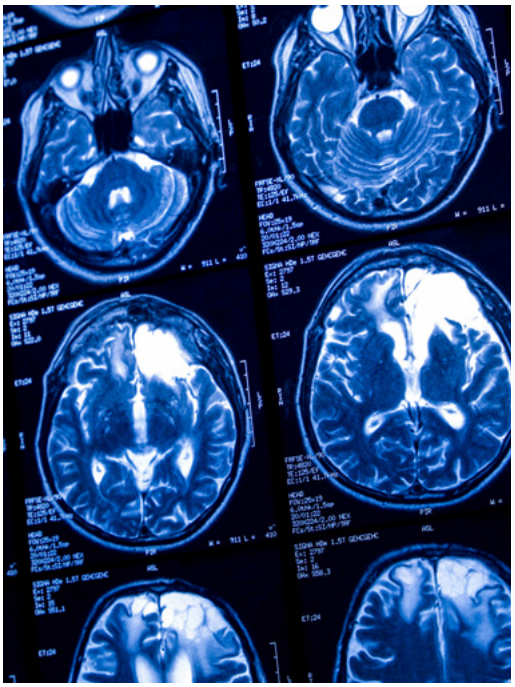

Anticoagulation in the context of post-intracerebral haemorrhage: A narrative review

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Background
Recommencement of oral anticoagulation (OAC) for patients post-intracerebral haemorrhage (ICH) remains a challenging decision for clinicians. High-quality evidence to assist with this decision is lacking and current guidelines primarily focus on balancing thromboembolic and bleeding risk.

Objective
This study evaluated the literature and current guidelines for recommencement of OAC in patients who have experienced an incident ICH.

Discussion
Patients with recurrent ICH while on anticoagulation therapy have associated poor outcomes. However, predicting which patients will experience recurrent ICH with OAC resumption remains challenging, and failure to resume OAC carries risks of thromboembolic events. Current data suggest that it is reasonable to resume OAC in many patients post-ICH, depending on careful consideration of individual risk factors for haemorrhagic and thromboembolic events. The application of existing risk stratification tools for thromboembolism and haemorrhage, and radiological biomarkers such as cerebral microbleeds, might also assist in decision making.

THE RISK OF STROKE associated with atrial fibrillation (AF) is 1.5% at age 50–59 years, increasing to 23.5% by age 80–89 years.[1] Oral anticoagulation (OAC), with warfarin or direct oral anticoagulants (DOACs), is highly effective at reducing risk of embolic stroke in the presence of AF by approximately two-thirds, and this is supported by multiple randomised controlled trials and Class I guidelines.[2,3]

The incidence of intracerebral haemorrhage (ICH) and other haemorrhages while on OAC is comparatively low (0.8% for warfarin, and <0.3% for DOACs),[4] but is important to consider when commencing anticoagulation medication for the first time.

Patients with ICH while on OAC have high morbidity and mortality, with adverse effects usually more severe compared to patients with spontaneous ICH who are not on OAC.[3] The decision when or if to resume OAC after ICH is challenging for clinicians and patients because of a lack of high-quality evidence. Carefully balancing risks of thromboembolism and bleeding, especially recurrent ICH, is the primary concern.[2]

Background

Warfarin has undoubted efficacy in stroke prevention in patients with AF, with evidence spanning >30 years.[5] Meta-analysis of six placebo-controlled studies (N=2900) demonstrated a significantly reduced risk of stroke for patients by 64% (95% CI: 49–74%) versus placebo in patients with AF.[6] However, the rate of ICH averaged 0.3% per year versus 0.1% for placebo. The relative risk for major extracranial haemorrhage was 2.4 (95% CI: 1.2–4.6; absolute risk reduction [ARR] 0.3% per year).

In recent years, DOACs have superseded use of warfarin in many patients, with a 2014 meta-analysis of trials involving four DOACs demonstrating superiority compared to warfarin, with reductions of 19% for stroke and systemic embolism (risk reduction [RR] 0.81, 95% CI: 0.73–0.91; P<0.0001), 10% for all-cause mortality (RR 0.90, 95% CI: 0.85–0.95; P=0.0003) and 52% for ICH (RR 0.48, 95% CI: 0.39–0.59; P<0.0001). Only gastrointestinal bleeds were higher in patients treated with DOACs compared with warfarin (RR 1.25, 95% CI: 1.01–1.55; P=0.04).[7]

Apixaban demonstrated superiority to warfarin in preventing stroke or systemic embolism, causing less bleeding, with lower mortality, in patients with AF.[4] The rates of primary outcome (ischaemic or haemorrhagic stroke or systemic embolism) were 1.27% per year and 1.60% per year in apixaban and warfarin groups, respectively (HR for apixaban: 0.79 [95% CI: 0.66–0.95]).

