ORAL ANTICOAGULATION RELATED INTRACEREBRAL HEMORRHAGE: MORE QUESTIONS THAN ANSWERS

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ABSTRACT

Intracranial hemorrhage (ICH) is the most feared and devastating complication of oral anticoagulant therapy. When an ICH occurs, the patient's situation hinges on the balance between how great is the embolic risk while not receiving anticoagulants, and how big is the threat of the hemorrhage if the anticoagulant effect is not reversed promptly. Although several studies which compared the use of different reversal agents failed to demonstrate any improvement in prognosis and survival, at the present moment the consensus seem to be that anticoagulation should be rapidly reversed after an ICH. The second question to be answered is whether and when should be oral anticoagulation treatment restarted. Although the risk of thromboembolism in patients off anticoagulation seems to be higher than the risk of ICH recurrence, there is a marked paucity of prospective large studies on the real risk of ICH recurrence when OAC is resumed, paucity that probably emphasizes the ethical challenge of prescribing patients a medication to which they have an apparent contraindication. The little evidence available suggests that the optimal time for resumption is between 10 days and 30 weeks.

Key words: intracerebral hemorrhage, oral anticoagulation, re-bleeding, atrial fibrillation, reversal of anticoagulation, resumption of anticoagulation

Intracranial hemorrhage (ICH) is the most feared and devastating complication of anticoagulant treatment, leading to death or disability in two thirds of cases (1).

Vitamin K antagonists (VKA, warfarin and acenocumarol) have long been the mainstay of anticoagulation therapy in atrial fibrillation. A strenuous effort has been made for many years in order to develop new oral anticoagulants as effective as VKA but with a superior pharmacological profile. For the moment there are two directions of research: the direct inhibitors of thrombin and the Xa factor antagonists. Unlike VKA, dietary restrictions and frequent blood sampling to monitor the degree of anticoagulation are unnecessary with the currently available new agents.

The sole representative of the former category is dabigatran etexilate, which was recently included in both the ESC and AHA/ACC Guidelines for the management of atrial fibrillation as a result of the RE-LY trial (2). Dabigatran can be administrated either 110 mg twice a day or 150 mg twice a day, the lower dose being non-inferior to warfarin but having fewer hemorrhagic complications whereas the higher dose is superior in terms of thromboprophylaxis with the cost of a slightly higher incidence of bleeding, but not exceeding warfarin bleeding rate. The category of factor Xa antagonists is represented at the moment by two drugs: rivaroxaban and apixaban, both of them being in Phase III of development. In the double-blind randomized ROCKET-AF trial (3), based on a population of over 14,000 patients with atrial fibrillation, rivaroxaban (20 mg once a day) was non-inferior to warfarin in terms of stroke and non-central nervous system embolism prevention and had a lower rate of ICH but a higher risk of gastrointestinal bleedings. At the end of last year rivaroxaban was ap-

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proved for the prevention of non-valvular atrial fibrillation-related stroke and systemic embolism in USA and Europe. Apixaban has completed to the date two major trials. In the AVERROES trial (4), which included almost 6,000 patients unsuitable for VKA treatment, apixaban was significantly superior to aspirin in terms of reducing the risk of stroke and systemic embolism with no increase of major bleeding or ICH rates. The results of ARISTOTLE trial (5), a double-blind randomized trial which included over 18,000 patients, were also made public last year. In this study apixaban was found superior to warfarin for the prevention of thromboembolism in patients with atrial fibrillation. Besides, apixaban had a lower rate of major bleeding and of all-cause mortality. To the date apixaban is under reviewing for approval.

The enthusiasm for these agents, however, must be tempered by two notables concerns: there are no readily available means for assessing the degree of anticoagulation and there is no readily available a reversal strategy. Currently, the only reversal option for dabigatran is emergency dialysis which can be a challenge when it comes to a patient with a threatening ICH.

The new oral anticoagulants-related ICHs may have different epidemiology, mechanism, characteristics, acute and long term management from the vitamin K antagonists-related ICHs and are beyond the purpose of this article. This subject will be reviewed in a future paper.

Further on we will refer only to cerebral hemorrhage related to oral anticoagulation with vitamin K antagonists.

