Comorbid Atrial Fibrillation in Cerebral Amyloid Angiopathy-related Intracerebral Hemorrhage: Between a Rock and a Hard Place

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Atrial fibrillation (AF) and intracerebral hemorrhage (ICH), including cerebral amyloid angiopathy (CAA)-related ICH, are age-related conditions that additionally share hypertension as a common risk factor. A Spanish population-based study reported a 50% increase in the prevalence of AF in ICH patients between 2003 (10.5%) and 2012 (15.5%).[1] The prevalence of AF and ICH, and their ensuing comorbidity, are expected to continue increasing with global aging demographics.

In this issue of the *Journal of Stroke and Cerebrovascular Diseases*, Kaiser et al, report a ~26% prevalence of AF in 74 patients with CAA-related ICH (mean age 71, 57% female) admitted to a single center (University of Regensburg Hospital) neurosurgical ward between 2002 and 2016. Some misclassification of ICH subtype is likely present in their cohort, as 20% of probable CAA (without supporting pathology) patients and 80% of possible CAA patients did not have MRI available to confidently exclude deep/brainstem hemorrhagic lesions or alternate causes, and 14 cases classified as CAA-related ICH had concurrent deep hemorrhagic lesions (microbleeds) on MRI, which would prohibit a diagnosis of possible/probable CAA according to the modified Boston Criteria.[2] Among patients with a diagnosis of probable CAA supported by pathology however, the reported prevalence of AF was even greater (33%).

In their discussion, the authors suggest the intriguing possibility of a direct biological link between brain derived β-amyloid and AF to account for the high prevalence of AF in CAA-related ICH. Although this is a novel hypothesis in need of further exploration, there has yet to be any compelling data to suggest that the high prevalence of AF in CAA-related ICH is independent of shared vascular risk factors, or that AF is more common in CAA-related ICH relative to ICH resulting from hypertensive arteriopathy.

Kaiser et al's timely manuscript highlight a growing challenging clinical dilemma regarding optimal stroke prevention in ICH patients with competing thromboembolic/occlusive diseases that indicate antithrombotic therapy. CAA-related ICH has baseline recurrence rate of ~7%/year.[3] In clinical practice, about 25% of CAA-ICH patients with AF receive resumption of oral anticoagulation after the index ICH. The net benefit analysis of anticoagulant therapy requires balancing the established 67% relative risk reduction in AF-related ischemic strokes with anticoagulation, against the potential for increasing the risk of recurrent CAA-related ICH. The potential for larger recurrent ICH volumes and worse clinical outcomes, and conversely smaller breakthrough infarcts, while on anticoagulation need to additionally be considered. As prior ICH was an exclusion criterion from all randomized trials investigating the benefit of anticoagulation or left atrial appendage closure in AF patients, current guidelines do not provide firm recommendations.

Historically, the prevalent dogma has been that CAA-related ICH contraindicates further use of anticoagulation.[4] However, the significant greater safety profiles of direct oral anticoagulants (DOAC), which halve the risk of incident ICH compared to warfarin—with absolute rates of ICH that are similar to aspirin—without compromising efficacy, and recent observational data have begun to challenge this notion.[5]

A recent survey of academic stroke neurologists, neurosurgeons and thrombosis experts demonstrated broad community equipoise on the matter, with two out of three and one out of three of respondents indicating that they would restart anticoagulation after lobar and CAA-related ICH, respectively.[6] Individual-level pooled analysis of three observational cohorts reported a ~70% RR in 1-year mortality and ~3-fold increased likelihood of a

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Table 1. *Ongoing randomized controlled trials investigating optimal stroke prevention in AF patients following intracranial hemorrhage*

Trial; principal investigator	Population	Intervention	Target sample	Status
Antithrombotic therapy				
APACHE-AF; Karin Klijn NCT02565693	Atrial fibrillation and ICH	Apixaban vs. no antithrombotic therapy/antiplatelet monotherapy (open-label)	100	Recruiting
NASPAF-ICH; Ashkan Shoamanesh NCT02998905	Atrial fibrillation and ICH	Any DOAC vs. aspirin (open-label)	100	Enrollment completed/ stopped at 30 participants
SoSTART; Rustam Al-Shahi Salman NCT03153150	Atrial fibrillation and intracranial hemorrhage	Any anticoagulant vs. no antithrombotic therapy/antiplatelet monotherapy (open-label)	190	Recruiting
STATICH; Eivind Berge NCT03186729	Thrombo-occlusive disease indicating antithrombotic therapy and ICH	Any antithrombotic therapy vs. no antithrombotic therapy/antiplatelet monotherapy (open-label)	500	Recruiting
PRESTIGE AF; Roland Veltkamp NCT03996772	Atrial fibrillation and ICH	Any DOAC vs. no antithrombotic therapy/antiplatelet monotherapy (open-label)	654	Recruiting
ASPIRE; Kevin Sheth NCT03907046	Atrial fibrillation and ICH	Apixaban vs. aspirin (double-blind)	700	Activating
ENRICH-AF; Ashkan Shoamanesh NCT03950076	Atrial fibrillation and intracranial hemorrhage	Edoxaban vs. standard of care (no antithrombotic therapy/ antiplatelet monotherapy; open-label)	1200	Activating
LAAO				
A3ICH; Charlotte Cordonnier NCT03243175	Atrial fibrillation and ICH	Apixaban vs. no antithrombotic therapy/antiplatelet monotherapy vs. LAAO (open-label)	300	Recruiting
STROKECLOSE; Mårten Rosenqvist NCT02830152	Atrial fibrillation and ICH	LAAO vs. medical therapy (open-label)	750	Recruiting

Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulant; ICH, intracerebral hemorrhage; LAAO, left atrial appendage occlusion.

favorable outcome (mRS 0-3) in possible and probable CAA patients who were restarted on anticoagulation (predominantly with warfarin) compared to patients not receiving anticoagulation.[7] These results seemed consistent in patients with multiple lobar microbleeds and/or cortical superficial siderosis on MRI. Although these results challenge our conventional notions regarding avoidance of anticoagulation (particularly with warfarin) following CAA-related ICH, the likelihood of confounding by indication limits their interpretation and mandates randomized trials to guide clinical decision-making.

Toward this aim, the RESTART trial recently reported a 35% (P = .025) relative risk reduction in the composite (secondary) outcome of non-fatal myocardial infarction, non-fatal stroke and vascular death in spontaneous ICH patients with concomitant thrombo-embolic/occlusive diseases who were randomized to antiplatelet therapy (either aspirin, clopidogrel, and/or dipyridamole) compared to no antithrombotic therapy, without potential for a meaningful increase in the primary outcome of recurrent ICH (aHR 0.51 [95% CI 0.25-1.03], P = .06).[8] Specific to CAA, there was no effect modification for the primary outcome of recurrent ICH in RESTART participants who had either index lobar ICH location, presence of cortical superficial siderosis or strictly lobar microbleeds on MRI.[9] ICH patients with AF were however not the focus of RESTART, and several randomized controlled trials investigating optimal stroke prevention, with either DOACs and/or left atrial appendage closure, in ICH survivors with AF are currently underway (Table 1). Based on the totality of current evidence, the enrollment of CAA-related ICH patients into these trials is justified and essential to ultimately understanding how best to optimize the individualized care of this vulnerable comorbid population.

In the interim, while we await more definitive guidance from the completion of ongoing trials, Kaiser et al's results suggest that stroke physicians will be frequently placed "between a rock and a hard place" surrounding

the uncertainty of optimal stroke prevention in the prevalent proportion of CAA-related ICH patients who have comorbid AF.

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