Should oral anticoagulants be restarted after warfarin-associated cerebral haemorrhage in patients with atrial fibrillation?

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Summary
Intracranial haemorrhage (ICH), which affects up to 1% of patients on oral anticoagulation per year, is the most feared and devastating complication of this treatment. After such an event, it is unclear whether anticoagulant therapy should be resumed. Such a decision hinges upon the assessment of the competing risks of haematoma growth or recurrent ICH and thromboembolic events. ICH location and the risk for ischaemic cerebrovascular event seem to be the key factors that lead to risk/benefit balance of restarting anticoagulation after ICH. Patients with lobar haemorrhage or cerebral amyloid angiopathy remain at higher risk for anticoagulant-related ICH recurrence than thromboembolic events and, therefore would be best managed without anticoagulants. Patients with deep hemispheric ICH and a baseline risk of ischemic stroke >6.5% per year, that corresponds to CHADS\textsuperscript{2} ≥ 4 or CHA\textsubscript{2}DS\textsubscript{2}-VASc ≥ 5, may receive net benefit from restarting anticoagulation. To date, a reasonable recommendation regarding time to resumption of anticoagulation therapy would be after 10 weeks. Available data regarding the role of magnetic resonance imaging in assessing the risks of both ICH and warfarin-related ICH do not support the use of this test for excluding anticoagulation in patients with atrial fibrillation.

Keywords
Cerebral haemorrhage, warfarin, anticoagulants, atrial fibrillation

Introduction
Oral anticoagulants are effective for stroke prevention in patients with atrial fibrillation. Intracranial haemorrhage (ICH), which affects up to 0.6-1% of patients per year (1, 2), is the most feared and devastating complication of anticoagulant treatment. In-hospital mortality has been reported to be 40-50%, and at least half of survivors remain severely disabled (3). Once ICH occurs, the decision whether to resume anticoagulation is a dilemma (4-6). Such a decision hinges upon the assessment of the competing risks of haematoma growth or recurrent ICH and thromboembolic events.

Risk of thromboembolic events in patients with atrial fibrillation
For patients with atrial fibrillation, the risk of ischaemic stroke is 2%-5% per year (7, 8). The overall risk of stroke varies widely among patients with atrial fibrillation. Various risk stratification schemes have been developed in attempts to evaluate and quantify individual risk (9). Currently, the most frequently implemented schemes for assessing the risk of stroke in patients with atrial fibrillation are CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc. In CHADS\textsubscript{2}, a cumulative score (range 0–6) is calculated according to the presence of defined risk factors. In the same score, risk factors are given different weightings: two points are assigned for a previous stroke or transient ischaemic attack and one point is assigned for each of the following: age older than 75 years, hypertension, diabetes mellitus and recent cardiac failure. Scores of 0, 1 and ≥2 denote low (1% per year), moderate (1-2.5% per year) and moderate-to-high (>2.5% per year) risk of stroke, respectively (10, 11). In CHA\textsubscript{2}DS\textsubscript{2}-VASc, like CHADS\textsubscript{2}, a cumulative scoring system is used (12). However, the scoring for age is stratified and relatively younger age (≥65 years) is recognised as a risk factor, whereas CHADS\textsubscript{2} only takes into account patients over the age of 75 years. In addition, female gender and vascular disease are included in the evaluation of stroke risk, whereas these risk factors are not included in CHADS\textsubscript{2}. CHA\textsubscript{2}DS\textsubscript{2}-VASc is the score recommended by the European Society of Cardiology (ESC) and the Asia Pacific Heart Rhythm Society (APHRS) (13, 14). Indeed, in patients categorised as "low risk" using a CHADS\textsubscript{2} score=0, the CHA\textsubscript{2}DS\textsubscript{2}-VASc score significantly improves the predictive value of the CHADS\textsubscript{2} score, so that a CHA2DS2-VASc score=0 could clearly identifies "truly low risk" subjects (15).
Risk of haemorrhagic events in patients with atrial fibrillation

