**Article:**
Nadarajah, R orcid.org/0000-0001-9895-9356 and Gale, CP orcid.org/0000-0003-4732-382X (2021) Outcomes following major bleeding in atrial fibrillation. European Heart Journal - Quality of Care and Clinical Outcomes, 7 (2). pp. 119-120. ISSN 2058-5225

https://doi.org/10.1093/ehjqcco/qcaa096

**Title:** Outcomes following major bleeding in atrial fibrillation

**Authors:** Ramesh Nadarajah[123], Chris P Gale[123]

**Affiliation:**

[1]Leeds Institute for Cardiovascular and Metabolic Medicine, University of Leeds, UK

[2]Leeds Institute of Data Analytics, University of Leeds, UK

[3]Department of Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

**Correspondence:**

Ramesh Nadarajah

British Heart Foundation Clinical Research Fellow

Leeds Institute of Cardiovascular and Metabolic Medicine

University of Leeds

6 Clarendon Way

Leeds, UK

LS2 9DA

Tel +44 (0) 113 343 3241

Email umrna@leeds.ac.uk

Twitter @RameshNadaraja2

**Keywords:**

Atrial Fibrillation; Bleeding; Stroke; Mortality; Oral anticoagulation

**Conflict of Interest:** none declared

Atrial Fibrillation (AF) increases the risk of thromboembolic strokes which are typically a more severe and debilitating phenotype.(1) Oral anticoagulation (OAC) with the vitamin K antagonist warfarin reduces the risk of stroke at the expense of an increased risk of major extracranial haemorrhage and intracranial haemorrhage.(2) International guidelines recommend non-vitamin K antagonist oral anticoagulants (NOACs) in preference to warfarin (excluding patients with mechanical heart valves or moderate-severe mitral stenosis),(3) as they provide a relative reduction of 19% for all stroke or systemic embolism, 51% for haemorrhagic stroke and 52% for intracranial haemorrhage (ICH).(4) However, they are associated with a 25% relative increase in the risk of gastrointestinal bleeding (4) and, whilst major bleeding events in the context of anticoagulation for AF are associated with increased mortality,(5)(6) little is known about long-term outcomes after major bleeding in patients with AF.

In the accompanying paper *Ogawa et al* describe, for patients who have received OAC for stroke prophylaxis, clinical outcomes after a major bleeding event over a median period of follow up of 3.5 years.(7) They report findings for 4,304 patients with AF enrolled since 2011 across 81 primary and secondary care institutions in Kyoto, Japan. In line with other studies, a high proportion were not prescribed OAC and many were prescribed an antiplatelet agent.(8)

As expected, major bleeding was more frequent among those prescribed OAC (2.2 per 100 person-years vs. 1.8 per 100 person-years). Notably, the group with major bleeds were older, more comorbid and had higher baseline thromboembolic ($CHADS_2$ and $CHADS_2VA_2SC$ score) and bleeding (HAS-BLED) risk scores. The cohort who suffered a major bleeding event subsequently had at least a 2-fold higher risk of death, and were nearly 3 times more likely to have stroke or systemic-embolism. Follow-up using electronic case record form collection found that at 5 years the cumulative all-cause mortality following a major bleed approached 60% compared with approximately 20% in the non-major bleed group.

*Ogawa et al* also collected annual prescription information after a major bleeding event. They observed that 84% of patients restarted OAC (higher than previous studies), with 12.8% of patients having been converted from warfarin to NOAC. Notably, patients who re-started OAC were found to have a lower incidence of the composite outcome of mortality, stroke, systemic embolism or recurrence of major bleeding over 5 years versus the patients who did not.(7)

So, how should we approach the use of OAC after a major bleeding event? For patients with AF at high risk of stroke the benefit of OAC is well established.(2, 4) Yet, it is understandable that clinicians may be wary of prescribing OAC for fear of recurrent bleeding, especially if this could prove fatal. The question becomes one of safety - does restarting OAC after a bleed increase the risk of recurrence, and if so, does this increased risk of bleeding outweigh the benefits of thromboembolic prophylaxis? Patients with preceding major bleeding events are under-represented in randomised controlled trials and have left a gap in the evidence base. The vast majority of information has, therefore, been derived from retrospective observational studies which predominantly comprise patients anticoagulated with warfarin.

A meta-analysis of 10 studies, consisting of 5400 patients, found that re-initiation of warfarin after a gastrointestinal bleed was associated with a reduction in thromboembolic events and mortality, but that there was also an increase in recurrent bleeds.(9) One retrospective observational study of 2991 patients compared the recommencement of NOACs versus warfarin for AF after a gastrointestinal bleed. Both warfarin and NOACs were associated with decreased risk of thromboembolism. However, whilst warfarin and rivaroxaban resumption were associated with an increased risk of recurrent gastrointestinal bleeding on time-varying analysis, there was no association with resumption of dabigatran and apixaban and recurrent bleeding.(10)

