Is there a period of liability with initiation of warfarin in patients with atrial fibrillation?

Hans-Christoph Diener1*, Christopher B. Granger2, and Manesh R. Patel2

1Department of Neurology and Stroke Center, University Hospital Essen, Hufelandstrasse 55, D-45147 Essen, Germany; and 2Duke Clinical Research Institute, Durham, NC, USA

This editorial refers to ‘Initiation of warfarin in patients with atrial fibrillation: early effects on ischaemic strokes’1, by L. Azoulay et al., on page 1881.

Patients with atrial fibrillation (AF) have a high risk of ischaemic stroke. This risk can be dramatically reduced by anticoagulation with vitamin K antagonists (VKAs; e.g. warfarin) or novel anticoagulants (direct thrombin inhibitors or factor Xa inhibitors). Theoretically, warfarin at initiation could lead to a hypercoagulable state with an increased risk of thrombo-embolic events. Azoulay et al. have performed a post-hoc nested-control analysis using the UK Clinical Practice Research Datalink in a cohort of 70 766 patients with AF.1 The hypothesis of an increased early stroke risk after the initiation of warfarin in patients with AF was based on the early effect of warfarin preventing production of the natural anticoagulants protein C and S, and the suspicion that the early labile nature of warfarin’s effect could result in thrombotic events. Azoulay et al. observed a 71% increase of stroke in the first 30 days of warfarin use, while a decreased stroke risk was observed afterwards.

The study of Azoulay et al. highlights some possible important lessons regarding the initiation of warfarin. The authors should be congratulated for exploring this important clinical topic. However, the analysis underscores some of the potential limitations associated with observational analyses from large databases in medicine. Any retrospective observational analysis from administrative databases, despite major statistical efforts to avoid bias, by its nature must be biased. The biggest problem in these kinds of analyses is undetected bias often due to unmeasured confounders.

A careful review identifies some of the possible biases. The observation in the study by Azoulay et al. may be confounded by the clinical decision to anticoagulate. Often the patients at highest risk are clinically identified and treated, leading to an early hazard compared with the control lack of treatment. Although it is possible to partially adjust for this decision to treat, residual physician decision variables are often not fully captured. Additional caveats regarding the case–control study presented include: (i) 21.6% of patients had a CHADS2 score of 0 and therefore oral anticoagulation may not have been clearly indicated; and (ii) not surprisingly; the risk of stroke was increased in AF patients who had suffered a transient ischaemic attack (TIA) or stroke. A median time from diagnosis of AF to warfarin initiation of 30 days is not currently the standard of care in the majority of stroke units and may also present some selection bias.

It should be noted that the current study authors based the hypothesis for the study on the data on the transition phase of rivaroxaban to warfarin or acetylsalicylic acid (ASA) at the end of the ROCKET-AF study. A total of 9248 patients transitioned from study medication with rivaroxaban to open-label therapy (>90% VKA) at the end of the study. A published analysis included events from 3 to 30 days after the last dose of study drug; >90% of study completers transitioned to a VKA or ASA.1 Twenty-two strokes or systemic embolisms were observed in patients receiving rivaroxaban originally and six events in patients treated with warfarin. The explanation of this difference is simple and straightforward: at day 30 after the transition, 81.3% of patients originally on warfarin reached an international normalized ratio (INR) ≥2, whereas only 48.8% of patients originally treated with rivaroxaban reached the therapeutic INR. Additionally, it should be noted that the patients at the end of the randomized trial represent a unique cohort of patients comprised of patients most of whom did not have a stroke during the conduct of the clinical study, have survived well on anticoagulation therapy (either study drug or warfarin), and the comparison is transition from study drug to warfarin compared with continuing warfarin (as evidenced by the INR data). Published data from the discontinuation of both drugs (in contrast to transition at the end of the trial) did not find an increase in clinical events from discontinuation in the rivaroxaban arm.1

In the ARISTOTLE trial, 5723 patients had a transition from apixaban to warfarin at study end. Within the next 30 days, 14 strokes and systemic embolisms were observed.6 In the warfarin group, 5570 patients remained on warfarin and two had strokes. The ENGAGE study had a very sophisticated surveillance method to guard the transition phase from blinded edoxaban to open-label warfarin,5 with frequent INR controls. In this study, no excess of strokes was observed. The last result clearly indicates that the increased stroke risk during the transition from a NOAC (new oral anticoagulant) to warfarin is
driven by the long time interval required to achieve a therapeutic INR and not by prothrombotic properties of warfarin. The early risk of stroke seems to be mitigated with careful and frequent monitoring and transition.