EPIDEMIOLOGY

Approximately 1% of the european population is currently receiving oral anticoagulation treatment (OAC) with vitamin K antagonists, and this proportion has increased to 1.7% in some countries (6) (7). The rate of ICH in patients undergoing long-term oral anticoagulation is about 2-9 per 100,000 population/year, an incidence 7- to 11- fold higher than in the not treated population of similar age (8) (9) (10) (11). About 5-12% of ICH are related to OAC (12) (9). The incidence of OAC-related ICH is increasing and this continuous increment can be explained by the larger number of elderly patients that receive OAC, the increased use of combined anticoagulant and antiplatelet regimens, or the increasing use of OAC for secondary stroke prevention (13). Although the greater number of bleeding complications is counterbalanced by a more effective prophylaxis of thromboembolic events, the methods of recognition of those patients with a high risk of bleeding must be improved and the therapeutic attitude carefully weighted.

RISK FACTORS FOR OAC-RELATED ICH

Many factors contribute to the variability of the anticoagulation effect and accordingly, to the risk of bleeding. OAC – drug interactions have been shown to increase the risk of serious bleeding (14). Warfarin interaction with at least one drug was considered in a retrospective study recently published (15) the main contributor to bleeding in almost half of the cases.

Non-steroidal anti-inflammatory drugs, lipid-lowering drugs, acetaminophen, selective serotonin reuptake inhibitors, amiodarone, omeprazole, antifungal agents and cimetidine are some of the widely used drugs prone to interact with oral anticoagulants (warfarin or acenocoumarol). The main mechanism of interaction implies the inhibition of CYP2C9, which increases the plasma concentration of the drug and leads to stronger anticoagulation effect and higher bleeding risk. Several studies have shown that antiplatelet drugs raise the bleeding risk associated with anticoagulation therapy.

A number of predisposing factors for cerebral hemorrhage in patients receiving OAC has been identified. These factors are summarized in Table 1 (16) (9) (17).

Table 1. *Risk factors for ICH during oral anticoagulation*

Established:
Advanced age (especially > 75 years)
Hypertension (especially systolic blood pressure > 160 mmHg)
History of cerebrovascular disease
Intensity of anticoagulation
Possible:
Concomitant use of aspirin
Increased variation of INR
Cerebral amyloid angiopathy
Tobacco smoking
Heavy alcohol consumption
Diabetes
Serious heart disease
Liver disease
Malignancy
Imaging and genetic markers:
Leukoaraiosis detected by brain CT/MRI
Microbleeds by T2*-weighted MRI
APO ε II or IV genotype
CT: computed tomography; MRI magnetic resonance imaging

Relationship between intensity of anticoagulant effect and risk of ICH: It is increasingly clear that the relative and absolute risks of OAC-associated ICH are proportional to the intensity of anticoagulation. Excessive anticoagulant effect is well-established as a powerful risk factor for ICH (18) (17) (19). In a case-control study of 170 patients with nonvalvular atrial fibrillation who developed ICH while taking warfarin, the adjusted odds ratios for ICH (relative to an INR of 2.0 to 3.0) were 4.6 and 8.8 for INRs in the range of 3.5 to 3.9 and ≥4.0, respectively (20).

Data from the Stroke Prevention in Reversible Ischemia Trial (21), a secondary stroke prevention trial in which patients with transient ischemic attack or minor ischemic stroke were randomly assigned to receive either aspirin (30 mg/day) or warfarin (to achieve an international normalized ratio (INR) of 3.0 to 4.5), add further evidence of the effect of excessive anticoagulation and frequency of ICH: the trial was stopped early, after the occurrence of 24 ICHs (14 fatal) in the warfarin group in comparison with only three ICHs (one fatal) in the aspirin group; there was a strong relationship between bleeding complications and rise in INR values. However, there is no absolutely "safe" INR; many patients given OAC experience ICH with the INR well within the conventionally therapeutic range.

Duration of anticoagulation therapy before onset of ICH: In two series, most ICHs (70% – 22, 54% – 23) occurred during the first year of treatment. In another report, only one third of ICHs occurred after that period of time (8); the other two thirds appeared between 2 and 18 years after the start of treatment.