For ICH, deciding on whether to re-initiate OAC is complicated by the high fatality rate associated with ICH and the shared risk factors between ischaemic stroke and ICH. Retrospective observational data from Germany and Denmark has suggested that re-introduction of OAC (overwhelmingly warfarin) for AF was associated with reduced rates of thromboembolic events and mortality without increased rates of re-bleeding.(11, 12) Conversely, the largest registry study of re-initiation of warfarin in AF, conducted in Taiwan, found an increased risk of ICH and suggested that the net benefit, calculated by numbers needed to treat versus numbers needed to harm, only occurred among patients with $CHADS_2VA_2SC$ score < 6.(6) Nonetheless, a meta-analysis of 12 cohort studies, involving 3431 patients, has supported a long-term survival benefit from OAC resumption without an increase in ICH recurrence.(13) One observational study has compared the use of NOACs versus warfarin after ICH in AF, and showed that use of NOACs were associated with lower (though non-significant) risk of ischaemic stroke and recurrent ICH.(14)

Whilst this study by *Ogawa et al* provides new insights into longer term outcomes after a major bleeding event for OAC, one must be mindful of its limitations. Most importantly, as an observational study, it provides only insights into associations and not causation. Information is not provided for factors such as the severity of major bleeding and ICH subtypes, which may have different associations with outcomes, or influenced clinical decisions to restart OAC. The time in therapeutic range for patients prescribed warfarin is not reported, which could also have bearing upon the safety and efficacy rates.

So where does this leave us? From the current observational evidence it appears that OAC re-initiation after a major bleeding event does not carry a prohibitively high bleeding risk. Even so higher levels of evidence are needed and will only arise from randomised controlled trials such as the on-going APACHE-AF (Apixaban versus Antiplatelet drugs or no antithrombotic drugs after

anticoagulation-associated intraCerebral HaEmorrhage in patients with Atrial Fibrillation) trial.(15) Given the complexities of competing thrombotic and bleeding risks, decisions about recommencing OAC for stroke prophylaxis in AF should be made following multi-disciplinary consultation.(3)

References

1. Lin H-J, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, et al. Stroke severity in atrial fibrillation: the Framingham Study. Stroke. 1996;27(10):1760-4.

2. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Annals of internal medicine. 2007;146(12):857-67.

3. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2020.

4. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, 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. The Lancet. 2014;383(9921):955-62.

5. Staerk L, Lip GY, Olesen JB, Fosbøl EL, Pallisgaard JL, Bonde AN, et al. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. Bmj. 2015;351.

6. Chao T-F, Liu C-J, Liao J-N, Wang K-L, Lin Y-J, Chang S-L, et al. Use of oral anticoagulants for stroke prevention in patients with atrial fibrillation who have a history of intracranial hemorrhage. Circulation. 2016;133(16):1540-7.

7. Ogawa H, An Y, Ishigami K, Ikeda S, Hamatani Y, Fujino A, et al. Long-term clinical outcomes after major bleeding in patients with atrial fibrillation: the Fushimi AF registry. European Heart Journal-Quality of Care and Clinical Outcomes. 2020.

8. Cowan C, Healicon R, Robson I, Long WR, Barrett J, Fay M, et al. The use of anticoagulants in the management of atrial fibrillation among general practices in England. Heart. 2013;99(16):1166-72.

9. Tapaskar N, Pang A, Werner DA, Sengupta N. Resuming Anticoagulation Following Hospitalization for Gastrointestinal Bleeding Is Associated with Reduced Thromboembolic

Events and Improved Mortality: Results from a Systematic Review and Meta-Analysis. Digestive diseases and sciences. 2020.

10. Tapaskar N, Ham SA, Micic D, Sengupta N. Restarting Warfarin versus Direct Oral Anticoagulants after Major Gastrointestinal Bleeding and Associated Outcomes in Atrial Fibrillation: A Cohort Study. Clinical Gastroenterology and Hepatology. 2020.

11. Kuramatsu JB, Gerner ST, Schellinger PD, Glahn J, Endres M, Sobesky J, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. Jama. 2015;313(8):824-36.

12. Nielsen PB, Larsen TB, Skjøth F, Gorst-Rasmussen A, Rasmussen LH, Lip GY. Restarting anticoagulant treatment after intracranial hemorrhage in patients with atrial fibrillation and the impact on recurrent stroke, mortality, and bleeding: a nationwide cohort study. Circulation. 2015;132(6):517-25.

13. Zhou Z, Yu J, Carcel C, Delcourt C, Shan J, Lindley RI, et al. Resuming anticoagulants after anticoagulation-associated intracranial haemorrhage: systematic review and meta-analysis. BMJ open. 2018;8(5).

14. Nielsen PB, Skjøth F, Søgaard M, Kjældgaard JN, Lip GY, Larsen TB. Non–Vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Atrial Fibrillation Patients With Intracerebral Hemorrhage. Stroke. 2019;50(4):939-46.

15. van Nieuwenhuizen KM, van der Worp HB, Algra A, Kappelle LJ, Rinkel GJ, van Gelder IC, et al. Apixaban versus Antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intraCerebral HaEmorrhage in patients with Atrial Fibrillation (APACHE-AF): study protocol for a randomised controlled trial. Trials. 2015;16(1):393.