Several clinical prediction rules have been proposed for the assessment of the risk for bleeding during anticoagulant treatment for atrial fibrillation. These risk scores are based on the combination of treatment- and person-associated factors and may help physician to evaluate the individual risk/benefit ratio of antithrombotic therapy (16). Friberg et al. (2), reported that the ability for predicting ICH and major bleeding with both bleeding risk schemes, HAEMORRHAGES and HAS-BLED, were similar (17, 18) but HAS-BLED score has the advantage of simplicity (2). To obtain a patient’s HAS-BLED score, one point is added for the presence of each of the following: hypertension, abnormal renal function, abnormal liver function, stroke, bleeding history or predisposition, labile international normalised ratio (INR), age older than 65 years, drug use and alcohol use. HAS-BLED is closely related to haemorrhagic risk and patients with a score ≥3 are considered at high risk (19).

Olesen et al. studied the efficacy and safety of warfarin and aspirin in patients with non-valvular atrial fibrillation, with separate analysis according to predicted thromboembolic and bleeding risk using CHADS2, CHA2DS2-VASc and HAS-BLED scores (20). The risk of bleeding was increased with warfarin treatment but the net clinical benefit (ischaemic stroke vs ICH) was clearly positive in favour of patients with increased risk of stroke/thromboembolism.

Location of cerebral haemorrhage and risk of re-bleeding

Primary haemorrhages are those that are associated with chronic arterial hypertension or amyloid angiopathy. Chronic hypertension usually results in deep-seated or subcortical haemorrhages called deep haemorrhages (Figure 1), located in the basal ganglia, thalamus, pons or the cerebellum. These haemorrhages are attributed to long-standing small vessel disease due to fibro-hyalinosis. Many of the superficial haemorrhages, called lobar haemorrhages (Figure 2), are generally associated with cerebral amyloid angiopathy, an extensive deposition of β-amyloid within the walls of small vessels, especially in the elderly (21). Lobar haemorrhages are generally located in the frontal, parietal, temporal or occipital lobes. An adequate neuroradiological workup for secondary causes is always warranted in patients with lobar haemorrhages. Currently available imaging techniques are able to show a number of structural lesions, including cavernomas. Specifically, on Gradient-Echo T2 Weighted Magnetic Resonance Imaging (GE-MRI), multiple hypo-intense areas of previous haemorrhages can be shown. These, especially if small (microbleeds), are suggestive of small vessel disease or amyloid angiopathy, depending on their topographic distribution. Multifocal hypo-intense lesions, within the basal ganglia, thalamus, or other deep cerebral structures, are more commonly found in patients with a history of chronic hypertension. Conversely, cortical multifocal hypo-intense lesions on GE-MRI are more commonly observed in patients with amyloid angiopathy.

Patients with lobar location of ICH have a higher probability of re-bleeding compared to those with deep hemispheric bleeding (22). To this regard, Eckman et al. (7) calculated a one-year risk of recurrence of 15% after lobar ICH and 2.1% after deep ICH. Another retrospective review of 207 patients surviving an ICH, reported that the two-year risk of recurrence was 22% after lobar and 4% after deep hemispheric haemorrhage (23).

The risk of re-bleeding in patients with secondary ICH due to vascular malformations, tumour, coagulation disorders, granulomatous angiitis and other vasculitis, drugs (simpaticomimetics), mieloproliferative disease, eclampsya, moyamoya and trauma depends to the underlying cause and to it specific treatment.

Risk of recurrent intracerebral bleeding and anticoagulants in patients with atrial fibrillation

A limited number of observational studies have addressed the resumption of oral anticoagulants after ICH. The Canadian Stroke Network registry on 284 consecutive patients, admitted to 13 different Ontario hospitals with warfarin-associated intracerebral or subarachnoid haemorrhage, reported that the one-year mortality rate in patients who resumed warfarin therapy was not higher than that in
those who did not restart warfarin (48% and 61%, respectively). ICH expansion or re-bleeding was recorded in 15% of patients in both groups (24). Majeed et al. (25) described the outcomes of 234 patients admitted to three hospitals (2 in Sweden and 1 in Canada) with VKA-associated intracerebral, subarachnoid, or subdural haemorrhages. Recurrent ICH occurred in 14% of patients who resumed warfarin therapy and in 8% of those who did not.

