

Editorial Focus

Understanding low INR in clinical practice

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By human nature we focus more intently upon the harm that we may cause by doing too much than the harm that we may allow by doing too little (1, 2). It is well known that while vitamin K antagonists (VKA) are highly effective in preventing thromboembolic events, their use can also lead to serious haemorrhagic complications (3–7), some of which may be disabling or fatal. This very real risk is almost certainly part of the reason why VKA are underutilized in many patients with atrial fibrillation (8). Heightened fear of haemorrhage also evokes a heightened avoidance of elevated International Normalised Ratio (INR) as evidenced by the fact that, in most studies, patients spend more time below than above the target INR range (9–14). The research literature also reflects this tendency to focus on overanticoagulation, with previous studies contributing to a much greater understanding of the causes of high INR than low INR. This tendency may also reflect a difference in perceived risk: the daily risk of an adverse event is almost certainly greater when the INR is high (15) than when it is low (16). Nevertheless, subtherapeutic anticoagulation is associated with more frequent and more severe strokes and represents a more important phenomenon than our limited understanding of it might suggest (17).

In this issue, Rombouts et al. (18) report their findings on the frequency of low INR and risk factors for low INR among patients cared for by the Leiden Thrombosis Service. Of 13,443 patients initiating VKA therapy, 7,419 met the study eligibility criteria for stability defined as four consecutive INR determinations within the target range. Within four weeks of this stable period, 12% of patients had a subtherapeutic INR, a proportion that approximately doubled by eight weeks, and reached 50% after 40 weeks. Use of acenocoumarol (22% of the cohort) doubled the risk of a subtherapeutic INR compared to phenprocoumon and shortened the time to occurrence. The median time to first low INR was 13 weeks versus 51 weeks, respectively.

Higher target intensity and use of VKA therapy for prophylaxis of venous thromboembolism (VTE) were also associated with increased risk. The authors additionally found that 30% of low INR episodes were preceded by an invasive procedure, haemorrhage, or elevated INR.

This study highlights the common occurrence of subtherapeutic INR levels and provides a clear estimate of the incidence of low INR in a meticulously constructed inception cohort of patients deemed stable on anticoagulant therapy. Nearly one-fourth of patients in this study experienced a low INR within two months of a period marked by stability (four consecutive INR determinations in the target range). It is notable that 45% of the initial cohort never achieved stable INR which emphasises the challenges inherent to VKA and the gross underestimate of low INR that occurs in routine practice. Importantly, the authors also found that nearly one-third of low INR episodes resulted from clinically justified interventions to minimise risk of haemorrhage, and therefore, reflective of informed clinical care rather than substandard anticoagulation management.

In this study, acenocoumarol was associated with a twofold increase in risk for low INR (adjusted hazard ratio [HR] 2.14) compared to phenprocoumon. Fihn et al. had previously reported more time in the therapeutic range with phenprocoumon compared to acenocoumarol, and phenprocoumon has been shown to exhibit less INR variability over a 24-hour period (19, 20). Potential mechanisms for these observations include differences in pharmacokinetics (the half-life of acenocoumarol is 8–11 hours versus 5–6 days for phenprocoumon), pharmacogenetics, and timing of blood sample collection in relation to dose. Phenprocoumon is less affected by CYP2C9 polymorphisms compared to other VKA (21).

Extrapolating from time-in-range analyses and known effects on INR variability, the authors suggest preferential use of phenprocoumon in clinical practice. However, the study was not

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designed to assess differences in clinical outcomes (two thromboembolic events occurred) and published data are conflicting on the overall safety of phenprocoumon compared to acenocoumarol. Widely disparate results range from increased major bleeding with phenprocoumon to an isolated increase only in minor bleeding, to no difference in bleeding, and to decreased bleeding compared to acenocoumarol (10, 22–24). Without definitive data on efficacy and safety, treatment recommendations based on surrogate endpoints should be interpreted with caution.

As acknowledged by the authors, the retrospective design of the study prohibited a detailed assessment of other potential risk factors for low INR, particularly medication adherence and dietary change. The authors invoke non-adherence due to patient perception of risk as a potential explanation for the differential rates of low INR by indication for therapy. After adjustment for covariates, patients receiving a VKA for thromboprophylaxis had the highest rate of first low INR (HR 1.88), followed by secondary prevention of VTE (HR 1.36), atrial fibrillation (refer-

ence category), and mechanical heart valves (HR 0.69). A more comprehensive accounting of the reasons for unintentional low INR values in routine practice is needed to facilitate interventions to improve time in the therapeutic range.

Understanding the precipitants of low INR is long overdue, and from that standpoint alone, this study is an important contribution. However, many pivotal issues regarding thromboembolism and low INR remain unexplored. Is risk affected by the length of the subtherapeutic period? What is the association between low INR, factor VIIa and molecular markers of thrombin activation? What ultimately drives thrombus formation and embolisation? Is the risk of low INR modified by the clinical context? Do concomitant medications attenuate or magnify the risk of low INR and what is the effect of temporal changes in thrombogenicity? Answers to these questions will provide important insights to fundamental mechanisms. In the interim, optimization of anticoagulant therapy as guided by innovative investigation such as that by Rombouts et al. remains a pressing need.

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