Intracerebral Hemorrhage and Warfarin
Perceived Versus Actual Risk

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See related article, pages 2431–2435.

Oral anticoagulation (OAC) reduces risk of thromboembolism and is recommended for a wide range of indications, including deep vein thrombosis, pulmonary embolism, and mechanical heart valves, although the most common reason for OAC use is still atrial fibrillation (AF). For over 60 years, the vitamin K antagonist class of drugs (eg, warfarin) has been the mainstay of OAC, but with the advent of new OACs such as the oral direct thrombin inhibitors and oral Factor Xa inhibitors, the situation is changing.

Despite proven efficacy in prevention of stroke in AF and thromboembolism (versus both aspirin and placebo), warfarin is not always prescribed or taken by patients for a variety of reasons, including its narrow therapeutic range, the need for attendance at anticoagulation clinics, and bleeding risk. However, the most feared complication of OAC remains intracerebral hemorrhage (ICH).

In this issue of Stroke, Huhtakangas and colleagues report the results of their population-based study of incidence of warfarin-associated ICH in Finland. Despite a nearly 4-fold increase in the proportion of warfarin users among the population in the study period (1993 to 2008), the annual incidence and case-fatality of warfarin-associated ICHs decreased. They also observed a decrease in the annual 28-day case-fatality rates among warfarin users, but not among nonusers. One-year survival rate after onset of stroke was 35.2% among warfarin users and 67.9% among nonusers.

The strengths of the study are that ICH was verified by autopsy and that this is a large population-based, prospective cohort of 982 patients with ICH, 182 (18.5%) of whom had warfarin-associated ICH. The authors went to great lengths to rule out structural abnormalities causing the hemorrhage with a control CT done on 58%, CT angiography on 18%, digital subtraction angiography on 18%, MR angiography on 8%, and MRI on 3% of survivors. Also, 60% of patients were on warfarin for AF, which is higher than the observed proportion in other cohort studies of warfarin users. Huhtakangas and colleagues observed similar case fatality rates of primary ICH as other studies from Finland, and so their results are more likely to be generalizable.

Unfortunately, there were very few patients who were on combination therapy, that is, warfarin and 1 antiplatelet drug (9 patients in the cohort) or triple therapy (OAC plus 2 antiplatelet drugs), which has become more common, at least in the short-term, with increasing use of drug-eluting stents in symptomatic coronary artery disease. More recently, improved risk stratification of patients both for risk of bleeding and for risk of stroke and thromboembolism has also led to changes in the way in which OAC is used. In the case of AF, the increasingly elderly population would lead to a higher prevalence of AF, and changes in guidelines mean that OAC is recommended for patients with AF with ≥1 stroke risk factors, leading to more OAC use.

Interestingly, the study by Huhtakangas and colleagues showed that admission international normalized ratio values above the therapeutic range (2.0 to 3.0) decreased through the observation period, suggesting improved control of anticoagulant therapy over time. This is encouraging given the clear relationship between the quality of anticoagulation control (as measured by the time in therapeutic range) and thromboembolism and bleeding events. Recent bleeding risk assessment tools such as the HAS-BLED score (1 point each for: Hypertension [systolic >160 mmHg]; Abnormal renal and liver function; Stroke; Bleeding tendency or predisposition; Labile INR [if on warfarin]; Elderly [age >65]; Drug or alcohol) also includes “labile international normalized ratio” as a risk factor for bleeding among patients with AF.

Novel anticoagulants are changing the therapeutic landscape not just for AF, but for all indications for OAC, and it is hoped that these agents will offer new treatment options in patients either unsuitable or unwilling for initiation of warfarin therapy, particularly because they appear to cause less major bleeding (or ICH) complications. The emerging concept of a “net clinical benefit” can be used to tailor treatment decisions in individual patients by weighing bleeding risk versus risk of stroke and thromboembolism, but the benefit of OAC is likely to far outweigh the risk of ICH in the majority of patients, especially if precursors of ICH can be identified at an earlier stage. Indeed, one recent analysis examining the net clinical benefit balancing the risk of ischemic stroke and intracranial hemorrhage found a neutral or positive net clinical benefit (balancing ischemic stroke vs. intracranial hemorrhage) with oral anticoagulation in patients with a CHADS2 score of ≥0, and a negative net clinical benefit at a CHADS2 score of ≥1, and a negative net clinical benefit at a CHA2DS2-VASc score ≥0 (showing the “truly low risk” status of these patients). Of interest, the net clinical benefit was higher at HAS-BLED scores of ≥3.

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The study by Huhtakangas et al suggests some cause for quiet optimism in that despite marked increase in warfarin use, the annual incidence and case-fatality of warfarin-associated ICHs seem to be decreasing. If we are getting better at using OAC, by either well-controlled warfarin therapy or by the use of new OACs that seem to be associated with lower rates of ICH compared with warfarin, this is good news. After all, the rate of ICH on aspirin may not be significantly different to OAC, especially in the elderly, who stand to gain most from thromboprophylaxis by the use of OAC.13,14

Given the importance of bleeding in patients taking OAC, especially in those with AF, a position document was recently published by the European Society of Cardiology Association and endorsed by the European Society of Cardiology Working Group on Thrombosis. Antithrombotic management of atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing coronary stenting: executive summary—a Consensus Document of the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2010;31:1311–1318.


Disclosures
G.Y.H.L. has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, and Boehringer and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer, and Sanofi.

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