Rivaroxaban demonstrated non-inferiority to warfarin for prevention of stroke or systemic embolism,[8] with rates of primary outcome being 1.7% and 2.2% per year in the rivaroxaban and warfarin groups, respectively. Bleeding rate was 3.4% for the

warfarin group and 3.6% for the rivaroxaban group. The ICH rate was 0.7% and 0.5% for the warfarin and rivaroxaban groups, respectively.

In the randomised evaluation of long-term anticoagulation therapy (RE-LY) study, dabigatran (110 mg twice daily [BD] dose) reduced rates of stroke or systemic embolism (1.53% per year) similarly to warfarin (1.69% per year, RR with dabigatran: 0.91, 95% CI: 0.74–1.11], $P<0.001$ for non-inferiority), with lower rates of major haemorrhage.[9] A higher dose of dabigatran (150 mg BD) further lowered rates of stroke and systemic embolism (1.11% per year; RR 0.66, 95% CI: 0.53–0.82, $P<0.001$ for superiority), but there were similar rates of major haemorrhage.[9]

Current guidelines and evidence

Current guidelines for starting or restarting OAC in the context of recent ischaemic stroke, but not ICH, are largely based on expert consensus[10] and the '1–3–6–12' rule recommended by the European Society of Cardiology (ESC) in 2013, with similar variations used in American and Australian Stroke Foundation (SF) guidelines. These do not specifically mention infarct size, tending to use the National Institutes of Health Stroke Scale (NIHSS) as a proxy for severity and bleeding risk, along with subjective assessment by the physician.[10] SF guidelines recommend anticoagulation one day after transient ischaemic attack (TIA), three days after a small stroke, five to seven days after a moderate stroke and 10–14 days after a severe/large stroke.

New trial evidence in 2023 has supported this approach, or an even earlier re-commencement of anticoagulation medication after ischaemic stroke. The ELAN trial randomly assigned participants to receive early anticoagulation (within 48 hours of a minor or moderate stroke, day six or seven after a major stroke) or later anticoagulation (day three or four after a minor stroke, day six or seven after a moderate stroke and day 12–14 after a major stroke). Recurrent ischaemic stroke occurred in 1.4% of the early-treatment group and in 2.5% of the later-treatment group (OR 0.57; 95% CI: 0.29–1.07) by 30 days; and in 1.9% and 3.1%, respectively, by 90 days (OR 0.60; 95% CI: 0.33–1.06). Symptomatic ICH occurred in only two participants (0.2%) in both groups by 30 days.[11]

Guidelines and high-quality evidence for restarting OAC after ICH are more lacking, and again, mostly based on consensus. The optimal timing for resumption of OAC after ICH is uncertain without randomised trial data to guide the decision. Although DOACs have a lower associated risk of ICH than warfarin, their usefulness as alternatives after ICH is undetermined.[12]

Clinical features associated with recurrent ICH include Asian ethnicity, ICH history, cerebral microbleeds, amyloid angiopathy, arteriovenous malformation, cerebral aneurysm and lacunar infarcts.[3]

Observational studies of anticoagulant-related ICH have found low rates of cardioembolic events when patients are not receiving anticoagulation, and low rates of recurrent ICH when anticoagulation therapy resumed, but results are limited by small sample sizes and short durations of follow-up.[13] Among 141 patients who discontinued warfarin, only three suffered ischaemic events within 30 days compared to none who restarted. In the 35 patients who restarted OAC during hospitilisation, with a median of 10 days (range 0–30) off OAC, there was no recurrence of bleeding. This study concluded that brief (one- to two-week) discontinuation of OAC was relatively safe. It also demonstrated that ICH occurring with anticoagulation therapy resulted in a higher mortality rate of 43%.

A retrospective, multicentre study of 2869 patients with ICH, of which 234 were warfarin-related and with 59 resuming warfarin, found recurrent ICH risk was highest with early OAC resumption in the first 35 days, exceeding the risk of thromboembolism compared to when resumption of warfarin was delayed.[14] Recurrent ICH risk was 0.75% per day within the first 35 days if anticoagulation was restarted, compared to 0.18% if not (HR 4.13). The observed rate of ischaemic stroke was low in the first 77 days whether OAC was restarted (0%) or not (0.068% per day; HR 0). A time period of 10–30 weeks was recommended as optimal for OAC resumption, when the combined risk of recurrent ICH or ischaemic stroke approached a nadir.