Brain abnormalities that have been associated with a greater risk of complications in anticoagulated patients include: microhemorrhages, leukoaraiosis, and previous strokes (19) (24). Individuals with microhemorrhages are more likely to be hypertensive and have history of stroke, leukoaraiosis, or old hemorrhages. In patients with acute ischemic stroke, those with coexistent microhemorrhages more frequently develop subsequent ICH (25). Sporadic reports also suggest that microhemorrhages are preferential focuses of ICH in patients receiving OAC, most likely because the drug unmasks ICH that would otherwise remain asymptomatic (24). Microhemorrhages, leukoaraiosis and previous stroke frequently coexist and this may confound the interpretation of the risk of spontaneous or drug related cerebral bleeding. Severe and confluent areas of leukoaraiosis were associated with a higher risk of ICH in warfarin-anticoagulated subjects in the Stroke Prevention in Reversible Ischemia Trial in a dose-dependent manner even among patients with an INR ≤ 3 (21) (19). In other studies, patients with advanced leukoaraiosis but without microhemorrhages tended to experience ischemic strokes rather than ICH (26). Recently, leukoaraiosis was not found independently associated with the incidence of OAC-ICH after adjustment for the presence of microhemorrhages (27) but the presence of microhemorrhages was a predictor of ICH in patients with no or mild leukoaraiosis (26).

In light of these inconsistent findings, it is probably wise to not avoid OAC in patients with leukoaraiosis or microhemorrhages.

PREDICTION OF OAC-ICH

Several methods have been developed to estimate the risk for OAC-related bleeding and identify the patients in whom the risk of therapy might outweigh the benefits. These methods are valid but should not be used as an unique tool to decide whether to initiate or not a therapy with OAC in individual patients. Moreover, none of these methods have differentiated between the risk of intracranial or systemic bleedings, or incorporated the predictive role of INR values.

The European Society of Cardiology proposes in The Guidelines for the Management of Atrial Fibrillation the HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history, labile INR, elderly (>65 years-old), concomitant intake of drugs or alcohol to assess the bleeding risk in patients with atrial fibrillation (28). A score of ≥3 indicates a high-risk, and caution is advised before starting antithrombotic treatment.

CLINICAL AND IMAGISTIC ASPECTS OF OAC-RELATED ICH

These hemorrhages have a tendency to occur in the absence of signs of systemic bleeding. Frequently a slow progression of the focal neurologic deficits can be seen (sometimes over periods as long as 48 to 72 hours). This is in contrast to spontaneous ICH in patients who are not anticoagulated, in whom the duration of bleeding is usually brief (approximately 10% show progressive enlargement in the first 24 hours). In addition, OAC-related ICHs are associated with a high risk of hematoma expansion (29).

On CT scan, the hemorrhages often show blood-fluid levels, which result from "sedimentation" of red blood cells in a hematoma that does not clot because of the anticoagulation effect (30) – see figure 1. While some studies found a high frequency of cerebellar location (23) (31) aggregate data do not suggest special involvement of the cerebellum and consider no differences regarding the ICH location between patients who are and are not receiving anticoagulation therapy (9).

The prognosis of OAC-ICH varied in different studies, although most studies were small, retrospective, did not have clear diagnostic protocols, and the care of patients was not standardized. Available data shows that the outcome of patients with OAC-ICH is worse than in patients with spontaneous ICH and that obeys as much to a higher incidence of larger hemorrhages, as to the older age and severe comorbidity frequently observed in patients with OAC-ICH (32). The mortality is high (approximately 60%, range 46% to 68%) (23) (33). The increased mortality risk is more relevant during the first 3 months of stroke, and detrimental factors include decreased level of consciousness, hemorrhage volume, hematoma expansion, and intraventricular extension of hemorrhage (34) (35). Some studies found an association between higher INR levels at presentation and poor functional outcome, while others not (36).

