**Invited Review - Treatment strategies for patients with atrial fibrillation and anticoagulant-associated intracranial haemorrhage: an overview of the pharmacotherapy**

**Abstract**

**Introduction:** Oral anticoagulants (OAC) reduce stroke/systemic embolism and mortality risks in atrial fibrillation (AF). However, there is an inherent bleeding risk with OAC, where intracranial hemorrhage (ICH) is the most feared, disabling and lethal complication of this therapy. Therefore, the optimal management of OAC-associated ICH is not well defined despite multiple suggested strategies.

**Areas covered:** In this review, we describe the severity and risk factors for OAC-associated ICH, and the associated implications for using DOACs in AF patients. We also provide an overview of the management of OAC-associated ICH and treatment reversal strategies, including specific and non-specific reversal agents as well as a comprehensive summary of the evidence about resumption of DOAC and the optimal timing.

**Expert opinion:** In the setting of an ICH, supportive care/measures are needed, and reversal of anticoagulation with specific agents (including administration of vitamin K, prothrombin complex concentrates, idarucizumab and andexanet alfa) should be considered. Most patients will likely benefit from restarting anticoagulation after an ICH and permanently withdrawn of OAC is associated with worse clinical outcomes. Although the timing of OAC resumption is still under debate, reintroduction after 4-8 weeks of the bleeding event may be possible, after a multidisciplinary approach to decision-making.

**Keywords:** atrial fibrillation, oral anticoagulants, vitamin K antagonists, direct oral anticoagulants, intracranial hemorrhage, intracranial bleeding.

1. **Introduction**

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder with a prevalence ≈15% in older than 65 years and ≈1-2% in the overall population (1-3). The risk of stroke and thromboembolism is 5-fold higher in AF and thus an important proportion of patients require oral anticoagulation (OAC) therapy (4-6). This risk of stroke and thromboembolism is estimated by using the CHADS2 and CHA2DS2-VASc scores (7, 8), as recommended in most guidelines.

The use of OACs, including both Vitamin K Antagonists (VKAs) and Direct Oral Anticoagulants (DOACs), has been demonstrated to reduce stroke/systemic embolism and mortality when compared to control or placebo treatments (6, 9). For example, VKAs reduce stroke risk by 64% and mortality risk by 26%, compared to control or placebo treatments (10). The DOACs, which include a direct thrombin inhibitor (dabigatran) and three factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), were non-inferior to warfarin for preventing stroke/systemic embolism in their pivotal clinical trials, but thes rate of intracranial haemorrhage (ICH) in their respective trials ranged from 0.23%/year to 0.49%/year for the DOACs, compared to 0.74%/year to 0.85%/year for warfarin (11-14). Importantly, DOACs have shown a clear benefit over warfarin with regard to lower risks of haemorrhagic stroke and ICH (15-17). Hence, DOAC use has therefore been increasing globally, although some regional differences are evident (18, 19). Nevertheless, OAC underuse, premature discontinuation and non-adherence are common, and independently associated with higher stroke risk and all-cause mortality (20, 21). Important efforts to improve OAC prescription uptake and appropriate use are needed [ref].

Despite the well-known benefits of oral anticoagulation, there is an inherent risk of bleeding with this therapy, irrespective of the anticoagulant type used. However, ICH is rare but severe, and oral anticoagulants related ICHs lead to poorer clinical outcomes and are more disabling and lethal than ICH that is non-related to OACs (22-24).

Given the current lack of high-quality evidence, decision-making on resuming oral anticoagulant after ICH is challenging. In the present review article, we provide an overview of the management of OAC-associated ICH and treatment reversal strategies, including specific and non-specific reversal agents as well as a discussion about the resumption of OAC and the optimal timing for the latter.

1. **Intracranial hemorrhage: Implications, severity and risk factors**

As mentioned above, ICH is the most feared complication in AF patients taking OAC therapy, and could be clinically devastating due to its high mortality (approximately 50% at 30 days) and post-ICH disability The term ‘intracranial haemorrhage’ encompasses bleeding inside different intracranial compartments, including intraparenchymal (or intracerebral), subdural, epidural, and subarachnoid hemorrhages (Figure 1).

Mortality rates after an ICH are highly variable between studies, ranging from 46% to 68% (27). For example, in-hospital mortality is about 20%-30% in anticoagulated AF patients (28, 29). In the overall population or non-anticoagulated patients, ICH has a 30-day mortality ranging from 25% to 52% (30-33). With respect to poor survival rates in ICH, these are worse in those patients taking OAC (34).

Several important risk factors for ICH have been reported. Elderly age is one of the stronger and most commonly reported risk factors (35-37). These patients are usually at higher risk of severe falls, which have also been demonstrated to be associated with higher risk of ICH (38, 39). It is important to note that approximately 30-40% of ICHs in anticoagulated AF patients are traumatic (35, 40). In addition, hypertension (especially if uncontrolled systolic blood pressure) (41, 42), prior stroke/transient ischemic attack, leukoaraiosis, tobacco use, liver impairment, antihypertensive medication noncompliance, history of bleeding and concomitant or prior antiplatelet use (35, 38, 43-45). An increased burden of cerebral microbleeds (CMBs) on brain imaging in patients with AF is related to an increased risk of ICH (46, 47). Although the presence of CMBs is not a contraindication for anticoagulation, an increasing number of CMBs is associated with a higher risk of hemorrhagic complications with the long-term OAC use (48).