The potentially more relevant question is whether patients in the trials on NOACs had an increased risk of stroke when warfarin was initiated after randomization in warfarin-naive patients. In the ARISTOTLE trial, the stroke rate per 100 patient-years among warfarin-treated patients in the first 30 days was higher in the warfarin-naive (5.41) than the warfarin-experienced (1.42) groups [hazard ratio (HR) 3.8]. The stroke rates were similar in the apixaban treated population regardless of prior warfarin status. In RE-LY, the risk of stroke in the first 30 days was 0.12% for the pooled dabigatran groups and 0.26% for warfarin (odds ratio 2.23, 95% confidence interval 0.81–6.15) in the warfarin-naive population, a pattern not seen in the warfarin-experienced group. In ROCKET-AF, the stroke rate per 100 patient-years in patients treated with warfarin compared with rivaroxaban in the first 30 days after randomization was 2.84 for rivaroxaban and 4.40 for warfarin (HR 1.6) in the warfarin-naive group. In warfarin-experienced patients, the rates were 1.92 for rivaroxaban and 2.86 for warfarin. All these data have been presented as part of the overall trial data, but these findings within the first 30 days specifically are presented here. These data taken together while limited by small numbers and the post-hoc nature of the analysis, argue for two possible mechanisms for the increased stroke rates in patients treated with warfarin de novo: a long delay until therapeutic INR values are reached (NOACs work within the first several hours) and a possible prothrombotic activity of warfarin at treatment initiation. It is also possible that these two phenomena could be linked, such that a variable warfarin effect that often occurs with initiation could enable a modest prothrombotic effect to be clinically manifest. Indeed warfarin-naive patients may in fact be at the highest risk when anticoagulation is started.

A number of studies have investigated the bridging concept in patients with AF and cardio-embolic strokes. These studies used heparin, heparinoids, or low molecular weight heparin compared with aspirin for a short time period before oral anticoagulation was implemented. Indeed these trials showed a decrease in the rate of early recurrent ischaemic stroke that was offset by a significant increase in cerebral haemorrhage. 

In conclusion, warfarin-naive patients with AF might be at increased risk of thrombotic events in the first 30 days after initiation of warfarin. This might be due to an early prothrombotic state induced by warfarin or the long time interval until a therapeutic INR is usually achieved.

**Practical clinical consequences**

Patients with AF and high risk of stroke either with a high CHA2DS2-VASc score or a recent TIA or ischaemic stroke should be treated with an NOAC instead of warfarin to avoid the early risk of thrombotic events possibly associated with the initiation of warfarin treatment.

**Conflict of interest:** H.-C.D. received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from: Abbott, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Corinmun, Covidien, Daichii-Sankyo, D-Pharm, EV3, Fresenius, GlaxoSmithKline, Janssen Cilag, Knoll, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, Thrombogenics, Wyeth, and Yamanouchi. Financial support for research projects was provided by AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis, and Talecris. The Department of Neurology at the University of Duisburg-Essen received research grants from the German Research Council (DFG), German Ministry of Education and Research (BMBF), European Union, NIH, Bertsellsman Foundation, and Heinz-Nixdorf Foundation. H.-C.D. has no ownership interest and does not own stocks of any pharmaceutical or medical device company. C.B.G. has received grants from Bristol-Myers Squibb, AstraZeneca, Pfizer, Boehringer Ingelheim, GlaxoSmithKline, the Medtronic Foundation, Merck, Sanofi-Aventis, Astellas, and The Medicines Company; consulting fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Hoffmann-LaRoche, Novartis, Otsuka Pharmaceutical, Sanofi-Aventis, Lilly, Pfizer, and The Medicines Company; and support for travel from Hoffmann-LaRoche, Novartis, and Pfizer. M.R.P. received research grants from AstraZeneca, NHLBI, AHRQ, Johnson and Johnson PRD, and Maquet; and advisory board and consulting fees from Genzyme, Jansen, and Bayer.

**References**


