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Cerebral haemorrhage in the patient with atrial fibrillation: do we employ the direct oral anticoagulants without waiting too long?

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Intracranial haemorrhage (ICH) is the most feared haemorrhagic complication of oral anticoagulant therapy (OAT), although the risk is significantly lower with direct oral anticoagulants (DOACs) compared with warfarin. Intracranial haemorrhage is generally considered, by clinicians, to be an absolute contraindication to starting or resuming OAT in patients with atrial fibrillation (AF). On the other hand, the pivotal trials with DOACs excluded patients with previous ICH. Observational studies actually indicate a net clinical benefit in favour of DOAC in patients with AF and previous ICH. This benefit is confirmed by randomized clinical trials which, however, have the limitation of the small number of cases, but larger clinical trials comparing DOACs vs. aspirin or no therapy are underway. While OAT is certainly contraindicated in patients with lobar ICH and cerebral amyloid angiopathy, in other cases, the decision must be made in the individual patient through an accurate balance between thromboembolic risk and haemorrhagic risk and a multidisciplinary cardio-neurological evaluation.

Introduction

The new oral anticoagulants, now better defined as direct oral anticoagulants (DOACs), have made it possible to ensure effective stroke prophylaxis for a greater number of patients with atrial fibrillation (AF), especially elderly people, who were often excluded from oral anticoagulant therapy (OAT) with warfarin. Although DOACs have a better safety profile than warfarin, the risk of bleeding and, in particular, of intracranial haemorrhage (ICH) persists however significantly reduced.

Intracranial haemorrhage represents the most feared complication of OAT, associated with significant morbidity and mortality (estimated at around 43% at 30 days).[1] When ICH occurs in a patient with AF, the doctor is faced with the clinical dilemma of whether or not to resume OAT for the prevention of ischaemic stroke, with which drug and with what timing.

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Risk of intracranial haemorrhage during anticoagulant therapy in patients with atrial fibrillation

During warfarin therapy, the incidence of ICH is estimated at around 0.8%/year and is influenced by various factors, primarily age and the concomitant intake of antiplatelet agents. After ICH, the risk of recurrence is variable, from 1.3 to 7.4% based on observational studies. Studies on DOACs in patients with AF have documented, with the same reduction in ischaemic events, a lower incidence of severe haemorrhages compared with warfarin, with a dramatic reduction of ICH which are almost halved at the cost of a slight increase in gastrointestinal bleeding.[2] The exclusion of patients with previous ICH in the registration trials of DOACs, however, did not contribute to clarifying the role of these drugs in patients who have had a cerebral haemorrhagic complication.

The identification of the pathogenetic process underlying ICH has significant prognostic information with consequent

repercussions on therapeutic choices. Spontaneous ICH is generally a consequence of the disease of the small cerebral vessels, the two most frequent forms of which are represented by arteriolosclerosis (concentric hyalinization of the vascular wall of the penetrating arterioles of the basal ganglia, pons, and cerebellum—defined as deep territories—associated with age, diabetes, and hypertension) and from cerebral amyloid angiopathy (CAA) (deposition of β-amyloid protein in the tunica media and adventitia of the leptomeningeal and cerebral cortical vessels—defined lobar territories—associated with age and specific genotypes of apolipoprotein E). The risk of ICH recurrence appears significantly higher in patients with CAA (7.4%/year) compared with patients with arteriolosclerosis (1.1%/year).[1]

Cerebral amyloid angiopathy has an extensive prevalence in the elderly population, is highest in Alzheimer's patients, and is not associated with systemic amyloidosis. It may remain asymptomatic or result in lobar ICH, cognitive dysfunction, or transient ischaemic attack-like episodes. The ultimate diagnosis of CAA is only at autopsy but should be suspected in patients aged >55 years with a history of lobar or cortical ICH, subarachnoid haemorrhage of the convexity, subcortical micro-bleeds, and marginal siderosis. A high number of subcortical micro-bleeds, in particular >5, is associated with a greater risk of ICH and an unfavourable risk/benefit ratio for OAT. While there is no data to support the routine use of brain MRI before starting OAT, this test is important for diagnostic–therapeutic purposes in patients with previous ICH.[3]

Fear of intracranial haemorrhage with early initiation of oral anticoagulant therapy after ischaemic stroke in patients with atrial fibrillation

There has long been a broad debate on the optimal timing of resumption of OAT after an ischaemic stroke in patients with AF, since in the first days after the stroke, both the risk of recurrence of cerebral ischaemic events appears particularly high (estimated 1% per day in the first 2 weeks) than that of haemorrhagic evolution of the cerebral infarction. The available guidelines in this regard are largely based on expert consensus and are mainly based on the assessment of the clinical severity of stroke using the National Institutes of Health Stroke Scale.[4-6]