As expected, OAC therapy per se increases the risk of ICH but this risk depends on the anticoagulant type. For example, in patients taking VKAs, labile INR or poor anticoagulation quality is associated with raised risk of ICH (49). Most clinical AF guidelines recommend an INR between 2.0 and 3.0 for patients taking VKAs (4, 5, 50); however, an INR between 2.0 and 2.5 may provide the best balance between ischemic stroke and ICH, as well as optimal protection against death (51), although the maintenance of such a narrow range can be very difficult and common practice in some countries is to aim for lower INR target ranges despite the lack of evidence [ref].

On the other hand, all DOACs have demonstrated significantly lower rates for ICH and have a positive net clinical benefit compared with VKAs (15, 16, 52-55), even amongst those with well-managed anticoagulation using VKAs (56). Moreover, DOAC-related ICH is associated with smaller baseline hematoma volume, lesser neurologic deficit and lower risk of in-hospital mortality compared to VKA-related ICH (55, 57-59). In some special populations, DOACs are probably safer than VKAs, for example, in AF patients with a prior history of ICH (60). In elderly patients, DOACs also seem to be a more favorable choice compared with warfarin (61-64), even when using the high doses of DOACs (65). Amongst patients needing concomitant antiplatelet therapy, concomitant DOAC-antiplatelet use is associated with a decreased risk of ICH and other major bleeding, when compared with concomitant VKA-antiplatelet use (66, 67).

In contrast, cirrhotic AF patients have similar risk of ICH when treated with VKAs or DOACs (68). This is also applicable for patients with chronic kidney disease (creatinine clearance or eGFR between 15 and 60 mL/min), in whom DOACs may reduce ICH compared with warfarin (69, 70). Despite the different safety profiles between DOACs in real world practice, there are no head-to-head clinical trials to date (71). Observational data suggest that apixaban is safest, and rivaroxaban is likely worst in terms of safety (19, 72-74).

Some of the aforementioned risk factors have been used to propose risk scores in order to assess the probability or the risk of suffering a major bleeding (of which ICH is the most serious) when on OAC therapy. However, all contemporary bleeding risk scores have modest predictive performance and ICH is not predicted by the most commonly used risk scores (37). The HAS-BLED score has consistently showed the best predictive ability for major bleeding and ICH, and the approach focusing only on modifiable bleeding risk factors alone is an inferior strategy for bleeding risk assessment (75-77). In an independent PCORI systematic review and evidence appraisal, the HAS-BLED score had the best predictive value amongst all scores (78). Of note, stroke and bleeding risks closely track each other and overlap (79) (Figure 2). Thus, patients at high risk of stroke are usually at high risk of bleeding. For this reason CHADS2 and CHA2DS2-VASc have been also tested for estimate the risk of bleeding and ICH but the HAS-BLED score has shown a higher predictive ability (80, 81).

The use of biomarkers to refine the bleeding risk stratification process has also been proposed. Several biomarkers such as NT-proBNP, von Willebrand factor, and more recently GDF-15 has been tested and related to bleeding events in AF patients (82-84). Nevertheless, these biomarkers can be non-specific and can be predictors of diverse adverse events at the same time even in non-AF patients[ref], particularly when biomarkers are investigated in real world patients (85, 86). In addition, the clinical usefulness and predictive ability have not demonstrated to be significantly higher than the clinical factor-based HAS-BLED score (78, 87).

1. **Management of oral anticoagulant-associated intracranial haemorrhage and treatment reversal strategies**

All bleeding complications entail an opportunity to carefully review the correct choice and dosing of the anticoagulant regimen and to evaluate the potential modifiable bleeding risk factors including non-optimally controlled hypertension, labile INR (if on VKA) or erratic dosing, excessive alcohol intake and concomitant antiplatelet therapy, non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids (88). In addition, a specific protocol for managing oral anticoagulant-associated ICH is recommended for all centers (Figure 3). This protocol should detail at least: 1) supportive care and measures, and 2) reversal of anticoagulation.

Information about patients’ prior comorbidities worsening bleeding and subsequent outcome could be very helpful. In addition, the date and time of most recent dose of anticoagulant prior to onset of event is important, as well as the dosing regimen, and other factors influencing plasma concentrations (including co-medication), and other factors influencing haemostasis (such as concomitant use of antiplatelet drugs) (89). Among patients taking DOACs, concurrent use of drugs that inhibit the activity of P-glycoprotein and/or cytochrome P450 3A4, such as antiarrhythmics (e.g., amiodarone, diltiazem, verapamil), antiretrovirals, antifungals and immunosuppressives, antidepressants agents (such as selective serotonin re-uptake inhibitors [SSRIs] and serotonin and noradrenaline re-uptake inhibitors [SNRIs] which are known inhibitors/inducers of CYP3A4 or P-gp) and other medications (e.g.; fluconazole, rifampicin, and phenytoin) is associated with increased risk of major bleeding (88, 90). In relation to antiarrhythmics, which are common drugs in the particular case of AF, some warnings must be noted. For patients concomitantly taking verapamil, amiodarone or quinidine, a dose reduction in dabigatran is needed (91). Caution should also be taking when using these antiarrhythmics drugs concurrently with rivaroxaban and edoxaban and consider a dose adjustment or different DOAC if two or more slight interacting factors are present (88, 92, 93). In addition, dabigatran and rivaroxaban are contraindicated in dronedarone users, and a dose adjustment or different DOAC is need in edoxaban users (88).

