed with dose adjustment or holding warfarin in the study setting, as mentioned in a previous study.⁴ Also, decreased bleeding events among patients on warfarin therapy with implementation of the pharmacist-managed protocol was a finding of another study in the same center.⁵ Thus, in a center where a well-established protocol was implemented and monitored by pharmacists, some of the factors that can lead to rapid INR rise or even bleeding might have been prevented as part of the standard of care. It seems that there is a theoretical possibility of the impact on outcomes and noticing risk factors associated with bleeding. This was pointed out by Olson et al¹ in the context of discussing why they found that older age was associated with decreased risk of rapid rise in INR. Second, although bleeding can occur at any INR, the risk is generally higher with elevated INR. Because of the previous reports on the association between elevated INR and intensity of anticoagulation with bleeding risk in patients with prosthetic heart valves,⁶ it would have been useful if the author elucidated why this factor was not included in the univariate analysis.

Niloofar Khoshnam-Rad, PharmD
*Department of Clinical Pharmacy,
Faculty of Pharmacy, Tehran University of
Medical Sciences, Tehran, Iran*

Mona Kargar, PharmD 
*Research Center for Rational Use of Drugs, Tehran
University of Medical Sciences, Tehran, Iran*

Authors' Note

Mona Kargar is responsible for the content and correspondence of the article.

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ORCID iD

Mona Kargar  <https://orcid.org/0000-0002-2572-4991>

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