The hazards of interrupting anticoagulation therapy in atrial fibrillation

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This editorial refers to 'Increased short-term risk of thrombo-embolism or death after interruption of warfarin treatment in patients with atrial fibrillation\textsuperscript{5}', by J. Raunsø et al., on page 1886

Atrial fibrillation (AF) is the most commonly encountered clinical arrhythmia and is associated with a substantial burden of morbidity (mainly thrombo-embolism) and mortality. Vitamin K antagonists such as warfarin are highly effective for the prevention of stroke and systemic embolism in patients with AF,\textsuperscript{1} but their use is hampered by multiple food and drug interactions, the need for routine coagulation monitoring, and a high risk of bleeding complications.\textsuperscript{2} Hence warfarin not only is underutilized, but among those who are prescribed warfarin the treatment is frequently interrupted or permanently discontinued.\textsuperscript{3,4} No large studies have explored the possible impact of stopping warfarin on the short-term risk of subsequent major adverse cardiovascular outcomes, such as stroke and death, in patients with AF.

Raunsø and co-workers have now reported the results of a Danish nationwide retrospective cohort study in which they explored outcomes after warfarin interruption in patients with AF.\textsuperscript{5} Patients with a first hospitalization for AF in the period 1 January 1997 to 31 December 2008 were identified using the Danish National Patient Registry, and warfarin interruption was determined by cross-linkage with prescription claims from the Danish Registry of Medicinal Product Statistics. The primary outcome of the study was hospitalization for thrombo-embolism (ischaemic stroke, transient ischaemic attack, or unspecified stroke), pulmonary embolism or systemic arterial embolism, or all-cause death.

Among 149,151 patients with a first hospitalization for AF during the 12 year study period, 48,989 filled a prescription for warfarin a median of 6 days after being discharged from hospital. Remarkably, 35,396 patients or 72% of the entire cohort had at least one warfarin treatment interruption during a mean of 3.5 years of follow-up. The median age for patients receiving warfarin was 71 years, the median CHADS\textsubscript{2} score was 1.41, and the overall incidence rate of thrombo-embolism or death was 6.9 per 100 patient years. One-half of these events occurred during treatment interruption, and the incidence rate of thrombo-embolism or death during the first 90 days after stopping warfarin was 31.6 per 100 patient years.

The strengths of the report by Raunsø et al. are the inclusion of an unselected ‘real-life’ AF population, the long follow-up duration, and the use of a robust primary outcome measure, hospitalization for thrombo-embolism and all-cause death. The study also has several limitations, including lack of information on bleeding, uncertainty about the accuracy of warfarin dosing estimations (which may have led to error in estimating the timing of warfarin interruption), and inability to distinguish temporary from permanent interruption. The most important limitation would appear to be lack of information concerning the reason for warfarin interruption, which complicates interpretation of the association between treatment interruption and outcome.

Potential explanations for the findings of an association between treatment interruption and risk of thrombo-embolism or death are illustrated in Figure 1. One possible explanation is that the event that prompted the treatment interruption (e.g. bleeding, trauma, or surgery) might also have been the cause of thrombo-embolism or death (‘confounding’). Without detailed information on the reason for interruption, the potential for confounding cannot be excluded. A second possible explanation is that the events that occurred during interruption of warfarin simply reflect loss of protection against thrombo-embolism in patients with persistent risk factors (‘indirectly causal’). However, this explanation cannot account for the very high rate of thrombo-embolism or death observed during the first 90 days because patients who underwent warfarin interruption had a mean CHADS\textsubscript{2} score of 1.34 which, if untreated, is associated with an annual risk of stroke of <5%. A third possible explanation is that warfarin interruption is associated with rebound hypercoagulability that increases the risk of thrombo-embolism (‘directly causal’). Warfarin prevents thrombosis by inhibiting synthesis of vitamin K-dependent coagulation proteins, thereby preventing thrombin generation. Withdrawal of
antiocoagulant treatment leads to recovery of normal thrombin generation, as reflected by a rise in previously suppressed blood levels of markers of thrombin generation/activity (e.g. prothrombin fragments F1.2, fibrinopeptide A, and thrombin–antithrombin). Biochemical studies have reported transient elevation of blood markers of thrombin generation/activity to above pre-treatment levels soon after stopping warfarin, a finding that is consistent with rebound hypercoagulability.6,7 However, an impact of a transient rise in blood markers of thrombin generation/activity on risk of clinical events remains unproven.

The observations by Raunsø and colleagues of an increase in thrombo-embolic events after interruption of effective antithrombotic therapy are consistent with several previous reports. In an individual patient (n = 2925) meta-analysis of seven trials of long-term anticoagulant therapy for the prevention of recurrent venous thrombo-embolism, Boutitie and colleagues demonstrated an increased risk of recurrent events during the first 6 months after stopping anticoagulant therapy.8 The ROCKET-AF trial comparing the new factor Xa inhibitor rivaroxaban with warfarin for stroke prevention in 14,264 patients with AF demonstrated an excess of thrombo-embolic events in the rivaroxaban arm when double blind therapy was stopped and patients were transitioned to warfarin.9 The increase in events after stopping rivaroxaban coincided with a delay in achieving therapeutic international normalized ratio (INR) values after initiation of open-label warfarin. A similar phenomenon has been reported after stopping aspirin, clopidogrel, and heparin.10–12 However, in each of these studies it remains unclear whether the increase in events following interruption of treatment was due to rebound hypercoagulability or loss of effective protection against thrombo-embolism, or whether confounding played a role.

What are the implications for clinical practice? The key message for physicians is that interruption of warfarin therapy is both common and a powerful marker of risk of thrombo-embolic events and death. Even though the mechanism of the relationship between drug discontinuation and outcome remains to be clarified, it would seem prudent to avoid unnecessary interruption of warfarin. Bridging anticoagulation with heparin or low molecular heparin for temporary interruptions may mitigate the risk of adverse outcomes, but a benefit of this approach in patients with AF remains unproven.13–15 Reflecting this uncertainty, the current European Society of Cardiology (ESC) treatment guidelines for AF recommend no bridging for temporary interruption of anticoagulation, except in AF patients at particularly elevated risk for stroke (e.g. a history of prior stroke).16 Several large-scale randomized controlled trials evaluating the efficacy and safety of bridging anticoagulation compared with no bridging, and continued compared with interrupted anticoagulation therapy for elective surgical procedures such as pacemaker or defibrillator implantation are due to report in the next few years and should help to clarify these issues.

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