Only recently have some randomized clinical trials shed light on the timing of the initiation/resumption of DOACs in patients with AF and acute ischaemic stroke. The most important of these trials is the Early vs. Late initiation of direct oral Anticoagulants in post-ischaemic stroke patients with atrial fibrillatioN (ELAN) study[7] which enrolled 2013 patients (average age 67 years) with AF hospitalized for ischaemic stroke and randomized in an open-label manner to receive early resumption of OAT with DOAC (within 48 h after minor or moderate stroke, within 6–7 days in major stroke) compared with a later recovery (3–4 days after minor stroke, 6–7 days after moderate stroke, and 12–14 days after major stroke). The incidence of the composite endpoint of recurrent ischaemic stroke, systemic embolism, major extracranial haemorrhage, symptomatic ICH, and cardiovascular death within 30 days was significantly higher in patients with delayed initiation of OAT (4.1%) compared with early resumption (2.9%), a difference driven mainly by the reduction of cerebral and peripheral embolic events. In addition, a low incidence of ICH was observed (0.2% in each group), even in patients with major stroke.

Two other important randomized clinical trials, Optimal Timing of Anticoagulation after Acute Ischaemic Stroke (OPTIMAS) and Timing of Oral Anticoagulant Therapy in Acute Ischaemic Stroke with Atrial Fibrillation (TIMING), were conducted almost simultaneously with the ELAN study, evaluating the safety and the effectiveness of early anticoagulant therapy after stroke demonstrating superiority of the early strategy over the late one.[8] The novelty of the ELAN study was to evaluate a greater precocity of resumption of DOACs compared with other studies and to use imaging methods which are more objective and reproducible than the clinical evaluation, to grade the severity of the stroke.

Anticoagulant therapy after intracranial haemorrhage in patients with atrial fibrillation

Patients with AF and ICH are a population at increased risk of future ischaemic stroke and ICH recurrence.[9] The majority of available evidence regarding the resumption of OAT after ICH comes from retrospective observational studies that have predominantly used warfarin, while little evidence comes from randomized clinical trials.

Observational studies

A retrospective observational study involving 566 patients with AF admitted for spontaneous ICH on OAC (warfarin) in tertiary care centres in Germany showed that in the 1-year follow-up after the event, resumption of OAT was associated with lower mortality (8.2 vs. 37.5%—$P < 0.001$) and lower incidence of ischaemic events (5.5 vs. 14.9%—$P < 0.008$) in the presence of similar haemorrhagic events (7.3 vs. 5.7%—$P = 0.53$).[10]

A retrospective Danish cohort study conducted through linkage with 3 national registries examined 1752 patients with AF in OAT 6 weeks after discharge for ICH. The cumulative annual incidence of ischaemic events (ischaemic stroke or systemic embolism) and total mortality was significantly lower in patients for whom OAT was restarted (13.6%/year), compared with patients treated with antiplatelet agents (25.7%/year) or no antithrombotic therapy (27.3%/year), suggesting the need for further randomized clinical trials to guide clinical practice.[11]

A meta-analysis considered the data from 8 retrospective observational studies involving 5306 patients with ICH during OAT (mainly warfarin) prescribed for different indications (35% AF), evaluating the incidence of ischaemic events (stroke and myocardial infarction) and the recurrence of ICH depending on whether OAT was resumed or not.[12] Resumption of OAT (occurred in 36% of patients, over a variable time with a

median of 10–39 days) did not determine an increase in ICH recurrence [relative risk (RR) 1.01] while it was associated with a significant reduction of ischaemic events (RR 0.34). This meta-analysis, despite all the limitations of the observational nature of the studies and the absence of data on the type of ICH, suggests the possibility of safely resuming OAT.

A more recent meta-analysis that included 20 mainly observational and cohort studies evaluated the incidence of ICH or ischaemic events after spontaneous ICH in over 50 000 patients with AF, depending on whether or not long-term antithrombotic therapy (anticoagulant or antiplatelet therapy).[13] Studies performed on patients with spontaneous ICH of any size and location (intracerebral, subdural, or subarachnoid) in addition to cerebral micro-bleeds were included. The main result of this meta-analysis was the finding of a significant reduction in both thromboembolic events (RR 0.51; $P = 0.01$) and total mortality (RR 0.52) in patients treated with OAT compared with the absence of antithrombotic therapy, in the absence of a significant increase in the risk of ICH recurrence (RR 1.44). Among anticoagulant drugs, DOACs proved to be more effective than warfarin in reducing thromboembolic events (RR 0.65) in the presence of a lower risk of ICH recurrence (RR 0.52). The authors, while underlying the mainly observational origin of the data, highlight the advantage of OAT in the reduction of thromboembolic events and mortality from all causes in patients with AF who survived ICH, in the absence of a significant increase in ICH relapses.