Renal function and creatinine clearance is also relevant in DOACs users, and particularly in patients taking dabigatran which is excreted in 80% to 85% by the kidneys. This may increase the plasma concentrations of the drug leading to longer half-lives (88). Finally, there is a high inter-individual variability associated with dabigatran (3 to 7% of bioavailability), so this should borne in mind (94).

* 1. *Initial management of intracranial haemorrhage*

The initial step should focus on classical actions for stopping or at least minimizing the bleeding. This includes proceedings such as mechanical compression, rapid reduction of systolic blood pressure, surgical haemostasis, fluid replacement, the use of prohemostatic agents, blood product transfusion when appropriate; ensure an appropriate diuresis and other haemodynamic support (4, 25, 88, 95). Focusing on achieving an hemodynamic stability aggressive volume resuscitation using intravenous isotonic crystalloids such as 0.9% NaCl or Ringer’s lactate could be beneficial (96), whereas there are not enough data to support the use of antifibrinolytics (e.g. tranexamic acid), or desmopressin(88) (97).

The second step is the reversal of anticoagulation by using specific agents. Different approaches should be taken according to the anticoagulant. Thus, for patients taking VKAs several options exist, including administration of vitamin K, four factor prothrombin complex concentrates (4F-PCCs), and fresh-frozen plasma. Vitamin K can be given orally, subcutaneously, or intravenously, but the administration of 5-10 mg intravenously showed the best results. However, this does not result in immediate correction of coagulopathy, and for patients with major bleeding, the administration of vitamin K must be accompanied by a repletion strategy. Ideally, this is achieved by 4F-PCCs which contain the vitamin K-dependent clotting factors (II, VII, IX and X) and protein C and S. 4F-PCCs are preferred to fresh-frozen plasma since those contain approximately 25 (25 U/mL) the concentration of vitamin K-dependent factors as compared with plasma (1 U/mL) (4, 25, 95). In the particular case of vitamin K related-ICH with an INR ≥1.3, the combination of plasma and PCCs is associated with the lowest case fatality (98). However, this was tested in patients with 3F-PCCs (which is not available worldwide) plus low-dose fresh frozen plasma, and it would be interesting to compared the classic 4F-PCCs with higher-dose fresh frozen plasma group (99).

Similarly, support of haemostasis using other agents such as PCCs can be used to reverse the OAC effect in patients taking DOACs. Administration of activated PCCs may be considered for severe bleeding on DOAC treatment, but there is still limited evidence for efficacy and the appropriate dosage is unclear and thus, they are recommended only if specific antidotes are not available. Majeed et al. showed that the administration of PCCs at a median dose of 2000 IU (IQR 1500-2000 IU) for the management of major bleeding associated with rivaroxaban or apixaban was effective in most cases and associated with a low risk of thromboembolism (100). In a study by Gerner et al, PCC administration was not significantly associated with a reduced rate of hematoma enlargement regardless of PCC dosage given. Indeed, PCC administration had no effect on mortality and functional outcome either at discharge or at 3 months (101). Finally, Arachchillage et al. did not observe differences in the effectiveness or safety (30-day mortality, re-bleeding) when using PCC (median dose of 2000 IU, IQR 1000-4500) for major bleeding events in patients on warfarin, rivaroxaban or apixaban (102). One randomized clinical trial comparing 40 IU/kg versus 25 IU/kg 4F-PCC did not found differences in haematoma volume, mortality and thrombotic events between both PCC dose regimes (103). Similarly, a there were no significant differences in clinically effective haemostasis, adverse events, length of stay, or in-hospital mortality using a fixed-dose or a weight-based dose of 4F-PCC (104).

On the other hand, there is no role for vitamin K supplementation or protamine administration in patients taking DOACs, unless in the context of bleeding under DOACs when vitamin K deficiency is suspected or in case of concomitant treatment with heparin. The use of fresh-frozen plasma is also not considered a useful reversal strategy (4, 88, 95, 105).

In the phase III trials, DOACs have consistently shown less intracranial and life-threatening bleedings rates than warfarin, despite the absence of specific reversal strategies in these studies (11-14). In Even in the absence of a reversal agent, clinical outcomes in AF patients with ICH related to DOACs are not worse than that of AF patients with ICH related to VKAs in whom anticoagulation is reversed. As DOACs use is growing worldwide, the probability of suffering ICH and other major bleeds in AF patients is also increasing and therefore specific reversal agents have been developed.

