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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