Finally, a further meta-analysis of three observational studies specifically evaluated the long-term prognosis, in terms of mortality and functional outcome at 1 year, after resumption of OAT in relation to the location of the ICH (lobar vs. non-lobar).[14] This meta-analysis included 1012 patients who survived ICH secondary to OAT (633 non-lobar and 379 lobar) from the German-wide Multicentre Analysis of Oral Anticoagulation-associated Intracerebral Haemorrhage (RETRACE) study ($n = 542$), the Ethnic/Racial study Variation of Intracerebral Haemorrhage (ERICH) ($n = 209$), and a North American single-centre study ($n = 209$). On multivariable analysis, the resumption of OAT was associated with a reduction in mortality both after non-lobar ICH [hazard ratio (HR) = 0.25] and after lobar ICH (HR 0.29) and with a favourable functional outcome both after non-lobar ICH (HR 4.22) and after lobar ICH (HR 4.22). Furthermore, the resumption of OAT was associated with a reduction in the incidence of all-cause stroke in both types of ICH (both $P < 0.01$).

Randomized clinical trials

Regarding randomized clinical trials, the evidence on the timing of resumption of OAT after ICH in patients with AF comes from four prospective randomized controlled clinical trials, the subject of a recent meta-analysis.[15] Three studies were specifically dedicated to patients with AF and ICH, the Start or Stop Anticoagulants Randomized Trial (SoSTART) study with 203 participants, the Apixaban vs. Antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intracerebral haemorrhage in patients with Atrial Fibrillation (APACHE-AF) study with 101 participants, the Non-Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Patients with Atrial Fibrillation and previous Intracerebral Haemorrhage (NASPAF-ICH) study with 30 participants, and the Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients (ELDECARE-AF) study which included a subgroup of 80 patients with AF and previous ICH. The intervention arm was a DOAC in 209 of 212 patients assigned to start OAT, and the control arm was antiplatelet therapy in 67 (33%) of 200 patients assigned to avoid OAT.

The primary outcome of stroke of any type or cardiovascular death occurred in 29 (14%) of 212 patients in whom OAT was initiated and in 43 (22%) of 200 patients in whom OAC was avoided ($P = $ ns). OAT reduced the risk of major ischaemic cardiovascular events which occurred in 9 (4%) of 212 patients in the OAT arm vs. 38 (12%) in the non-OAT arm (HR 0.27). In the OAT arm, there was no significant increase in major bleeding (7 vs. 5%), although a recurrence of ICH occurred in 12 patients (6%) in the OAT arm and 5 (3%) in the non-OAT arm.

The results of this meta-analysis of randomized clinical trials indicate a net clinical benefit in favour of OAT in patients with AF who have experienced ICH, but there are limitations related to the overall limited number of patients enrolled in these pilot trials. Uncertainties about which is the best strategy to pursue have stimulated the planning of larger trials, five of which are Study of Antithrombotic Treatment after Intracerebral Haemorrhage (STATICH), Prevention of Stroke in Intracerebral Haemorrhage survivors with Atrial Fibrillation (PRESTIGE AF), Anticoagulation in ICH survivors for Stroke Prevention and REcovery (ASPIRE), Avoiding Anticoagulation After Intracerebral Haemorrhage (A3-ICH), and Edoxaban for Intracranial haemorrhage survivors with Atrial Fibrillation (ENRICH-AF) which should enrol a total of over 2200 patients comparing a DOAC vs. aspirin or no antithrombotic therapy. The largest of these trials is the ENRICH-AF which compares edoxaban (60/30 mg) vs. non-OAT with the aim of enrolling 1200 patients with AF and ICH of any type, whether occurred or not undergoing OAT/antiplatelet therapy, in 239 hospitals in 29 countries. The primary endpoint of the study is a stroke of any type (ischaemic, haemorrhagic, and indeterminate). Following an interim safety analysis of the first 699 patients [174 (25%) of 699 with lobar ICH and 34 (5%) of 699 with subarachnoid haemorrhage] of the convexity the Data Safety Monitoring Board recommended discontinuing the enrolment of the lobar ICH and convexity subarachnoid haemorrhage subtypes, based on the finding of an unacceptable high risk of ICH recurrence in patients assigned to the edoxaban arm. The ENRICH-AF trial continues to enrol patients with other types of ICH.[16]

The cognitive uncertainty on what to do after ICH in patients with AF is expressed by the data obtained in a 2018 survey where the responses of 228 professionals (neurosurgeons, neurologists, or angiologists) to specific questions on clinical cases relating to the resumption of OAT were analysed after ICH, documenting a wide variability of behaviours.[17] Resumption of OAT was suggested in variable proportions (from 30 to 98%) on the basis of both the underlying pathology (where the most valued contraindication was the recurrence of ICH during

OAT, followed by lobar or very large haemorrhages) and of the specialty to which the responding doctor belongs (neurosurgeons were found to be the most favourable to resuming OAT in cerebral haemorrhages of any type). Even in cases in which resumption of OAT was recommended, there was wide variability in the timing of resumption (21% after 1–3 weeks and 25% after 1–3 months), with neurosurgeons favouring an earlier resumption in each case compared with other specialists.