Idarucizumab is a specific monoclonal antibody antidote that specifically binds dabigatran and rapidly, safely and dose-dependently reverses its effects without over-correction or thrombin generation. In the REVERSE-AD (Reversal of Dabigatran Anticoagulant Effect with Idarucizumab) study, idarucizumab 5 grams was administered intravenously in two bolus doses of 2.5 grams no more than 15 min apart to dabigatran-treated patients with anticoagulation emergencies (either ongoing severe or life-threatening hemorrhage, or emergency procedures on therapy). In this study, the primary endpoint of maximum reversal of the anticoagulant effect of dabigatran within 4 hours was 100% as assessed by dilute thrombin or Ecarin clotting time and was achieved in all patients. Based on these results, idarucizumab was approved in 2015 by the US Food and Drug Administration and the European Medicines Agency (4, 21, 25, 88, 95, 106-110). The full cohort analysis of the REVERSE-AD showed that the median time to the cessation of bleeding was 2.5 hours in patients with uncontrolled bleeding. Treatment with idarucizumab was safe with no significant adverse effects and a 6.3% and 7.4% rate of thrombotic complications (in the group with severe/life-threatening hemorrhage, and emergency procedures on therapy, respectively) (106). However, if thrombolysis is performed after dabigatran reversal in acute ischemic stroke patients, the effectiveness and safety of the antidote could be underestimated.

In May 2018, andexanet alfa, a recombinant protein that acts as a decoy for the direct oral FXa inhibitors, received its first global approval in the USA by the Food and Drug Administration (FDA) for use in patients treated with rivaroxaban and apixaban with life-threatening or uncontrolled bleeding (111). On February 28, 2019, it received a positive opinion for a conditional marketing authorization by the European Medicines Agency (112). The ANNEXA-4 (Andexanet Alfa in Patients Receiving a FXa Inhibitor Who Have Acute Major Bleeding) study included patients with major/life-threatening bleeding who received apixaban, rivaroxaban, edoxaban or enoxaparin were included, unless any of the following exclusion criteria were met: scheduled surgery in less than 12 hours; Glasgow coma score <7; intracerebral hematoma >60 cc as assessed by CT or MRI; visible, musculoskeletal or intra-articular bleeding; expected survival of less than 1 month; recent history of a thrombotic event; severe sepsis or septic shock; pregnant or a lactating female; received VKA, dabigatran, PCC or recombinant factor VIIa (rfVIIa), whole blood, plasma fractions within 7 days of screening; treated with other investigational drugs <30 days before; planned administration of PCC, fresh frozen plasma or rfVIIa. Andexanet alfa was administered as a bolus over 15-30 min, followed by a 2-hours infusion and it substantially reduced anti-factor Xa activity with effective haemostasis in 79% of patients (4, 21, 25, 88, 95, 110, 113-115). The full study report of ANNEXA-4 study has been recently posted and demonstrated that in patients with acute major bleeding associated with the use of factor Xa inhibitors, treatment with andexanet alfa markedly reduced anti-factor Xa activity, and 82% of patients had excellent or good haemostatic efficacy at 12 hours (116).

Finally, Ciraparantag (PER977), a novel reversal agent, is currently under development, and phase IIIa and IIIb trials are planned. It is a small, synthetic, watersoluble molecule that binds to direct and indirect inhibitors of FXa and thrombin, and thus it is purported to reverse all DOACs. PER977 has a more generalized antagonistic effect, so it is expected that also prevents the anticoagulant effect of unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs). Its clinical usefulness awaits further evaluation (4, 88, 110, 114, 117, 118).

To date there are no randomized trials confirming that DOAC reversal agents would provide a clear clinical benefit. Patients who had DOAC-related hemorrhage who were at relatively high risk of death within the first month were excluded from observational studies and a ~15% mortality was seen despite such exclusion criteria in these studies. For this reason, results regarding the ultimate clinical usefulness of DOAC reversal agents should be interpreted with caution.

1. **Resumption of oral anticoagulation and timing**

During the first phase after an ICH, there is a considerable risk of early haematoma expansion, which is particularly high in anticoagulant-related ICH. For this reason, anticoagulation is commonly withheld even in AF patients with a strong indication (i.e. with a high CHA2DS2-VAsc score). One of the main clinical challenges during the management of an ICH in AF patients receiving OAC therapy is the decision whether to restart (or not) this therapy (119). In addition, if OAC is restarted, the optimal timing to do so remains under debate

Any decision of resuming OAC needs to be carefully evaluated in an individualized manner, by a multidisciplinary team. This should include, at least, reassessment of bleeding and stroke risks, characteristics of the ICH, potential factors related with bleeding and the type of anticoagulant previously used. Thus, in the setting of a major bleed such as an ICH, the indication and net clinical benefit of OAC must be considered (120). Patients at high risk of stroke will likely benefit from restarting anticoagulation, even if the risk of rebleeding is high. Indeed a recent population-based study showed that patients with AF and/or valvular heart disease had a substantially increased risk of an arterial ischemic event in the first 3 months after ICH (121). Importantly, stroke and bleeding risks track each other (122, 123), so clinical scores such as the HAS-BLED score should be used to identify those patients potentially at risk of bleeding for more careful review and follow-up, and such proactive risk management can mitigate bleeding risks (124). Of note, the HAS-BLED score has been validated to predict ICH and recurrent ICH after first spontaneous ICH (81, 125).

