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Optimal Target International Normalized Ratio For Patients With Mechanical Heart Valves

Vink et al. (1) compared the occurrence rates of bleeding and thrombo-embolism among patients with mechanical heart valves who had either high-intensity or low-intensity vitamin K antagonist therapy (VKA). Based on their findings of lower combined bleeding and thrombo-embolic occurrence rates in the high-intensity VKA group, they concluded that “both aortic and mitral valves will benefit from a treatment strategy with a target INR higher than 3.0.” This is a controversial conclusion because most recent publications recommend a valve-specific and lower target international normalized ratio (INR) (2,3). Therefore, we closely studied Vink’s analyses and have the following comments.

When trying to identify the optimal target INR for patients with mechanical heart valves, not only the occurrence rates of bleeding and thrombo-embolism but also the consequences of these events need to be considered. It may well be possible that although the combined occurrence rates of bleeding and thrombo-embolism are lower in the high-intensity VKA group, the combined mortality associated with bleeding and thromboembolism is lower in the low-intensity VKA group.

We repeated the reported meta-analysis for the aortic valve replacement group, and we pooled the mortality rates of bleeding and thrombo-embolism from those studies that reported on mortality resulting from these events (11 of the 21 studies in the low-intensity and 5 of the 9 studies in the high-intensity VKA group). We found in the low-intensity VKA group versus the high-intensity VKA group, a pooled mortality rate for bleeding of 12% (95% confidence interval [CI] 7.7% to 16.3%) versus 20% (95% CI 13.3% to 26.6%; p = 0.05), for valve thrombosis 27% (95% CI 12% to 42%) versus 33% (95% CI 3.5% to 63.5%; p = NS), and for thrombo-embolism 14% (95% CI 9.6% to 18.4%) versus 14% (95% CI 8.3% to 19.7%; p = NS). We entered the occurrence rates and mortality rates of bleeding, valve thrombosis, and thrombo-embolism from the meta-analysis in a microsimulation model that we previously developed (4) to estimate patient prognosis after aortic valve replacement with mechanical prostheses, and we simulated 10,000 life histories of a 56-year-old (mean age in meta-analysis) male patient after aortic valve replacement in order to estimate the expected lifetime risk of death due to bleeding, valve thrombosis, and thrombo-embolism for either a low-intensity or high-intensity anticoagulation regimen. We found that the combined lifetime risk of death due to bleeding, valve thrombosis, and thrombo-embolism in the low-intensity versus the high-intensity VKA group was 6.3% versus 7.8% (p = NS). This shows that, when considering the mortality due to bleeding and thrombo-embolic events, for aortic valve patients nothing is gained by a target INR higher than 3.0.

In conclusion, a meta-analysis of only bleeding and thrombo-embolic event rates is methodologically insufficient to determine the optimal anticoagulation regimen for patients with mechanical heart valves. Modelling techniques are essential to evaluate the burden of the competing risks of bleeding and thrombo-embolism and their consequences during the lifetime of the patient.

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The Optimal Intensity of Vitamin K Antagonists in Patients With Mechanical Heart Valves: A Meta-analysis

I enjoyed the article by Vink et al. (1), which again revisits an old and most important clinical chestnut, but I have serious misgivings about their conclusions. Some years ago, we did a detailed and comprehensive analysis of 1,134 patients who had received St. Jude prosthetic valve(s) over a 13-year period (2). The follow up was 100% complete—4,936 patient years—and the study had a 60% post-mortem examination rate for early deaths.

The recommendation we made as the result of our analysis, namely that the INR should be kept between 2.5 and 3.0, is at complete variance with that of the authors. I believe that the problem arises from the fact that the target international normalized ratio (INR) range on which the authors focused may have no bearing whatsoever on the INR at the actual time of the anticoagulant-related complication. In contrast, we based our recommendations on the INR measured at the actual time of the anticoagulant-related complication, which we had in 88% and 58% of the major thromboembolic and hemorrhagic complications, respectively. Furthermore, in a more recent study (3), we found that at any given time 21.8% to 32.5% of patients were outside the target INR set for them; indeed, other authors have found an even greater number of patients (up to 52%) outside the target INR range (4).

It is essential therefore to base any recommendation regarding anticoagulation on an analysis of INR readings at the actual time of the anticoagulant-related complications rather than the target INR range, which is the ideal rather than the reality.

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Anticoagulation Management of Patients With Prosthetic Valves

As authors of previous European guidelines on anticoagulation of patients after valve surgery and as members of a committee currently revising those guidelines, we are concerned to read the paper of Vink et al. (1) Their recommendation that all patients should be managed with an international normalized ratio (INR) of 3.0 to 4.5 reverses current trends to individualize antithrombotic management for each patient based on an assessment of their particular thromboembolic risk (2–4). Although having a “one size fits all” approach to anticoagulation management may have advantages for anticoagulation clinics, this approach will not benefit individual patients who may be exposed to the risks of unnecessarily high anticoagulation.

Their meta-analysis raises several concerns. First, meta-analysis is a technique for amalgamating data from randomized controlled trials (RCT) that have used the same methodology, not observational studies with different methodology. Second, reported thromboembolic rates are heavily influenced by definitions, data collection methods (prospective vs. retrospective), size and length of study, patient risk factors, concomitant surgery, and type of prosthesis (5,6). Other than the prosthetic type, these factors are not mentioned. Valve thrombosis rates are influenced by the number of patients who experienced anticoagulation interruption, to which most cases are related (7). Third, we question the use of target INRs rather than achieved INRs. Many events occur when the INR is outside the target range.

Fourth, retrospective conversion of prothrombin time ratios to INR has the potential to introduce huge errors. In American studies, it is highly unlikely that a single thromboplastin reagent would have been used for all patients in the study (8).

Finally, there is a lack of acknowledgment of the five published RCTs comparing different anticoagulation intensity (9–13). Although most of these RCTs have limited applicability because of their methodologies, all reached the conclusion that a higher intensity of anticoagulation did not reduce the incidence of thromboembolism. Four RCT’s showed a higher incidence of bleeding with higher intensity anticoagulation. The only RCT not to show this effect used overlapping INR ranges and did not record events in the first three months (13).

Although Vink et al. (1) acknowledge that high-intensity anticoagulation results in a higher incidence of bleeding, they appear to minimize this danger. Use of a higher range of INR, 3.0 to 4.5, for all patients imposes an imperative for extremely tight INR control. High variability of INR, with >30% of INRs outside the range 2.0 to 4.0, is the strongest