Anticoagulation decisions in elderly patients with stroke

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Abstract

Primary and secondary prevention of stroke is often a challenge in elderly patients due to the increase in both thrombotic and hemorrhagic risks with age. In some cases, there is sufficient data in the elderly population to allow recommendations or anticoagulation decisions to be made, such as for the indication of anticoagulation to prevent stroke related to atrial fibrillation (AF) or the choice of oral anticoagulant therapy in this situation. In other situations, the less robust data leave some questions; this is the case for the delay to initiate an oral anticoagulant therapy after an AF-related ischemic stroke, for the management of antithrombotic treatment after a stroke of undetermined cause or after intracranial bleeding or in a high-risk bleeding situation associated with stroke in the elderly subject. These issues will be discussed in this paper.

Introduction

Age is the major non-modifiable risk factor for stroke. Stroke remains a common cause of death and disability in elderly patients (defined in the present paper as those aged 75 years and older) (1). Clinical outcomes after stroke are highly influenced by age and tend to be much worse for older patients even after adjusting for comorbidities (2). Epidemiological data show an increase in prevalence of stroke with advanced age and an important increase in atrial fibrillation (AF) cardioembolic stroke in the very elderly (3,4). Indeed, prevalence of AF in patients 80 years or older is about 10% with a rise in more elderly patients (5). Therefore, oral anticoagulant therapy (OAT) is often indicated for primary or secondary prevention of ischemic stroke in an elderly patient. When the indication of OAT has been retained in an elderly patient, there remains the question of the choice of the oral anticoagulant between antivitamin K antagonists (VKAs) and direct oral anticoagulants (DOAs). Despite clear guidelines regarding anticoagulation for elderly patients with AF, OAT remains challenging in frail older patients, with comorbidities and polypharmacy. Indeed, the both thromboembolic and bleeding risks are the highest in the geriatric population. Thus, some situations increasing the risk of intracranial hemorrhage (ICH) may affect the benefit-risk ratio of OAT: history of hemorrhagic stroke, cerebral amyloid angiopathy, microbleeds.

Older patients in guidelines

Elderly patients are mainly mentioned in the recommendations on the prevention of embolic stroke risk in AF. The prevalence of AF increases with age and is about 10-20% for patients aged 80 years or above (6, 7). Age is also one of the strongest risk factors for ischemic stroke in AF (8). OAT significantly reduces stroke and mortality in patients with AF; the net clinical benefit of OAT for stroke prevention in AF patients is almost universal, with the exception of patients at very low stroke risk. Advancing age is associated with increases of both thromboembolic risk and antithrombotic drug-related bleedings. But the high stroke risk without OAT often exceeds the bleeding risk on OAT, even in the elderly, in patients with cognitive dysfunction, or in patients with frequent falls or frailty (9-11). However, OAT is widely underused in the oldest patients and uncertainties in OAT prescription in these

patients seem to derive from safety rather than efficacy concerns (12). A recent real-world cohort study was conducted to assess the absolute benefit of OAT in very elderly AF patients (aged 85 and older) mainly treated with VKA (13). The absolute benefit was evaluated by a composite end point including ischemic stroke, systemic embolism, myocardial infarction, hemorrhagic stroke and major bleeding within 1-year follow up. The results confirmed that the risk of stroke increases with age more than the risk of bleeding; the absolute benefit of OAT is highest in very elderly patients and this outweighs the bleeding risk, achieving the most favorable net clinical benefit as patients get older.

In conclusion, guidelines support a policy of OAT for the very elderly patients with AF (14,15). In this age group, there is no need to perform the $CHAD_2DS_2VASc$ score for indication of anticoagulation as age 75 or older put them into a high thromboembolic risk population (16). However, a geriatric evaluation may be useful to address modifiable bleeding risk factors by assessing comorbidities and the patient's functional status (6,17). The comprehensive geriatric assessment enables the detection of “frailty” using screening tools assessing cognitive dysfunction or mood disorders, risk of falls, polymedication, nutritional status, autonomy and social environment.

DOAs vs VKAs in elderly patients with AF

To prevent stroke in patients with AF, VKAs have been a long time the reference anticoagulant treatment and they demonstrated a net benefit, including in elderly patients. The availability of the DOAs has simplified the OAT. The main advantages of DOAs are that they allow a fixed dose administration without monitoring of routine coagulation profiles and exhibit fewer drug interactions. Guidelines recommend DOAs over VKAs in non-valvular AF patients, namely patients without mechanical heart valves or moderate or severe mitral stenosis (14,15). However, data for the use of DOAs in frail elderly population were initially limited and their benefit-risk ratio remained questioning. Here we focus on three DOAs with authorization in this indication in France: a direct thrombin inhibitor (dabigatran etexilate) and two factor Xa inhibitors (rivaroxaban and apixaban)