Some characteristics of a bleeding event that contribute substantially to the risk of restarting anticoagulation are also relevant. For example, the anatomical location of the bleed (critical or noncritical site, and taking into account that the recurrence risk of lobar haemorrhage is about four times higher than non-lobar haemorrhage) since the risk of recurrent ICH differs between subarachnoid hemorrhage, epidural hematoma, subdural hematoma or intracerebral hemorrhage; the source of bleeding and whether it was definitively identified and treated; the mechanism of bleeding (i.e., traumatic or spontaneous); and whether further surgical or procedural interventions are planned (25, 126). Reevaluation of reversible risk factors needs to be addressed at this time point. Optimization of modifiable cardiovascular risk factors that may have contributed to the bleed such as uncontrolled hypertension, low TTR (for VKA user), concomitant use of antiplatelets/NSAIDs, alcohol or acute/worsening renal insufficiency leading to elevated anticoagulant levels, is important prior to oral anticoagulant restarting (127). In addition, the appropriateness of the anticoagulant needs to be determined. For example, if the patient suffered an ICH on VKAs, a switch to DOACs could be considered, especially if a history of labile INRs is present since TTR is an important predictor of major bleeding (128). In this case, the decision should focus on which of the available DOACs and dose to use, adjusted by age, weight, and renal function. If the patient suffered an ICH while taking any of the DOAC, then it seems reasonable to consider a DOAC with a lower bleeding risk or change to VKAs if a decrease in renal function is observed (25, 95, 105, 129). Functional status, life expectancy, compliance with therapy, and family support also may aid in decision-making (130).

* 1. *Patient Engagement in Restarting Oral Anticoagulation*

Restarting Anticoagulation is a complex decision and should not be taken in an arbitrary and unilateral manner. A consensus opinion by a multidisciplinary team including physicians (stroke neurologists, cardiologists, neuroradiologists, neurosurgeons) and nurses is necessary. However, this process should also involve patients, families and caregivers. The latter will need advice from healthcare professionals but they should have enough time to share their opinions, comments and questions, in order to have the feeling that the final decision has been agreed, and not imposed [ref]. Discussions should outline the risk-benefit of resuming anticoagulation, and particularly the risk of stroke if OAC is permanently withdrawn (4, 20, 25).

* 1. *Resumption. Is it effective, is it safe? Which anticoagulant?*

In patients with high stroke risk, it would be favorable for anticoagulation resumption once haemostasis is achieved and the patient is clinically and haemodynamically stable. OAC may be reinitiated with close monitoring in patients with high stroke risk and individualized strategies need to be considered for patients with moderate or high risk of recurrent bleeding (4, 25, 88). Parenteral anticoagulants are not harmless (131-133) and have no role for stroke prevention in AF, so whenever possible OAC should be resumed. In fact, cessation of OAC has been related with worse clinical outcomes in the long-term (20, 21) and seems to be a net clinical benefit to restarting OAC after a bleeding event (even after an ICH), which provides a reduction of the stroke/thromboembolism and mortality risks with no marked increment in the recurrent risk of ICH (134-140). This net clinical benefit seems to be reasonable from the second week following an initial ICH (141) and includes both VKAs and DOACs. For example, a nationwide observational study including AF patients who had suffered a spontaneous hemorrhagic stroke demonstrated that resuming warfarin was not related to ischemic or hemorrhagic stroke but was linked to reduced all-cause mortality. In those with trauma-induced ICH, resuming warfarin was linked to reduced stroke events and all-cause mortality (142). Another retrospective cohort study proved that resumption of warfarin following warfarin-associated ICH was not associated with increased risk of recurrent ICH but trended toward reduced thrombosis and all-cause mortality (143). A meta-analysis of observational studies from ICH survivors with AF showed that anticoagulation with VKAs was associated with a lower rate of ischemic stroke than antiplatelet therapy or no antithrombotic therapy without increasing recurrent ICH (144).

Most of the evidence regarding the resumption of OAC after an ICH is derived from observational (many of them retrospective) studies, with the potential for bias. In AF patients sustaining an ICH, when the study population was restricted to patients who received OAC therapy within 1 year after hospital discharge, the risk reduction of recurrence was 0.97% (95% CI -4.01% to 5.95%), and the adjusted risk ratio was 1.07 (95% CI 0.39-2.95); however, the recurrent ICH risk was 7.00% for warfarin and 5.07% for DOACs (145). Only controlled evidence will definitively resolve this important issue so the current evidence should be evaluated with caution. For example, an ongoing study, the NASPAF-ICH (NOACs for Stroke Prevention in Patients With Atrial Fibrillation and Previous ICH) trial is comparing a DOAC (particular agent at the discretion of the treating physician) with aspirin in high-risk patients with AF and history of previous ICH, but results have not been published (146). The RESTART (REstart or STop Antithrombotics Randomised Trial) trial included patients who were taking antithrombotic (antiplatelet or anticoagulant) therapy for the prevention of occlusive vascular disease when they developed intracerebral haemorrhage: At a median follow-up of 2 years, resuming antiplatelet therapy after ICH did not significantly increase the risk of recurrent intracerebral haemorrhage, suggesting that the risk of recurrent intracerebral haemorrhage is probably too small to exceed the established benefits of antiplatelet therapy for secondary prevention (147, 148). Only antiplatelets were investigated in the RESTART so further randomized trials are needed to assess if these results could replicated using OAC.