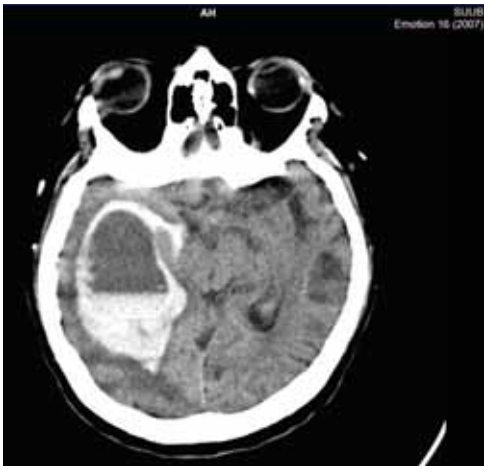

Figure 1. *Cerebral hemorrhage with blood-fluid level (black arrow) in a patient with OAC overdosage (INR 5.6) hospitalised in the department of Neurology, University Hospital Bucharest*

HEMORRHAGE MECHANISM

The actual mechanism of ICH in patients undergoing anticoagulation is unclear, in part because of the lack of adequate pathologic studies. Such studies should determine whether OAC-related ICHs have different microscopic pathologic features from that of spontaneous ICHs, in terms of the type of affected vessel as well as the eventual presence of local vascular disease (i.e., microaneurysm, fibrinoid necrosis, lipohyalinosis, or cerebral amyloid angiopathy) at the rupture's site, as a possible substrate for this complication of anticoagulation. Hart et al (9) have hypothesized that ICH in patients undergoing anticoagulation could result from enlargement of small, spontaneous hemorrhages that would otherwise occur without clinical consequence in individuals with normal coagulation function.

A possible explanation for the features of OAC-related ICH (slow progression of the focal neurologic deficits, high risk for hematoma growth) could be the inhibition of thrombin formation by OAC. Thrombin is a serine protease that is released from the hematoma and may affect the behavior of the hemorrhage. At low concentrations, thrombin is essential to stop the bleeding (37), but at higher concentrations, it can kill neurons and astrocytes (38) and may facilitate perihematomal edema formation (39). Therefore, it is plausible that thrombin might contribute to amplify the clinical effects of the initial bleeding. The "toxic" effect of blood (and thrombin) is further supported by experimental studies showing that the injection of blood into the brain is more harmful than the injection of an oil–wax mixture. Contrarily, injection of heparinized blood results in less perihematomal edema formation (40), and brain edema formation is also reduced after the administration of thrombin inhibitors (41). Thrombin formation is inhibited by the effect of oral anticoagulants, and it is conceivable that a lower thrombin concentration in the clot of patients with OAC-ICH facilitates the formation of larger hematomas and longer bleedings. Yet, the lower disposal of thrombin within the clot would also result in less toxicity to the surrounding brain parenchyma. Overall, the available clinical data highlight the predominant negative effect of larger hematoma volumes in anticoagulated patients (16).

The contributing role of local vascular disease, such as cerebral amyloid angiopathy (CAA), is favored by observation of a high frequency of this angiopathy in individuals with warfarin-related ICH. Rosand et al (42) documented CAA in brain tissue samples from 7 of 11 patients with warfarin-related ICH. In addition, these investigators found an overrepresentation of the ApoE ε2 allele, a marker of CAA, in patients with warfarin-related ICH in comparison with a control group.

REVERSAL OF ANTICOAGULATION

When an ICH occurs, the patient's situation hinges on the balance between how great is the embolic risk while not receiving anticoagulants, and how big is the threat of the hemorrhage if the anticoagulant effect is not reversed promptly. The weighting of the two sides of this coin provides the rationale for deciding on the best treatment on a patient-by-patient basis.

The evidence-based information about the most appropriate attitude regarding the OAC-related ICH is rather poor: there are no randomized clinical trials and therefore the current therapeutic guidelines differ in their recommendations.

At the present moment the consensus seem to be that anticoagulation should be rapidly reversed after OAC-related ICH. The rationale for this correction is that hematoma progression was found to occur in nearly 40% of ICH patients in the first few hours following symptom onset (11) and that this enlargement is the first brick of the poor prognosis and high mortality. But not all patients are at equal risk of hematoma expansion. A large hematoma volume on presentation, an early presentation (especially within 3 hours of symptom onset) and the „spot sign" defined as extravasation after contrast-enhanced computed tomography are all features associated with a high risk of hematoma expansion. Whether a higher INR at presentation implies a higher risk of hematoma growth or not is still a subject of debate (45).

Discontinuation of OAC therapy, fresh frozen plasma (FFP), vitamin K, prothrombin complex concentrate (PCC) which contains factors II, VII, IX and X and recombinant activated factor VII (rfVIIa) are all therapies that can be used for reversal of anticoagulation, alone or in combination.