A 2018 meta-analysis of 12 observational studies with 3431 patients showed that restarting anticoagulation after ICH significantly reduced thromboembolic events (RR 0.31, 95% CI: 0.23–0.42, $P<0.001$) with no increase in mortality or recurrent ICH.[15]

A 2023 Cochrane review concluded that the benefit or harms associated with antithrombotic treatment post ICH are uncertain.[16] Long-term OAC for AF post ICH was found to probably reduce the risk of major adverse cardiovascular events, but also likely to increase the risk of ICH, resulting in little or no difference in the death rate and minimal effect on independent function. It suggested further randomised controlled trials be conducted to resolve uncertainties, but made no specific recommendations for clinical practice.

Currently, Australian and New Zealand Clinical Guidelines for Stroke Management make no recommendation on commencement or recommencement of anticoagulation medication post ICH.[17] The American Heart Association and American Stroke Association guidelines recommend starting oral anticoagulation medication four days after ischaemic stroke and 14 days after ischaemic stroke with haemorrhagic transformation.[18]

European Society of Cardiology (ESC) 2020 guidelines on recommencement of OAC after ICH, stated as based on observational data with RCTs ongoing, offer more practical advice.[19] Consideration of non-modifiable risk factors such as age, male sex, Asian ethnicity, amyloid angiopathy and cerebral microbleeds; and optimising modifiable risk factors such as hypertension, smoking, alcohol consumption and concomitant anti-platelet medications is recommended to help weigh risks and benefits.[19] Although not specifying a treatment preference, the ESC guidelines offers three options: (i) recommencing anticoagulation two to four weeks after ICH; (ii) left atrial appendage closure; or (iii) no stroke prevention therapy.[19]

Although not the focus of this paper, re-commencing antiplatelet medication after ICH also appears to be safe, and perhaps even beneficial, with restart or stop anti-thrombotics randomized trial (RESTART) data demonstrating non-significant reductions in both ICH (8.2% versus 9.3%) and major vascular

events (26.8% vs 32.5%). The latter finding in particular is being further studied in the current anti-platelet secondary prevention international randomised study after intracerebral haemorrhage (ASPIRING) trial.[20]

Existing risk assessment tools for thromboembolism recurrence

Although several risk assessment tools have been developed to evaluate risk of thromboembolism, their application to post-ICH settings is more limited.

CHA_2DS_2-VASc score

The congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age, sex category (CHA_2DS_2-VASc) thromboembolism risk stratification score is validated in patients with AF for stroke, transient ischaemic attack and systemic embolism.[21] The apixaban versus no anticoagulation after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation (APACHE-AF) trial evaluated the CHA_2DS_2-VASc score in 101 AF patients with history of ICH and CHA_2DS_2-VASc of at least two, who survived ICH while on OAC.[22] Patients were randomised to resume or avoid anticoagulation, and followed for a median of 1.9 years, with the primary outcome of non-fatal stroke or vascular death. Overall, four of 50 (8%) patients resuming anticoagulation medication, compared to one of 51 (2%) avoiding medication, sustained ICH (adjusted HR 4.08 (0.45–36.91); P=0.21). There was no difference in the incidence of ischaemic stroke (12% in each group) or major vascular events including death (26% resume vs 25% avoid) between the two groups.

A retrospective cohort study suggested that resumption of anticoagulation medication post-ICH, with a strong indication for anticoagulation based on the CHA_2DS_2-VASc score, reduces risk of ischaemic stroke without increasing recurrent ICH.[23] Most participants had a CHA_2DS_2-VASc score above four. Patients either recommenced or avoided anticoagulation for a median follow-up period of 0.7 and 0.5 years, respectively. Risk of ischaemic stroke was 3.5% for patients who resumed treatment, compared to 4.9% who avoided treatment (adjusted HR 0.61, [95% CI: 0.42–0.89]). Recurrent ICH was similar, with 1.4% of patients resuming treatment and 1.6% avoiding treatment (adjusted HR 1.15 [95% CI: 0.66–2.02]), with a similar risk of major bleeding and all-cause mortality.

