

Nonadherence with INR Monitoring and Anticoagulant Complications

Abstract

Warfarin is a very effective anticoagulant for the prevention and treatment of thrombosis. An assessment of coagulation, the international normalized ratio (INR) is used to monitor the effect of warfarin on the hemostatic system. However, the INR response to warfarin can fluctuate as a result of interactions with a large number of other drugs, food, herbal agents, or for no apparent reason. Furthermore, warfarin is classified as a narrow therapeutic index drug because of the small differential separating beneficial and toxic therapeutic effects. Hence, in order to achieve optimal therapeutic outcomes, frequent INR monitoring is critical to allow timely warfarin dose adjustments when the INR falls outside the therapeutic range. Adherence can be defined as the extent to which patient's behavior conforms to the requirements of prescribed treatment. Adherence with warfarin therapy requires a high degree of commitment and cooperation from patients and/or their caregivers to ensure that the medication is taken correctly and the INR monitored as instructed by the anticoagulation provider. Episodes of nonadherence with various aspects of warfarin therapy, including INR testing, are common. Habitual nonadherence with INR testing results in long periods where the extent of warfarin anticoagulation is unknown. While habitual nonadherence with INR testing is commonly observed in clinical practice, it has yet to be definitively established that this behavior increases the risk for adverse outcomes. Available studies evaluating warfarin adherence have focused almost exclusively on pill taking behavior and not on adherence with INR testing. This omission is important because nonadherence with INR testing is easily and objectively identifiable in routine clinical practice whereas noncompliance with warfarin pill taking is not. Thus, commonly used measures of pill taking behavior such as pill counts, pharmacy dispensing records, self-report surveys, drug assays, biologic markers, and physician reports are not practical methods to inform 'real-world' clinical practice. Another shortcoming of using pill taking behavior as a measure of warfarin adherence is that the most commonly identified scenario is missed warfarin doses. While missed warfarin doses commonly cause subtherapeutic INR results, our prior research indicates that resultant low INRs rarely result in adverse clinical outcomes provided steps are taken to rapidly restore therapeutic anticoagulation. Similarly, we have shown that the risk of major bleeding in patients with high INRs (between 4.5 and 10.0) is quite low when the INR is corrected in a timely manner. Therefore, ensuring timely INR monitoring and adjusting doses of warfarin when necessary is of primary importance and we hypothesize that when patients habitually fail to return for INR testing, the likelihood of adverse events increases, probably as a result of extended time periods outside of the targeted INR range. In support of this hypothesis, we have previously demonstrated a significant inverse association between long-term INR control and adverse event risk. While several small studies have examined patient characteristics associated with nonadherence as defined by warfarin pill taking behavior such as education level, marital status, living arrangements, employment status, mental health functioning, and cognitive impairment, no studies have evaluated factors that might predict nonadherence with prescribed INR testing. The purposes of this study are to: (1) test the hypothesis that nonadherence with INR monitoring is associated with an increased risk for bleeding, thromboembolic and fatal warfarin-related adverse events within a large, diverse, real-world sample of patients receiving warfarin therapy, and (2) to describe patient characteristics associated with INR testing nonadherence. This study will provide important information regarding patients on warfarin therapy that might be at high risk for complications due to nonadherence with required INR testing. Ongoing assessment of each patient's risk:benefit ratio is critical to maximizing the positive impact of warfarin therapy within our health systems. Using proven practice-based

methodology in a large, validated, real-world dataset, we seek to assess the utility of an easily applied objective method for identifying patients at increased risk for anticoagulation therapy-related adverse events due to nonadherence with INR monitoring. Because identifying patients who fail to return for INR tests is both easily accomplished and a routine component of managing warfarin therapy, this simple measure of adherence would be feasible, durable, and have near universal applicability. Confirming our hypothesis that nonadherence with INR monitoring is significantly associated with the risk of warfarin-related adverse events would be valuable to clinicians as they determine the risk:benefit ratio of warfarin treatment for their individual patients. If our hypothesis that nonadherence with INR monitoring is associated with an increased risk of adverse events is confirmed, we plan to design and conduct additional studies aimed at determining how adherence with INR testing might be improved. We would test interventions such as focused patient education, the use of interactive voice response reminders, depression screening, psychological therapy and the use of warfarin self-management in selected patients.