Discontinuation of OAC therapy: This is an essential attitude in the acute setting of the OAC-related ICH. Phan et all. shows in a large retrospective study that a short discontinuation of OAC is not associated with a relevant increase in thromboembolic complications (46). Wijdicks et all. in another retrospective series showed that this short discontinuation can be safe even in the presence of a mechanical heart valve if there is no previous evidence of systemic embolization (47).

Vitamin K: Vitamin K is a necessary component within the liver in order to help carboxylate factors II, VII, IX, and X to their active forms. When warfarin is given, it blocks the reductase that converts oxidized vitamin K back to vitamin K for reuse. A vitamin K shortage within the liver creates a coagulation cascade deficit. Must be administered IV, because the effect is too slow using the oral or subcutaneous route. The time to onset is at least 2-6 h and often more than 24 h are needed to achieve effective response. The incidence of anaphylactic reaction to IV vitamin K is exceedingly rare, with a reported rate of 3 out of 10,000 doses. Many of the reported anaphylaxis episodes occurred with older vitamin K formulations containing polyethoxylated castor oil, while the modern micelle formulation is though t to have a lower risk of anaphylactoid reactivity. All patients with OAC-related ICH must be given vitamin K, otherwise a rebound coagulopathy might develop if the others reverting factors are administered.

Fresh frozen plasma (FFP): FFP has been used for many years as the main therapy for OAC rever-

Table 2. *Recommendations regarding reversal of OAC in patients with OAC-related ICH*

Guidelines	Recommendations
AHA/ASA (2010) (43)	– Patients with ICH whose INR is elevated due to OACs should have their warfarin withheld, receive therapy to replace vitamin K–dependent factors and correct the INR, and receive intravenous vitamin K (Class I; Level of Evidence: C). – PCCs have not shown improved outcome compared with FFP but may have fewer complications compared with FFP and are reasonable to consider as an alternative to FFP (Class IIa; Level of Evidence: B). – FVIIa does not replace all clotting factors, and although the INR may be lowered, clotting may not be restored in vivo; therefore, rFVIIa is not routinely recommended as a sole agent for OAC reversal in ICH (Class III; Level of Evidence: C). – Although rFVIIa can limit the extent of hematoma expansion in noncoagulopathic ICH patients, there is an increase in thromboembolic risk with rFVIIa and no clear clinical benefit in unselected patients. Thus rFVIIa is not recommended in unselected patients. (Class III; Level of Evidence: A). – The usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is unclear and is considered investigational (Class IIb; Level of Evidence: B)
EUSI (2006) (44)	– In patients with OAC-associated ICH and NR>1,4: OAC should be discontinued and the INR normalized with PCC or FFP. Intravenous Vitamin K should be added (Class IV Evidence)

PCC: prothrombin complex concentrates, FFP: fresh frozen plasma

sal. The administration of FFP rapidly restores clotting factor levels and a rapid correction of INR is possible. Requires concomitant administration of vitamin K. Contains all coagulation factors in non-concentrated form. FFP has some important disadvantages: being a blood product, requires compatibility testing and carries the risk of blood borne infection transmission and transfusion-related acute lung injury (TRALI); is stored frozen, thus requiring at least 15-20 min to thaw; large FFP volumes (800 to 3,500 mL) are often needed and this large volume may lead to an acute heart failure decompensation in patients with atrial fibrillation or cardiac valve disease and ventricular dysfunction; adverse events including allergic reactions and passive alloimune thrombocytopenia are rare but also possible.

Prothrombin complex concentrates (PCC): PCC are prepared from pooled plasma that is virally inactivated and contains vitamin K-dependent factors. PCC is the most widely OAC reversal agent used in Europe. There are two main types of PCC: the three-factor concentrates contain therapeutic amounts of factors II, IX, and X, while the four-factor concentrates additionally contain factor VII. The INR has to be monitored within 15 min of the dosage, and vitamin K must be added. PPC are administered more quickly than FFP, as they not require blood checking or thawing, and there is no risk of volume overload. INR reversal with PPT is very fast. PCC risks include potential thrombotic complications and disseminated intravascular coagulation.