Existing risk assessment tools for recurrent intracerebral haemorrhage

HAS-BLED

The hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (age >65 years), drugs/alcohol (HAS-BLED) score is the only tool validated for predicting recurrent ICH following initial spontaneous ICH.[3] The National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand AF guidelines suggest that HAS-BLED might be useful in detecting patients at higher risk of bleeding.[21] Chan et al sought to evaluate HAS-BLED as a prognostic tool for recurrent ICH in a cohort of 434 patients who had initial spontaneous ICH and were not subsequently prescribed antiplatelet medication or OAC. Risk of ICH recurrence increased with HAS-BLED score; a score of one corresponded to a risk of recurrent ICH of 1.37 per 100 patient-years, and a score of three corresponded to a risk of 3.39 per 100 patient-years.[24]

Application of biomarkers to improve existing risk assessment tools

Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for AF after acute ischaemic stroke or transient ischaemic attack (CROMIS-2), an observational cohort study, sought to determine whether cerebral microbleeds (CMB), as a magnetic resonance imaging (MRI) neuroimaging biomarker, could improve predictive ability of clinical risk scores like HAS-BLED for ICH.[25] In total, 1490 participants with AF and recent acute ischaemic stroke or TIA commenced on either warfarin or DOAC, were followed for 24 months with a primary outcome of symptomatic ICH. CMB presence was an independent risk factor for ICH. Compared with HAS-BLED alone (C-index 0.41, 95% CI: 0.29–0.53), models including CMB and HAS-BLED (C-index 0.66, 95% CI: 0.63–0.80) and CMB, diabetes, anticoagulant type and HAS-BLED (C-index 0.74, 95%CI: 0.60–0.88) predicted symptomatic ICH significantly better. However, this clinical and neuroimaging combination has not yet been validated in patients who have survived a previous ICH.

The presence of cerebral amyloid angiopathy, a predictor of ICH and therefore conferring a higher risk of ICH if anticoagulation recommenced, might be diagnosed on MRI by the presence of CMB and cortical superficial siderosis (cSS). CT scan biomarkers are less useful as they might identify the presence of cerebral amyloid angiopathy, but not reliably exclude it.[26]

Conclusion

ICH occurring while a patient is taking anticoagulation medication can result in high morbidity and mortality if it occurs. Deciding if and when to restart OAC in patients post-ICH remains challenging. Most studies, largely observational, demonstrate low rates of rebleeding and ischaemic events, with OAC recommencement recommendations varying from two to four weeks or after 10 weeks. Awareness, and modification if possible, of existing risk factors might mitigate the risk of recurrent bleeding. And use of individualised risk scores such as CHA_2DS_2-VASc and HASBLED, in conjunction with neuro-imaging biomarkers such as cerebral microbleeds, can assist in advising patients of relative risks when making an informed treatment decision.

Key points

- Spontaneous intracerebral bleeding while patients are being treated with anticoagulants carries a high mortality.
- Warfarin and DOAC significantly reduce risk of ischaemic stroke by 64%.
- Incidence of intracerebral haemorrhage while on DOAC varies between 0.5% and 1.6%.
- Most guidelines recommend delayed restarting of anticoagulant treatment after ICH, but recommendations differ on timing.

- Informed decision making about anticoagulant commencement and recommencement requires awareness of potential risks and benefits.

