A higher international normalized ratio may be better for your patient

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Physicians caring for patients who require anticoagulation therapy with vitamin K antagonists, such as warfarin, are correctly concerned about inducing bleeding. As a result physicians tend to underdose their patients. In fact, numerous studies have shown that patients spend more time below the accepted therapeutic range of international normalized ratios (from 2 to 3) than above it.[1–3] The elegant and carefully performed meta-analysis by Oake and colleagues[4] in this issue of *CMAJ* should help these physicians to understand the serious risks of underdosing. At the same time, the study provides some reassurance that international normalized ratios that are slightly above 3 are not that dangerous.

The first association between a mysterious bleeding disease in cattle and sweet clover, which was later discovered to contain vitamin K antagonists, was described by a Canadian veterinarian in 1922.[5] The efficacy of vitamin K antagonists in various arterial and venous thrombotic disorders is now supported by a large body of clinical studies, and the evidence is nicely summarized in guidelines.[1] The purpose of anticoagulation therapy is to reduce the risk of thrombosis while maintaining the lowest possible risk of bleeding. It is therefore appropriate, as Oake and colleagues present in their analysis, to look at the combined outcome of thrombosis and bleeding in the various ranges of international normalized ratios. Based on the data reported in the studies included in their analysis, they distinguished 4 categories of international normalized ratios (< 2, 2–3, 3–5 and > 5). The authors reported an absolute combined risk of thrombosis and bleeding of 10.6% per year at a ratio less than 2, 4.3% per year at a ratio of 2–3, 7.0% per year at a ratio of 3–5 and 52.3% per year at a ratio greater than 5.

The treating physician should carefully interpret these findings in the following way. Keeping his or her patient in the international normalized ratio range of 2–3 remains the best strategy. However, the often applied careful approach to treating patients with a ratio below 2 (i.e., slowly increasing the dose of vitamin K antagonists) should be reconsidered, since the risk of adverse outcomes is almost tripled when patients have a ratio below 2.

Interestingly, in the broad international normalized ratio range of 3–5, the absolute risk of thrombosis and bleeding is 7% per year.[4] Although this is higher than the absolute risk of 4.3% per year in the 2–3 range, it is much lower than many physicians think.

It is unfortunate that Oake and colleagues were not able to distinguish the effects of an international normalized ratio of 3–4. It is likely that in this range the absolute risk would even be lower than 7% per year. International normalized ratios above 5 should clearly be avoided, since not only the risk of bleeding but also the risk of thrombosis (partly influenced by stopping vitamin K antagonists or corrective treatment) is greatly enhanced at this range.

Key points

- The purpose of anticoagulant therapy is to reduce the risk of thrombosis with the lowest possible risk of bleeding.
- Slowly increasing the dose of vitamin K antagonists should be reconsidered, since the risk of adverse outcomes is almost tripled when patients have an international normalized ratio below 2.
- An international normalized ratio of 2–3 is optimal; however, ratios that are slightly higher than this therapeutic range are moderately safe.
- It is likely that the absolute risk of thrombosis and bleeding at a ratio of 3–4 would be lower than 7% per year.

Competing interests: None declared.

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DOI:10.1503/cmaj.080958