Recombinant factor VIIa (rfVIIa): rfVIIa is the cloned activated form of endogenous human hemostatic factor VII. Its original use was for hemophiliac patients. rfVIIa is given as an IV bolus over 2-5 min, with its onset of action being almost immediate and clinically apparent hemostasis observed within 10 min. However, due to its short half-life, a rebound increase in INR may occur. There is no risk of blood-borne pathogen transmission, but there is a clinically important risk of thrombotic complications (48). A systematic review of 35 clinical trials reported arterial and venous thromboembolic rates between 5.3% and 5.5% (49). Due to this high thrombotic risk it is not FDA approved for reversal of anticoagulation in patients with hemorrhagic complications and the current AHA/ASA Guidelines recommend against routine use (50) (16) (43).

Several studies have compared the use of PPC and FFP in patients with OAC-related ICH. The overall conclusion is that is that PPC is statistically significant faster in correcting the INR. In addition, the use of FFP was associated with more adverse events, primarily attributable to fluid overload. The question that still remained without a clear answer is whether a shorter time of OAC-effect reversal or whether even the reversal itself is associated with an improvement in prognosis and mortality. Multiple small retrospective studies failed to demonstrate any significant improvement in prognosis or survival (50). This may very well be due to the underpowered sample size of the studies. A large prospective study to determine whether rapid INR correction is effective in improving short and long term outcome is still needed.

RESUMPTION OF ANTICOAGULATION

The two major questions to consider are whether the benefits of restarting anticoagulation outweigh the risks of hematoma growth and ICH recurrence, and if so, when should anticoagulation be restarted?

The little evidence available on restarting oral anticoagulation after ICH comes from either expert opinions or nonrandomized mainly retrospective studies which showed nonconclusive and even discrepant results.

Dr. De Vleeschouwer and his colleagues (51) performed an observational study that included 108 patients with OAC-related ICH in whom they assessed the thrombotic event rate and the recurrent intracranial bleeding rate during a median follow-up period of 12 months. The overall thrombotic event rate in the group in which OAC were not restarted was low, with only eight thrombotic events during a period of 11590 unprotected patient-days, of which only 2 were cerebrovascular thrombotic events. In the group in which the OAC was restarted (25 patients), no thrombotic event was recorded, either before or after OAC was restarted, the median time of cessation of OAC being 11 days. On the other hand, eight recurrent bleedings was recorded, 6 of which were subdural. The majority of the rebleedings occurred early after the initial bleeding, while only one occurred after OAC were restarted. Their conclusion is that OAC can be stopped safely for a considerable period with a very low overall thrombotic event rate. The recurrent bleeding risk after restarting OAC was low in their study, the majority of the recurrent hemorrhages having occurred before restarting anticoagulation. They attributed these hemorrhages to the insufficient correction of the initial coagulation deficit.

Dr. Claassen and his colleagues (52) conducted a follow-up study (median follow-up period: 36

months) who included 50 patients. The study group was divided in two subgroups according to the resuming of anticoagulation. Of the 23 patients who restarted OAC treatment 1 had a recurrent nontraumatic OAC-related ICH, 2 had traumatic ICH, and 2 had major extra cranial hemorrhage. Of the 25 patients who did not restart OAC therapy, 3 had a thromboembolic stroke, 1 had a pulmonary embolus, and 1 had a distal arterial embolus. Survival analysis showed that 86.1% of the patients in the nonrestarted group were free of thromboembolic complication after 1 year, whereas 73.6% were free of thromboembolic event after 3 years. When all ICH events were accounted for, 100% of the patients who restarted warfarin therapy were free of ICH after 1 year, whereas 92.9% of the patients were free of ICH at 3 years. Furthermore, when all hemorrhagic and thromboembolic events were considered as a combined end point, there was no significant difference between the groups. Despite of the lack of statistically significant differences, their observational results suggest that recurrent ICH after resumption of warfarin therapy occurs less frequently than recurrent thromboembolic events do in patients who do not restart this therapy.

