Managing Risk After Intracerebral Hemorrhage in Concomitant Atrial Fibrillation and Cerebral Amyloid Angiopathy

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Case Description
A 77-year-old right-handed functionally independent man presented after waking with a right-sided frontal headache, associated with 3 episodes of vomiting. His headache progressed during the following 20 minutes, prompting presentation to the Emergency Department. He reported an unsteady gait but no focal weakness or sensory disturbance. He was known to be in atrial fibrillation (AF), for which he was anticoagulated with warfarin. His other comorbidities included a previous pulmonary embolus, hypertension, and benign prostatic hypertrophy.

On examination, there was no focal neurological deficit, and his Glasgow Coma Scale score was 15. In view of his severe headache while therapeutically anticoagulated, he was investigated with an urgent computed tomography scan of his head. This demonstrated a 58 by 37 mm right temporal lobe hemorrhage (Figure 1). His international normalized ratio on admission was 2.13, which was corrected with vitamin K and prothrombin complex. The hemorrhage was managed conservatively with blood pressure control, initially requiring a labetolol infusion followed by oral lisinopril and doxazosin.

He remained neurologically stable throughout his admission. He was discharged 14 days later with a minor deficit in short-term memory but no other focal neurological deficit. His modified Rankin score was 1. In view of the acute hemorrhage, anticoagulation was withheld because further hemorrhagic risk was deemed to outweigh antithrombotic benefit.

Magnetic resonance imaging was performed 1 month after discharge and demonstrated evolution of the hematoma (Figure 2A and 2B). Gradient echo images also demonstrated a small right parietal lobe hemorrhage (Figure 2C). These findings were suggestive of cerebral amyloid angiopathy (CAA) as the cause of his presenting right temporal lobe hemorrhage.

In view of the findings suggestive of CAA, it was felt that the risks of recurrent bleeding with long-term anticoagulation outweighed the benefits of stroke risk reduction from AF-related thromboembolism. He was therefore referred to the regional cardiothoracic center for consideration for a left atrial appendage closure.

Discussion
This case highlights the management challenge in balancing the ischemic stroke risk from AF against the recurrent hemorrhagic stroke risk from CAA after an intracerebral hemorrhage. The prevalence of CAA increases with age and was identified in 57% of patients aged >59 years in 1 autopsy study. Consequently, a large cohort in the general population will have concomitant AF and CAA, although the latter may be undetected unless gradient echo magnetic resonance imaging is performed. CAA is a common cause of intracerebral hemorrhage in patients aged >60 years, and it has been reported to underlie 12% to 20% of intracerebral hemorrhages in 2 large retrospective studies.

In contrast to intracerebral hemorrhages of hypertensive pathogenesis, which tend to occur in subcortical areas, hemorrhages secondary to CAA tend to occur in the cerebral cortex and display a lobar pattern. Histopathologic confirmation is required to make a definitive diagnosis of CAA, but the presence of lobar intracerebral hemorrhage on noncontrast computed tomography, or multiple cortical microhemorrhages on gradient echo magnetic resonance imaging in patients aged ≥55 years, is highly suggestive of CAA. The differential diagnosis of CAA can be further supported by the modified Boston criteria, which incorporates criteria including age, neuroimaging findings, and postmortem histology to offer a high sensitivity and specificity in the diagnosis of CAA.

The risk of cardioembolic stroke from AF is well recognized and is influenced by the presence of comorbidities, such as congestive cardiac failure, diabetes mellitus, previous stroke, and hypertension. The attributable risk of stroke for individuals with AF increases with age, rising from 1.5% for patients in their sixth decade to 23.5% in the ninth decade. In the absence of contraindications, anticoagulation with warfarin or a direct oral anticoagulant (either a direct thrombin inhibitor or a factor Xa inhibitor) is used to reduce the risk of cardioembolic ischemic stroke secondary to AF and is recommended in men with a CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes mellitus, stroke [doubled], vascular disease, age, and sex category [female]) score ≥1 and in women with a CHA2DS2-VASc score ≥2. In patients who have had an intracerebral hemorrhage with coexisting AF and CAA, the risk of ischemic stroke without...
anticoagulation must be carefully considered against the risks of recurrent intracerebral hemorrhage exacerbated by anticoagulation. A decision-analysis model for the use of warfarin in AF in the setting of a previous intracerebral hemorrhage suggests that the risks associated with warfarin outweigh the benefits, particularly when comparing lobar to deep intracerebral hemorrhage, with the withholding of warfarin resulting in an increase in quality-adjusted life expectancy by 1.9 and 0.3 quality-adjusted life years, respectively. The estimated risk of recurrent intracerebral hemorrhage in CAA varies, with a review by Poon et al estimating that the risk of recurrent hemorrhage for lobar hemorrhages after 1 year to be between 2.5 to 28.2%, compared with a lower risk of 1.3 to 10.6% in nonlobar hemorrhage. There are currently no guidelines on anticoagulant use in the setting of AF after intracerebral hemorrhage secondary to concomitant CAA. Consequently, management of such patients remains a challenge. The HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) score is not validated for use in CAA so risk stratification must be based on the aforementioned recurrence rates balanced against the CHA2DS2-VASc score. In the case of our patient, his CHA2DS2-VASc score was 5, giving him an adjusted ischemic stroke risk of 6.7% per annum, whereas the pooled results from Poon et al would suggest that the rate of lobar hemorrhage recurrence for those not taking anticoagulation exceeds this ischemic stroke risk even before the additional hemorrhagic risk from anticoagulation is considered.