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References

1. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: Population-based estimates. Am J Cardiol 1998;82(8A):2N–9N. doi: 10.1016/S0002-9149(98)00583-9.
2. Kittelson JM, Steg PG, Halperin JL, et al; Antithrombotic Trials Leadership and Steering (ATLAS) Group. Bivariate evaluation of thromboembolism and bleeding in clinical trials of anticoagulants in patients with atrial fibrillation. Thromb Haemost 2016;116(3):544–53.
3. Li YG, Lip GYH. Anticoagulation resumption after intracerebral hemorrhage. Curr Atheroscler Rep 2018;20(7):32. doi: 10.1007/s11883-018-0733-y.
4. Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981–92. doi: 10.1056/NEJMoa1107039.
5. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: A meta-analysis. Ann Intern Med 1999;131(7):492–501. doi: 10.7326/0003-4819-131-7-199910050-00003.
6. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146(12):857–67. doi: 10.7326/0003-4819-146-12-200706190-00007.
7. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. Lancet 2014;383(9921):955–62. doi: 10.1016/S0140-6736(13)62343-0.
8. Patel MR, Mahaffey KW, Garg J, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365(10):883–91. doi: 10.1056/NEJMoa1009638.
9. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139–51. doi: 10.1056/NEJMoa0905561.
10. Seiffge DJ, Werring DJ, Paciaroni M, et al. Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation. Lancet Neurol 2019;18(1):117–26. doi: 10.1016/S1474-4422(18)30356-9.
11. Fischer U, Koga M, Strbian D, et al; ELAN Investigators. Early versus later anticoagulation for stroke with atrial fibrillation. N Engl J Med 2023;388(26):2411–21. doi: 10.1056/NEJMoa2303048.
12. Hemphill JC 3rd, Greenberg SM, Anderson CS, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46(7):2032–60. doi: 10.1161/STR.0000000000000069.
13. Phan TG, Koh M, Wijdicks EF. Safety of discontinuation of anticoagulation in patients with intracranial hemorrhage at high thromboembolic risk. Arch Neurol 2000;57(12):1710–13. doi: 10.1001/archneur.57.12.1710.
14. Majeed A, Kim YK, Roberts RS, Holmström M, Schulman S. Optimal timing of resumption of warfarin after intracranial hemorrhage. Stroke 2010;41(12):2860–66. doi: 10.1161/STROKEAHA.110.593087.
15. Zhou Z, Yu J, Carcel C, et al. Resuming anticoagulants after anticoagulation-associated intracranial haemorrhage: Systematic review and meta-analysis. BMJ Open 2018;8(5):e019672. doi: 10.1136/bmjopen-2017-019672.
16. Cochrane A, Chen C, Stephen J, et al. Antithrombotic treatment after stroke due to intracerebral haemorrhage. Cochrane Database Syst Rev 2023;1(1):CD012144. doi: 10.1002/14651858.CD012144.pub3.
17. Stroke Foundation. Clinical Guidelines for Stroke Management. Stroke Foundation, 2022. Available at https://app.magicapp.org/#/guideline/8L0RME/rec/jNDxWn [Accessed 8 February 2024].
18. Powers WJ, Rabinstein AA, Ackerson T, et al; American Heart Association Stroke Council. 2018 Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49(3):e46–110. doi: 10.1161/STR.0000000000000158.
19. Hindricks G, Potpara T, Dagres N, et al; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42(5):373–498. doi: 10.1093/eurheartj/ehaa612.
20. Al-Shahi Salman R, Dennis MS, Sandercock PAG, et al; RESTART Collaboration. Effects of antiplatelet therapy after stroke caused by intracerebral hemorrhage: Extended follow-up of the RESTART randomized clinical trial. JAMA Neurol 2021;78(10):1179–86. doi:10.1001/jamaneurol.2021.2956.
21. Brieger D, Amerena J, Attia J, et al; NHFA CSANZ Atrial Fibrillation Guideline Working Group. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018. Heart Lung Circ 2018;27(10):1209–66. doi: 10.1016/j.hlc.2018.06.1043.
22. Schreuder FHBM, van Nieuwenhuizen KM, Hofmeijer J, et al; APACHE-AF Trial Investigators. Apixaban versus no anticoagulation after anticoagulation-associated intracerebral haemorrhage in patients with atrial fibrillation in the Netherlands (APACHE-AF): A randomised, open-label, phase 2 trial. Lancet Neurol 2021;20(11):907–16. doi: 10.1016/S1474-4422(21)00298-2.
23. Lin SY, Chang YC, Lin FJ, Tang SC, Dong YH, Wang CC. Post-intracranial hemorrhage antithrombotic therapy in patients with atrial fibrillation. J Am Heart Assoc 2022;11(6):e022849. doi: 10.1161/JAHA.121.022849.
24. Chan KH, Ka-Kit Leung G, Lau KK, et al. Predictive value of the HAS-BLED score for the risk of recurrent intracranial hemorrhage after first spontaneous intracranial hemorrhage. World Neurosurg 2014;82(1-2):e219–23. doi: 10.1016/j.wneu.2013.02.070.
25. Wilson D, Ambler G, Shakeshaft C, et al; CROMIS-2 Collaborators. Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): A multicentre observational cohort study. Lancet Neurol 2018;17(6):539–47. doi: 10.1016/S1474-4422(18)30145-5.
26. Schwarz G, Banerjee G, Hostettler IC, et al. MRI and CT imaging biomarkers of cerebral amyloid angiopathy in lobar intracerebral hemorrhage. Int J Stroke 2023;18(1):85–94. doi: 10.1177/17474930211062478.

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