* 1. *The optimal timing for resumption*

The European Stroke Organisation guidelines for the management of spontaneous ICH do not provide firm recommendations about when to resume antithrombotic drugs after ICH but suggest not earlier than 14 days from the onset date (149). The American Heart Association/American Stroke Association guidelines for the management of spontaneous ICH suggest avoidance of OAC for at least 4 weeks after an ICH, in patients without mechanical heart valves (150). The European AF guidelines state that anticoagulation can be reinitiated after 4-8 weeks, especially when the cause of bleeding or the relevant risk factor (e.g. uncontrolled hypertension) has been treated, and that such treatment leads to fewer recurrent ischaemic strokes and lower mortality (4). Indeed, evidence suggests that anticoagulation could be safely restarted at least 4 weeks following ICH (25, 129, 130, 142, 151, 152), although individualization is definitely needed given the heterogeneity of the ICH patient profile.

However, the timing of resumption remains controversial (5). In a retrospective analysis of AF patients with ICH, DOACs were resumed at a median of 11 days after ICH onset. Functional outcomes were better in patients with OAC resumption, and even higher in patients with earlier resumption (153). In a study including AF patients with history of ICH, the initiation of OAC at least 2 weeks after an index ICH was associated with improved clinical outcomes if the anticoagulation with VKAs was maintained optimal (i.e. TTR ≥60%) (154). Also, an analysis of Medicare Claims Data showed that among AF patients who survived an ICH, 69% reinitiated OAC within 6 weeks of the event, without differences in thromboembolic events between post-ICH OAC use and non-use. Importantly, post-ICH OAC use was associated with a lower risk of recurrent ICH and all-cause mortality compared with non-OAC use (155). A nationwide observational study of Swedish AF patients suggests that anticoagulant treatment may be initiated 7 to 8 weeks after first-ever ICH to optimize the benefit from treatment and minimize risk (156). Similarly, a meta-analysis of observational studies found that resuming OAC reduces the risk of ischaemic stroke without increasing the risk of ICH, with a median time to resumption of 10-39 days (138). A later timing of 10 weeks has also been proposed (157) (Table 1).

Even among different professionals there are disparate opinions. In a survey performed including members of the International Society on Thrombosis and Haemostasis, Canadian Stroke Consortium, NAVIGATE-ESUS trial investigators and American Association of Neurological Surgeons, 21.4% preferred to re-start oral anticoagulation after 1-3 weeks of ICH, while 25.3% opted to start after 1-3 months. Neurosurgery respondents preferred earlier oral anticoagulation resumption compared to stroke neurologists or thrombosis experts (158).

The absence of solid evidence whether resuming or not OAC and the optimal timing is related –at least in part– to the exclusion of patients with previous ICH from the randomized trials comparing DOACs with VKAs. Nevertheless, ongoing studies such as the SoSTART (Start Or STop Anticoagulants Randomised Trial) (159), APACHE-AF (Apixaban versus Antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intraCerebral HaEmorrhage in patients with Atrial Fibrillation) (160, 161) PRESTIGE-AF (PREvention of STroke in Intracerebral hemorrhaGE survivors with Atrial Fibrillation) (162), and ENRICH-AF (EdoxabaN foR IntraCranial Hemorrhage Survivors With Atrial Fibrillation) (163) trials, will provide stronger evidence about the appropriate management of antithrombotic therapy following an ICH (Table 2).

1. **Other non-pharmacological strategies: left atrial appendage occlusion**

The left atrial appendage (LAA), and particularly some LAA morphologies increase the risk of blood flow stasis in AF predisposing to in situ thrombus formation. Indeed, the majority (over 90%) of thromboembolic strokes are caused by a clot formed in the LAA (164). The most extended therapy for stroke prevention in AF is the OAC therapy. In some patients with a risk of ICH unacceptably high and a concomitant risk of stroke also elevated, non-pharmacological approaches such as the left atrial appendage occlusion (LAAO) could be considered [ref]. LAAO implantation may be of use in AF patients having sustained an ICH (4, 25, 38, 88, 95, 165). Indeed, guidelines suggest percutaneous LAAO in patients with AF at increased risk of stroke and contraindication to long-term OAC, considering surgical LAAO in AF patients undergoing cardiac or thoracoscopic surgery, as a part of an overall heart team approach to the management of AF (4, 166). Similarly, the 2017 Society of Thoracic Surgeons guidelines recommended surgical management of LAA for the longitudinal thromboembolic prevention in AF patients at the time of concomitant cardiac interventions, and in all surgical ablation procedures it is reasonable to perform the complete LAA obliteration (167).