In randomized clinical trials (RCTs) evaluating DOAs vs VKAs in AF, patients aged 75 or older are not so underrepresented. They are respectively 40% of the 18113 patients included in the RE-LY trial (dabigatran), 44% of the 14269 patients included in the ROCKET AF trial (rivaroxaban), and 31% of the 18205 patients included in the ARISTOTLE trial (apixaban) (18-20). But RCTs patients are selected elderly patients, with better clinical status than real-world frail patients as illustrated by the fairly low mean values of the thrombotic risk scores (mean $CHADS_2$ score of 2.1 in the RE-LY, 2.2 in the ARISTOTLE, and a little higher at 3.5 in the ROCKET AF). This is also illustrated by the low prevalence of patients with a creatinine clearance < 50 mL/min (estimated using the Cockcroft and Gault formula): 19% in the RE-LY, 20% in the ROCKET AF, and 17% in the ARISTOTLE. Several meta-analyses of theses RCTs were conducted to compare efficacy and safety of DOAs between elderly patients and non-elderly patients with AF compared with warfarin (21-24). Elderly patients were mainly defined as patients ≥ 75 years old but some data is available for patients over 80 years old. The primary efficacy outcome was stroke and systemic embolism and the primary safety outcome was major bleeding. The results of these meta-analyzes are concordant in favor of the use of DOAs in the elderly population. In elderly patients, stroke or systemic embolic events were significantly less frequent in DOAs group than in warfarin group with a relative risk (RR) reduction around 20%; this RR reduction is even around 30% when age subgroups were defined by age ≥ 80 years or age < 80 years (23). For major bleeding events in elderly patients, the results showed a nonsignificant reduction of a few percent between the DOAs group and the warfarin group ; this is mainly driven by neutral results of dabigatran in RE-LY and rivaroxaban in ROCKET-AF, and apixaban showed significant improvements in elderly patients' major bleeding risk (24). Some specific data is available for ICH and for gastrointestinal bleedings (GIB) (23). The risk of ICH in elderly patients is significantly lower in the DOAs group than in the warfarin group with a RR reduction of 51% to 58% for standard-dose DOAs or low-dose DOAs respectively. In contrast the risk of GIB is higher in the standard-dose DOAs group than in the warfarin group (RR 1.53, 95%CI 1.27-1.85). In summary of these meta-analyses, for elderly patients aged 75 years or older, DOAs showed better efficacy end equivalent safety compared to warfarin. Note that head-to-head

comparisons between DOAs should be extrapolated with caution due to different study designs ad patients characteristics (17). Moreover, results from phase III RCTs should be wisely generalized to real-life older AF patients.

During last years, many observational studies therefore evaluated safety and efficacy of DOAs and VKAs in real-life AF patients. To interpret their results, a selection bias inherent to this type of study must be taken into account: warfarin may still be preferred for elderly, patients with higher stroke or bleeding risk, and those with more comorbidities, as shown in pharmaco-epidemiological studies (25,26). Observational studies are now so numerous, with cohorts of AF patients from different regions of the world and with heterogeneous characteristics, that their data must be combined in reviews or meta-analysis. A recent one was conducted to provide evidence for the treatment of more than 428 000 AF patients aged ≥ 75 years (27). The primary effectiveness outcome was ischemic stroke and safety outcomes were major bleeding, ICH, GIB, and mortality. With the limitations related to the biases of such observational studies, the results were quite close to those of the RCTs. The risk of ischemic stroke was slightly lower for DOAs than for VKAs (RR 0.86, 95%CI 0.75-0.99). There were no significant differences between DOAs and VKAs for pooled major bleedings or for mortality, but there were a significantly lower risk of ICH (RR 0.56, 95%CI 0.48-0.67) and a significantly higher risk of GIB (RR 1.46, 95%CI 1.31-1.63) with DOAs than with VKAs. However, the authors note a persistent scarcity of evidence on the safety and effectiveness of DOAs in older AF patients. Data came from subgroup or sensitivity analyses within larger studies, which meant that detailed information was often lacking for the specific group of patients ≥ 75 years (27). For instance, it can be reported that older patients most frequently receive low-dose DOAs. There is some evidence from observational studies that dose-adjusted DOA therapy is often inappropriately prescribed, being underdosing more frequent that overdosing, and that this behavior might be associated with lower efficacy and safety outcomes (28-30).

Finally, it should be noted that the characteristics of patients initiated on DOAs have changed over time, underlining the need for ongoing surveillance of the use of DOAs in

different populations in clinical practice, especially in oldest and more vulnerable patients, and for longitudinal efficacy and safety analysis of these drugs (25,26).

In the previous sections, we detailed data concerning stroke prevention for elderly AF patients for which recommendations exist. Older patients are not specifically considered in guidelines for other situations such as anticoagulation management after an ischemic stroke, management of a hemorrhagic stroke, benefit-risk balance in case of cerebral lesions at high risk of bleeding.