The recurrence rate of intracerebral hemorrhage in CAA secondary to antiplatelet use is also unclear, largely because of randomized clinical trials often excluding patients with previous intracerebral hemorrhage in trials of antithrombotics. Longitudinal observational cohort studies (typically single-center studies of small numbers) have shown conflicting results for recurrence of lobar hemorrhage for individuals taking antiplatelet medication. This, coupled with the lack of efficacy for aspirin-preventing stroke in patients with AF, casts uncertainty on the role of antithrombotic agents in concomitant AF and CAA. Further research and meta-analysis into this area are required, and a Cochrane Library review is currently in progress.

In view of the inherent bleeding risk associated with anticoagulation in AF, there has been much interest in nonpharmacological methods for reducing thromboembolic stroke risk. The left atrial appendage has been shown to be the source of thromboemboli in 90% of patients with nonvalvular AF, and excluding the left atrial appendage from the systemic circulation has been investigated to reduce the risk of cardioembolism. Percutaneously implanted closure devices can be used to achieve this, potentially offering an avenue to reduce the risk of thromboembolism secondary to AF, while avoiding the risks of anticoagulation-associated intracerebral hemorrhage. Left atrial appendage closure was shown to be at least noninferior to anticoagulation with a relative risk of stroke, cardiovascular death, and systemic embolization of 0.62 (95% confidence interval,
0.35–1.25) for the intervention versus anticoagulation group. It should be noted that in this study, patients remained on warfarin until closure of the left atrial appendage was confirmed on transoesophageal echocardiogram, and the safety in patients in whom anticoagulation is contraindicated is yet to be fully determined. More recently, the procedure itself has been shown to be feasible and safe in individuals with concomitant AF and previous intracerebral hemorrhage who received periprocedural heparin, although such studies did not discriminate hemorrhages by pathogenesis. A further small study has suggested that left atrial appendage closure can be performed safely and effectively with antithrombotic agent cover rather than anticoagulation, but the safety of antithrombotic agents in CAA also remains uncertain. Superiority of either left atrial appendage closure or long-term anticoagulation requires further study, although it is difficult to demonstrate because of low event rates in each treatment arm. Nevertheless, because the facility for left atrial appendage closure becomes increasingly available, it may provide a safe alternative strategy for stroke risk reduction for patients with AF complicated with other bleeding risks.

Balancing the risk of ischemic stroke and hemorrhagic stroke in patients with coexisting AF and CAA remains a challenging area and requires careful consideration on a case-by-case basis. Guideline development requires a greater understanding of the safety of anticoagulant and antithrombotic drugs in these patients and of the safety of left atrial appendage exclusion procedures without the concomitant use of these agents. Future research and clinical management must consider the underlying pathogenesis of the hemorrhage for risk prediction to guide treatment.

**TAKE-HOME POINTS**

- Cerebral amyloid angiopathy is difficult to diagnose definitively but may be suspected based on imaging findings of lobar intracerebral hemorrhage on non-contrast computed tomography or microhemorrhages on gradient echo magnetic resonance imaging.
- There is a high risk of recurrent hemorrhage in patients with intracerebral hemorrhage secondary to cerebral amyloid angiopathy, above that expected with nonlobar hemorrhages.
- Anticoagulant and antithrombotic agents should be avoided in the setting of cerebral amyloid angiopathy unless the risk of ischemic stroke outweighs the high risk of hemorrhagic stroke.
- Left atrial appendage closure may provide a safe alternative for reducing the risk of ischemic stroke in atrial fibrillation for individuals in whom anticoagulation is contraindicated.

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None.

**References**


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