LAAO requires a period of antithrombotic therapy post-deployment, but overall, LAAO followed by single antiplatelet therapy has been proposed as an alternative to OAC in high-risk patients with previous ICH, with an acceptable periprocedural risk (168) and LAAO with attendant short-term OAC seems to be both safe and effective (169). It remains unclear the best management of antithrombotic therapy after surgical LAAO, as this will depend on risk factors and concomitant valvular procedures. Different anticoagulation and antiplatelet protocols have been described, including DOACs, VKAs, and single or dual antiplatelet therapy (170). There is still the need for randomized clinical trials comparing LAAO with OAC after OAC-related ICH, and assessment of the minimal antiplatelet therapy duration acceptable after the intervention [ref].

1. **Conclusions**

ICH is the most feared, disabling and lethal complication of the anticoagulation therapy in AF. There are several risk factors for ICH, including modifiable and non-modifiable. Therefore, in the setting of an ICH, it is necessary to review the correct choice and dosing of the anticoagulant regimen and to evaluate the potential modifiable bleeding risk factors including uncontrolled hypertension, labile INR, excessive alcohol intake and concomitant antiplatelet therapy or NSAIDs. In addition, appropriate management must include supportive care and measures and reversal of anticoagulation with specific agents. Once after the cause of bleeding or the relevant risk factor has been treated, restarting OAC is recommended, given the net clinical benefit of this therapy which seems to provide a reduction of stroke and mortality risks with no marked increment in the recurrent risk of ICH. Although the correct timing for restarting OAC therapy is unclear, reintroduction at 4-8 weeks after the bleeding has shown to be effective and safe in most studies.

1. **Expert opinion**

OAC reduces the risk of stroke/systemic embolism and mortality in AF patients but at the same time, it increases the risk of bleeding. Among these complications, ICH is the most severe and difficult to manage. Since OAC related ICHs would lead to poor clinical outcomes, the correct choice and dosing of the anticoagulant regimen, potential modifiable bleeding risk factors including uncontrolled hypertension, labile INR, excessive alcohol intake and concomitant antiplatelet therapy or NSAIDs, need to be reassessed whenever possible. We recommend using the HAS-BLED to identify modifiable bleeding risk factors and to ‘flag-up’ patients for more regular or early review and follow-up (eg. 4 weeks rather than 4-6 months).

In the setting of an ICH, mechanical compression, reduction of systolic blood pressure, surgical haemostasis, fluid replacement, blood product transfusion when appropriate; ensure an appropriate diuresis and other haemodynamic support should be the initial step, followed by reversal of anticoagulation by using specific agents. For patients taking VKAs, administration of vitamin K, 4F-PCCs, and fresh-frozen plasma could be considered. In DOACs users, activated PCCs are also useful as first reversal measure but idarucizumab for dabigatran and andexanet alfa for the FXa inhibitors, rapidly and safely reverses the anticoagulant effect of DOACs.

Once the ICH has been controlled, decision-making on resuming OAC is still challenging and need to be carefully evaluated in an individualized manner by a multidisciplinary team involving patients, families and caregivers. Even if the risk of rebleeding is high, these patients will likely benefit from restarting OAC since stroke and bleeding risks track each other. We also recommend here the use of the HAS-BLED score which has been validated to predict recurrent ICH.

Although the indication of OAC should be considered, it is important to note that there seems to be a net clinical benefit to restarting OAC after an ICH and permanently withdrawal of OAC is associated with mortality and worse clinical outcomes. Both, VKAs and DOACs are effective in reducing the risk of stroke/systemic embolism and mortality after an ICH, but the appropriateness of OAC needs to be determined. It seems reasonable to consider OACs with a low bleeding risk. In our opinion, DOACs should be selected as first choice if no contraindications are presented, given that they are associated with a lower risk of ICH than warfarin.

The last concern is about the timing of OAC resumption, which still remains controversial. Current guidelines recommend reintroduction of anticoagulation after 4-8 weeks of the bleeding event, based on retrospective evidence. Similarly, several studies suggest that OAC could be safely restarted within 4 weeks of ICH. In some selected patients with a concomitant high risk of stroke and extremely high risk of ICH in whom oral anticoagulation therapy is not possible, non-pharmacological approaches such as LAAO could be considered, which seems to be of major clinical benefit.

Finally, much of the evidence about DOAC reversal agents and timing of OAC resumption are derived from observational studies. Nevertheless, clinical trial data are not always reproducible in everyday clinical practice. Randomized clinical trial patients are usually highly selected with strict inclusion/exclusion criteria and careful followed-up, whereas ‘real world’ patients are often older, with many associated comorbidities that result in a difficult-to-treat population (171). In the absence of specific clinical trials, observational studies could provide some interim evidence; however, given observational could be biased by many confounders [ref], we appeal for pragmatic trials or prospective protocols that include large patient cohorts.

1. **Conflict of interest**

The authors state that there are no competing conflicts of interest to declare.