Dr. Romualdi and her team published a thoroughly review (53) of the studies published before January 2008, regarding OAC therapy in patients with mechanical heart valves and OAC-related ICH. Six observational cohort studies and 13 case-reports including a total of 138 patients were included in the analysis. Available evidence suggested that restarting OAC after few days and, indirectly, stopping OAC therapy for few days were both apparently safe. OAC was restarted after a broad range of time (2 days to 3 months): the heterogeneity of data did not allow a statistical analysis but many physicians stopped therapy for 7-14 days. On the basis that in the worst-clinical-case scenario, the incidence of thromboembolic events in the absence of anticoagulant therapy in patients with a mechanical bileaflet valve is 22 per 100 patient-years, which corresponds to a 0.06% daily risk (i.e. 6 in 10,000 patients), she concludes that a short interruption of anticoagulation may not be as dangerous as is often presumed taking into account that the risk of severe organs damage as a bleeding result when anticoagulation is not fully interrupted is probably much higher in these situations.

Another review published by dr. Hawryluk and his colleagues (54), which included 63 publications regarding OAC-related ICH in patients with different thromboembolic risk factors (a total of 492 patients), also advocates for an early resumption of OAC treatment. The authors found that patients who received OAC after 72 h from the beginning of the bleeding were significantly more likely to have a thromboembolic complication and those restarted before 72 h were more likely to have a hemorrhagic complication. They also found that re-initiation of OAC at a lower intensity significantly increased the risk of thromboembolic complications.

Data regarding this issue of resumption of anticoagulation after an OAC-related ICH is attributed a class IV of evidence in the current guidelines provided by the EUSI and a class IIa, level B of evidence in the ones provided by the AHA/ASA (Table 3).

Table 3. *Recommendations regarding resumption of OAC in patients with OAC-related ICH*

Guidelines	Recommendations
AHA/ASA (2010) (43)	– Avoidance of long-term anticoagulation as treatment for nonvalvular atrial fibrillation is probably recommended after spontaneous lobar ICH because of the relatively high risk of recurrence (Class IIa; Level of Evidence: B). – Anticoagulation after nonlobar ICH and antiplatelet therapy after all ICH might be considered, particularly when there are definite indications for these agents (Class IIb; Level of Evidence:B). – In situations where stratifying a patient's risk of recurrent ICH may affect other management decisions, it is reasonable to consider the following risk factors for recurrence: lobar location of the initial ICH, older age, ongoing anticoagulation, presence of the apolipoprotein E ε2 or ε4 alleles, and greater number of microbleeds on MRI (Class IIa; Level of Evidence: B)
EUSI (2006) (44)	– After having re-checked the indication for anticoagulation (following the EUSI recommendations on ischaemic stroke) oral anticoagulation treatment may be continued after 10-14 days, depending on the perceived risk of thromboembolic occlusion and ICH recurrence (Class IV evidence) – Currently the EUSI is recommending the preventive use of anticoagulations for patients who have had an embolic stroke associated with atrial fibrillation, prostethic heart valves or other proven cardioembolic sources. In a state-transition decision model stratified by location of haemorrhage, it was found that in patients with atrial fibrillation and a lobar location of ICH, restarting anticoagulation would not lead to a benefit in terms of quality-adjusted life years because the risk of rebleeding and a higher chance of death would outweight the risk of occurrence of cerebral ischaemia. This was different for patients with deep location ICH.

Accordingly to both the AHA/ASA and EUSI guidelines, the attitude regarding the resumption of OAC should be dictated by the underlying pathology that requires anticoagulation and the related thromboembolic risk and by the factors associated with a high risk of hemorrhage recurrence. These factors include older age, previous ICH, APO ε II or IV genotype, imagistic findings of extended leukoaraiosis and microbleeds (which are all factors associated with the risk of ICH in patients undergoing OAC) and the hemorrhage location (43) (44). The topographical location is often the clue for the underlying mechanism. A deep hemisferic or pontine bleeding, characteristic for hypertensive vasculopathy, seems to be associated with a lower risk of recurrence, assuming that a good control of the blood pressure can be achieved, while a lobar hemorrhage is more likely related to CAA in the aged population and therefore the risk of recurrence is considered to be higher (55). Currently, hypertension is considered to be the most important modifiable risk factor for prevention of ICH recurrence.