The risk for patients who resumed warfarin therapy appears to be a function of the underlying preexisting vascular damage. The risk of recurrent ICH on warfarin has been reported to be 5-fold higher in lobar compared with deep ICHs.

A demonstrated risk factor for the recurrence of lobar ICH is apolipoprotein-E genotype (26) while hypertension is a risk factor for the recurrence of deep and lobar ICHs. Anti-hypertensive treatment decreases the risk of ICH by more than half (27). Therefore, blood pressure control is essential for both lobar and deep ICH survivors.

**Risk/benefit balance of restarting anticoagulation after ICH in patients with atrial fibrillation**

In order to best decide whether to restart warfarin, the risk of re-bleeding as well as the risk of ischaemic stroke in absence of anticoagulation need to be evaluated. Specifically, patients with lobar location of ICH have a higher probability of re-bleeding, compared to those with deep hemispheric bleeding, and only patients with deep hemispheric location should restart warfarin. To this regard, Eckman et al. (7) have shown that in a setting where the risk of ICH recurrence is high, the increased mortality associated with warfarin ICH is in itself sufficient to argue against anticoagulation. This is the case for lobar ICH: for 1,000 patients with lobar haemorrhage, anticoagulation would result in about 31 fewer thromboembolic strokes with a tradeoff of 150 additional ICHs during the first year of treatment. The risks and benefits of anticoagulation have been reported to be more closely balanced when applied to patients with deep hemispheric ICH, where the reported risk of recurrence is substantially lower (28). This latter scenario suggests that anticoagulation is the preferred strategy when the risk of thromboembolic stroke is evaluated to be particularly high. For instance, in 1,000 patients with deep haemorrhage, anticoagulation would result in about 31 fewer thromboembolic strokes with the tradeoff of 19 additional ICHs during the first year of treatment. Eckman et al. (7), have indicated that anticoagulation is preferred when the baseline risk of ischaemic stroke is ≥6.5% per year, which corresponds to CHADS2 ≥ 4 or CHA2DS2-VASc ≥ 5. However, the conclusion of this analysis by Eckman et al. remains highly dependent on the relative risk of recurrent ICH during warfarin treatment. This is because few data are currently available on this topic. In fact, of the data available on resuming oral anticoagulation after ICH, they are solely based upon either expert opinions or non-randomised studies (6). Moreover, all of these studies have included highly selected high-risk patients and have reported non-conclusive and even divergent results (24, 25, 29, 30).

**Cerebral microbleeds**

Microbleeds on brain magnetic resonance imaging (MRI) can predict future risk of symptomatic intracerebral haemorrhage (31). In fact, studies on patients who have had either lobar intracerebral haemorrhage or ischaemic stroke and who have been prospectively followed up, suggest that this is the case, at least after stroke (32, 33). This association between cerebral microbleeds and future symptomatic ICH begs the question of whether this increased risk is high enough to disfavour the administration of anticoagulation for the prevention of thromboembolism in individuals with atrial fibrillation. However, this is not the case for patients with lobar haemorrhage who have a higher risk of anticoagulant-related ICH recurrence with or without microbleeds. Ueno et al. (34) have suggested that the presence of cerebral microbleeds is associated with ICH, independently of increased INR or hypertension in patients with atrial fibrillation-related cardioembolic infarction. Conversely, a European cohort of patients with microbleeds who had cerebral ischaemia, reported a higher risk of developing new ischaemic strokes than ICH (33). Moreover, Janaway et al. (35), quantified haemosiderin deposition and vascular pathology in the putamen of 200 brains donated to the population-representative MRC Cognitive Function and Ageing Study. The Authors reported that greater putamen haemosiderin was significantly associated with putaminal indices of small vessel ischaemia (microinfarcts, p<0.05; arteriolosclerosis, p<0.05; perivascular attenuation, p<0.001) and with lacunes in any brain region (p<0.023). Additionally, they concluded that the MRI-cerebral microbleeds concept should take into account brain iron homeostasis, as well as small vessel ischaemic changes which usually appear in later life, instead of considering microbleeds as only a marker for minor episodes of cerebrovascular extravasation. These data are of clinical relevance, because they suggest that basal ganglia MRI-microbleeds are a surrogate for ischaemic small vessel disease rather than exclusively a haemorrhagic diathesis. For this reason, currently available data on the role of MRI for the risk of ICH and warfarin ICH do not support the use of this test for withholding anticoagulation in patients with atrial fibrillation.