**Table 1.** Studies investigating clinical outcomes after oral anticoagulation resumption in intracranial haemorrhage survivors.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Year** | **Design and Patients** | **Resumption timing** | **Main efficacy outcomes after resumption** | **Main safety outcomes after resumption** |
| Majeed et al. (172) | 2010 | Retrospective cohort study  234 patients | 5.6 weeks | Significant lower risk of ischemic stroke | Non-significant higher risk of recurrent ICH |
| Witt et al. (143) | 2015 | Retrospective cohort  160 patients | 14 days | Non-significant lower risk of thromboembolism and all-cause mortality | Non-significant lower risk of ICH |
| Nielsen et al. (134) | 2015 | Nationwide cohort  1,752 patients | 34 days | Non-significant lower risk of thromboembolism and significant lower risk of all-cause mortality | Non-significant lower risk of ICH |
| Kuramatsu et al. (129) | 2015 | Nationwide cohort  719 patients | 31 days | Significant lower risk of all-cause mortality | N/A |
| Ottosen et al. (173) | 2016 | Population-based cohort  6,369 patients | N/A | Significant lower risk of thromboembolism and all-cause mortality | Non-significant lower risk of ICH |
| Park et al. (154) | 2016 | Retrospective  528 patients | 117 days | Significant lower risk of thromboembolism | N/A |
| Nielsen et al. (142) | 2017 | Nationwide cohort  2,415 patients | 31 days | Significant lower risk of thromboembolism and all-cause mortality | Non-significant higher risk of ICH |
| Murthy et al. (138) | 2017 | Meta-analysis  5,306 patients | 10-39 days | Significant lower risk of thromboembolism | Non-significant higher risk of ICH |
| Pennlert et al. (156) | 2017 | Nationwide cohort  2,619 patients | 4-16 weeks | Significant lower risk of thrombotic events. Greatest benefit in terms of reduced risk of vascular death and non-fatal stroke if anticoagulation was started at 7-8 weeks | Non-significant higher risk of severe hemorrhage |
| Poli et al. (174) | 2018 | Nationwide cohort  244 patients | N/A | Significant lower risk of thromboembolism and all-cause mortality | N/A |
| Proietti et al. (136) | 2018 | Meta-analysis  5,685 patients | N/A | A significant relative risk reduction of thromboembolism and absolute risk reduction of all-cause mortality | Non-significant higher risk of recurrent ICH |
| Newman et al. (155) | 2019 | Retrospective cohort study  1,502 patients | 0-6 weeks | Non-significant reduction of ischemic stroke/TIA, thromboembolism and ischemic stroke/TIA/thromboembolism. Significant reduction of all-cause mortality. | Significant lower risk of recurrent ICH |

**Table 2.** Ongoing studies investigating the safety and efficacy of resuming antithrombotic therapy after an ICH.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Official title** | **NCT number** | **Brief description** | **Target sample size** | **Primary outcome** | **Estimated completion date** |
| Start or STop Anticoagulants Randomised Trial (SoSTART) After Spontaneous Intracranial Haemorrhage (159) | NCT03153150 | To determine if re-starting full treatment dose OAC (DOACs or VKAs) in AF patients surviving spontaneous symptomatic ICH results in a beneficial net reduction of all serious vascular events compared with not starting OAC. | 203 | Recurrent symptomatic spontaneous ICH. | 2021 |
| Apixaban Versus Antiplatelet Drugs or no Antithrombotic Drugs After Anticoagulation-associated Intracerebral Haemorrhage in Patients With Atrial Fibrillation: A Randomised Phase II Clinical Trial (APACHE-AF) (161) | NCT02565693 | To obtain reliable estimates of the rates of vascular death or non-fatal stroke in AF patients with a recent OAC-associated ICH who are treated with apixaban versus those who are treated with antiplatelet drugs or no antithrombotic therapy. | 100 | Number of patients who experience the combination of vascular death or non-fatal stroke (cerebral infarction, intracerebral haemorrhage, or subarachnoid haemorrhage). | 2021 |
| PREvention of STroke in Intracerebral haemorrhaGE Survivors With Atrial Fibrillation (PRESTIGE-AF) (162) | NCT03996772 | To answer the question of whether people with ICH and AF should take an anticoagulant medication (DOAC) or if it is better for them to avoid it. | 654 | Time to the first incident ischemic stroke event; and time to the first recurrent intracerebral haemorrhage event. | 2022 |
| EdoxabaN foR IntraCranial Hemorrhage Survivors With Atrial Fibrillation (ENRICH-AF) (163) | NCT03950076 | To assess whether edoxaban (60/30 mg daily) compared to non-antithrombotic therapy reduces the risk of stroke in high-risk AF patients (CHA2DS2-VASc ≥2) with previous ICH. | 1200 | Time to composite of ischemic, hemorrhagic and unspecified stroke; and time to major hemorrhage as defined by the ISTH criteria | 2022 |
| AF = atrial fibrillation; DOAC = direct-acting oral anticoagulant; ICH = intracranial haemorrhage; ISTH = International Society on Thrombosis and Haemostasis; OAC = oral anticoagulation; VKA = vitamin K antagonist | | | | | |

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\* article of interest.

\*\* article of high interest.

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