Comparison between direct oral anticoagulants and warfarin in patients with atrial fibrillation and intracranial haemorrhage

The largest non-randomized comparison study between DOACs and warfarin in patients with AF and previous ICH was conducted in the Asian population. This is a large retrospective cohort study derived from Korean National Health System databases.[18] In total, 5712 patients (average age 72.5 years—average CHA2DS2-VASc 4) with AF and previous ICH in the absence of OAT were identified. In an average follow-up of 7 months, using propensity score matching, events were compared between 2434 patients on warfarin and 3278 patients on DOACs. Patients treated with DOACs had a reduced incidence of both ischaemic stroke (−23%) and ICH (−34%). A similar advantage was found for DOACs in the reduced incidence of fatal ischaemic stroke (HR 0.54) and total mortality (HR 0.83). A trend towards a lower incidence of fatal ICH was also observed with DOACs (warfarin 0.5%/year vs. DOAC 0.3%/year). The study, despite the limitations of its retrospective and observational nature, suggests greater safety of DOACs compared with warfarin in patients with AF and previous ICH.

Percutaneous closure of the left atrial appendage after intracranial haemorrhage in patients with atrial fibrillation

Percutaneous closure of the left atrial appendage (LAAO) is a therapeutic strategy that is often used in patients with reported absolute or relative contraindications to OAC, and the main proportion of patients referred for LAAO are patients with ICH. However, the ESC 2020 guidelines give a weak recommendation of Class IIb with Level of Evidence B for the LAAO procedure, and there is also the problem of the need for long-term antiplatelet therapy post-procedure to prevent thrombosis of the device.[19]

We do not have data comparing LAAO vs. medical therapy in patients with AF and ICH. Two randomized trials are currently underway, the Prevention of Stroke by Left Atrial Appendage Closure in Atrial Fibrillation Patients After Intracerebral Haemorrhage (STROKECLOSE) study which aims to enrol 750 patients comparing OAT vs. LAAO and the A3-ICH study which aims to enrol 200 patients randomized to apixaban vs. no antithrombotic therapy/antiplatelet therapy vs. LAAO.

Indications from the guidelines in patients with intracranial haemorrhage and atrial fibrillation

The 2020 ESC guidelines on AF recommend evaluating the pathogenesis of ICH and, in spontaneous forms, carefully evaluating the risk-benefit ratio in agreement with the neurologist.[19] In patients with post-traumatic forms or in the presence of reversible causes or modifiable risk factors, anticoagulation can be resumed preferentially with DOACs, however, not before 2–4 weeks (Class IIa recommendation; Level of Evidence C). In other cases, the guidelines suggest to consider the LAAO procedure in patients with non-modifiable risk factors for recurrence of ICH, such as advanced age and suspicion of CAA.

The recent North American ACC/AHA/ACCP/HRS guidelines on AF published at the end of 2023 indicate the possibility of resuming OAT 4–8 weeks after ICH following a careful evaluation of the risk/benefit ratio of the thromboembolic and haemorrhagic risk (Class IIb recommendation; Level of Evidence C-Limited Data LD).[20]

The 2022 AHA/ASA guidelines on the management of spontaneous ICH[1] agree with the need for a multiparametric evaluation to predict the risk of cerebral haemorrhagic recurrence, considering lobar location; advanced age, number, and location of micro-bleeds on brain MRI; the presence of poorly controlled hypertension; black or Asian ethnicity; and the presence of specific alleles of apolipoprotein E. In patients in whom OAT is indicated, it is recommended to wait at least 7–8 weeks (in the previous 2015 AHA guidelines the recommendation was of at least 4 weeks) before starting OAC (Class IIb recommendation; Level of Evidence C), preferring the use of DOACs. In patients judged to be at excessive bleeding risk, it is recommended to proceed with the LAAO procedure (Class IIb recommendation; Level of Evidence C).

Conclusions

In patients with AF and previous ICH, resumption or initiation of OAT is not necessarily precluded, particularly with DOACs. These patients are usually referred to the interventional cardiologist for the LAAO procedure which, however, involves the need for long-term post-procedural antiplatelet therapy. Intracranial haemorrhage are not all the same and, apart from lobar ICH and those associated with CAA for which OAT is not recommended, in other cases, a multidisciplinary cardiology, neurology, and neuroradiology evaluation is appropriate to evaluate the risk/benefit ratio in the individual patient. It is also important to try to correct any associated bleeding risk factors (hypertension, concomitant use of aspirin and NSAIDs, etc.).

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