The optimal timing of resumption of OAC was debated between many authors. While the above mentioned studies and reviews are in favor of a period between 3 and 14 days, dr. Majeed and his team conducted a large retrospective cohort study (56) that included 234 patients with OAC-related ICH who were receiving treatment with warfarin at the time of ICH diagnosis, with the aim to assess the optimal time for resumption of OAC. The median follow-up was 69 weeks (IQR:19-144). Their conclusion is that the resumption should be delayed by 10 to 30 weeks to avoid the early high-risk period for recurrent hemorrhage, during which full anticoagulation appears to increase this risk 5-fold. Based on the data obtained from this study, they calculated that resumption of OAC after 1 month would confer a 16% risk of recurrent ICH during the first year. This study is probably the first multicenter study with analysis of the optimal timing of resumption of anticoagulation performed by calculating hazards of recurrent hemorrhage and of ischemic stroke, with or without warfarin. It is worth mentioning that this study has some limitations, the main being the retrospective design with resumption of anticoagulation occurring at different time points and the fact that the conclusions are based on relatively few clinical events.

On the same side of the fence also stands dr. Eckman and his team (57). They used a decision analysis to evaluate whether warfarin should be restarted and they based this partly on the data from a prospective cohort of 435 patients with intracerebral hemorrhage, not specifically OAC associated. The authors calculated a risk of recurrence of 15% per year after lobar ICH and of only 2.1% per year after deep hemispheric hemorrhage. Unfortunately, according to some studies lobar hemorrhage appears to be approximately 50% more common than deep hemispheric hemorrhage among the survivors (56) (58).

In the light of these findings the optimal timing for resumption of OAC treatment after ICH seems to remain still undecided. In the acute phase, the risk of hematoma growth from restarting anticoagulation exceeds the risk of thromboembolism from discontinuing it. Later on, the risk of stroke and systemic embolism in the absence of OAC exceeds that of rebleeding. Therefore, the EUSI recommend that in patients with a high risk of thromboembolism, anticoagulation should be restarted between 10 and 14 days. Several authors however, disagree and suggest that the optimal time for resumption of anticoagulation should be between 10 and 30 weeks.

In patients with atrial fibrillation and an unfavorable risk/benefit profile to restarting OAC, antiplatelet therapy may be a reasonable alternative. The ACTIVE A, a randomized, double-blind study (59) reported the safety and efficacy of adding clopidogrel 75 mg daily to aspirin 75 to 100 mg daily in patients with high-risk atrial fibrillation and a contraindication to warfarin. Subjects who received clopidogrel and aspirin had a 0.8% per year absolute risk reduction of major vascular events at the cost of 0.7% per year increase in major bleeding events. However, the number of patients with previous ICH was not mentioned and therefore the results may not directly apply to the patients with previous ICH.

In some patients in whom the risk of hemorrhage recurrence is considered unacceptable, the use of a left atrial appendage (LAA) occlusion device may be taken into consideration. LAA occlusion is a treatment strategy in atrial fibrillation for preventing blood clot formation which in almost 90% of cases forms in this specific area. This technique presumes a cardiac catheterization during which an expandable frame is placed in left atrial appendage. To the date there is only one device approved by US Food and Drug Administration (WATCHMAN device by Atritech Inc.) and included in the 2010 European Society of Cardiology Guidelines for Management of Atrial Fibrillation based on the results of PROTECT-AF trial which showed a non-inferior rate of stroke in the group with LAA occlusion compared to warfarin group

and a lower rate of hemorrhagic stroke but with a higher rate of adverse events mainly due to periprocedural complications. These main adverse events consist in catheter-based techniques risks, pericardial effusion, incomplete appendage closure, dislocation of device and blood clot formation on the device (60).

Two new oral anticoagulants were approved last year and can be used for prevention of thromboembolic events in patients with atrial fibrillation. Although rivaroxaban and the 110 mg twice a day dose of dabigatran were proven to have the same efficacy as warfarin but fewer hemorrhagic adverse events, safety and efficacy in patients with prior ICH is completely lacking.

Once ICH occurs, the decision of whether and when to restart anticoagulation is a true therapeutic challenge that requires balancing the risks of hematoma growth or recurrent ICH and disabling thromboembolic events. Although the risk of thromboembolism in patients off anticoagulation seems to be higher than the risk of ICH recurrence, there is a marked paucity of prospective large studies on the real risk of ICH recurrence when OAC is resumed, paucity that probably reveals the ethical challenge of prescribing patients a medication to which they have an apparent contraindication (1). The current dilemma is likely to persist despite ongoing efforts to perform a large prospective study given the heterogeneity of the underlying causes of OAC-related ICH and patient populations.

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