**Optimal timing of resumption of anticoagulants**

The optimal timing for resumption of anticoagulation after ICH has yet to be defined. In the acute phase, the risk of continuous bleeding or re-bleeding, due to resuming anticoagulation, exceeds the risk of thromboembolism when withholding it. In an analysis by Majeed et al. (25), the risks of ICH per day were reported to be 0.18% in patients not receiving warfarin while it was 0.75% in patients on warfarin over the first 35 days from the index event. These risks were 0.44% and 0.20%, respectively, between days 64-217. The risk of ischaemic stroke per day was 0.068% in patients not receiving warfarin and 0.18% in patients not receiving warfarin while it was 0.75% in patients on warfarin over the first 77 days from the index event. These risks were reported to be 0.039% and 0%, respectively,
between the days 78-329. The combined risk of recurrent ICH or ischaemic stroke reached a nadir when warfarin was resumed after approximately 10 to 30 weeks. For this, to date, a reasonable recommendation regarding time to resumption of anticoagulation therapy would be after 10 weeks.

Alternatives to warfarin

In patients having both atrial fibrillation and an unfavorable risk/benefit profile for restarting anticoagulation, antiplatelet therapy should not be considered an alternative to warfarin. Indeed, Olesen et al. reported no clinical benefit of aspirin treatment on the risk of stroke/thromboembolism. The use of a left atrial appendage occlusion has been suggested as another viable alternative. Although all antithrombotic drugs can increase the risk of ICH, this complication has been reported to occur less frequently in patients taking new oral anticoagulants including dabigatran, rivaroxaban and apixaban compared to those taking warfarin (36). These new agents may improve the net clinical benefit. Indeed, when the risk of bleeding and stroke are both high, the new drugs appear to have a greater net clinical benefit than warfarin (37). Due to the reduction of ICH in patients treated with the new anticoagulants compared to warfarin, it could be reasonable to consider these new anticoagulants for restarting anticoagulation in patients who suffered from ICH during warfarin therapy.

Conclusions

In order to best decide whether to restart warfarin, the risk of re-bleeding as well as the risk of ischaemic stroke without anticoagulation need to be evaluated for. We suggest following the key points below:

- Patients with lobar haemorrhage or cerebral amyloid angiopathy remain at higher risk for anticoagulant-related ICH recurrence than thromboembolic events and, therefore would be best managed without anticoagulants.
- Patients with deep hemispheric ICH and a baseline risk of ischaemic stroke >6.5% per year, that corresponds to CHADS2 ≥ 4 or CHA2DS2-VASc ≥ 5, may receive net benefit from restarting anticoagulation. To date, a reasonable recommendation regarding time to resumption of anticoagulation therapy would be after 10 weeks.
- Available data regarding the role of MRI on the risks of both ICH and warfarin-related ICH do not support the use of this test for excluding anticoagulation in patients with atrial fibrillation.
- In patients having both atrial fibrillation and an unfavourable risk/benefit profile for restarting anticoagulation, antiplatelet therapy should not be considered as a valid alternative.
- Due to the reduction of ICH in patients treated with the new anticoagulants compared to warfarin, it could be reasonable to consider these new anticoagulants for restarting anticoagulation in patients who suffered from ICH during warfarin therapy.

Conflicts of interest

Dr. Agnelli reports personal fees from Boehringer Ingelheim, Sanofi, Daiichi-Sankyo, and Bayer Healthcare outside the submitted work. Dr. Paciaroni reports personal fees from Boehringer Ingelheim, Sanofi, and Bayer Healthcare outside the submitted work.

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