Initiation of OAT after a AF-related acute ischemic stroke

The patients with AF-related stroke typically have larger infarct areas and poorer outcomes (31,32). Long-term anticoagulation is standard therapy for secondary stroke prevention in patients with AF (33,34). However, there is a lack of consensus regarding the optimal time to initiate therapy. Current guidelines state that it is reasonable to initiate anticoagulation within 4 and 14 days after the onset neurological symptoms but do not currently point to a more specific time window (35). The guidelines also state that it is reasonable to delay initiation of anticoagulation in the presence of high risk for hemorrhagic conversion such as a large infarct or hemorrhagic transformation on initial imaging. The European Heart Rhythm Association proposes recommendations on the initiation of anticoagulation based on consensus opinion, in what is known as the '1-3-6-12 day rule': in patients with TIA and AF, oral anticoagulation can be initiated at day 1 in naive patients or can be continued in patients who were on anticoagulation. In patients with mild stroke (NIHSS < 8, National Institute of Health Stroke Scale), oral anticoagulation can be initiated after 3 days, or after ICH is excluded by imaging (CT or MRI). In patients with moderate stroke (NIHSS 8–16), anticoagulation can be started after 5–7 days, and in severe stroke (NIHSS > 16) after 12–14 days. In the last scenario, repeat cerebral imaging has to be performed to rule out significant hemorrhagic transformation of the initial ischemic stroke (36).

These data are derived almost exclusively from heparins and Vitamin K antagonists (e.g. warfarin) use. Now that DOAs have become the mainstay of stroke prophylaxis in AF, the

question of optimal timing of DOAs initiation is of increasing importance. Several observational studies suggest that early initiation of DOAs is associated with a low hemorrhage rate and later initiation is associated with increased frequency of recurrent ischemic stroke (37). To answer this question, four independent, randomized, multi-site trials are underway. Two of these rely on a dichotomized exposure of early versus late initiation and a third assigning intervals based on severity and imaging features of the index stroke (37).

The ongoing START trial (NCT03021928) proposes to determine if there is an optimal delay time to initiate anticoagulation after AF-related stroke that optimizes the composite outcome of hemorrhagic conversion and recurrent ischemic stroke. This study is the only one which randomly assigns patients to four distinct time intervals across the current window accepted as standard of care: the four arms for mild to moderate stroke are: Day 3, Day 6, Day 10, and Day 14. The time intervals for severe stroke are: Day 6, Day 10, Day 14, and Day 21 (38).

In some cases, a temporary therapy with full-dose low-molecular-weight heparin (LMWH) is administered alongside warfarin until the therapeutic international normalized ratio level is achieved. This bridging therapy must be avoided as much as possible because we know now that full-dose LMWH can be harmful in acute stroke care (39) in particular in the presence of AF (40), there are anecdotal reports of its use in selected patients (41,42). A recent study confirms that patients receiving low-molecular-weight heparin before the use of DOAs have a higher risk of early ischemic recurrence and hemorrhagic transformation compared with non-bridged patients (43).

Embolic strokes of undetermined source and DOAs

Embolic strokes of undetermined source (ESUS) represent 20% of ischemic strokes and are associated with a high rate of recurrence. Several studies have attempted to demonstrate the interest of DOAs in this situation.

An earlier randomized trial NAVIGATE ESUS compared the efficacy and safety of rivaroxaban (at a daily dose of 15 mg) with aspirin (at a daily dose of 100 mg) for the prevention of

recurrent stroke in patients with recent ischemic stroke that was presumed to be from cerebral embolism but without arterial stenosis, lacunar lesion, or an identified cardioembolic source. The primary efficacy outcome was the first recurrence of ischemic or hemorrhagic stroke or systemic embolism in a time-to-event analysis; the primary safety outcome was the rate of major bleeding. A total of 7213 participants were enrolled; 3609 patients were randomly assigned to receive rivaroxaban and 3604 to receive aspirin. The mean age of the patients was 67 years and 21% were older than 75 years. Patients had been followed for a median of 11 months when the trial was terminated early because of a lack of benefit with regard to stroke risk and because of bleeding associated with rivaroxaban. Rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke of undetermined source: 172 patients in the rivaroxaban group (annualized rate, 5.1%) and in 160 in the aspirin group (annualized rate, 4.8%) (HR 1.07; 95%CI 0.87-1.33). The results were comparable in the population over 75 years old. The rivaroxaban was associated with a higher risk of bleeding: 62 patients in the rivaroxaban group (annualized rate, 1.8%) and in 23 in the aspirin group (annualized rate, 0.7%) (HR 2.72; 95%CI 1.68-4.39; p<0.001) (44).

RE-SPECT ESUS study is a multicenter, randomized, double-blind trial of dabigatran at a dose of 150 mg or 110 mg twice daily as compared with aspirin at a dose of 100 mg once daily in patients who had had an ESUS. Dabigatran was administered at a dose of 150 mg twice daily, but in patients 75 years of age or older and in patients who had an estimated creatinine clearance of 30 to 50 mL/min, dabigatran was administered at a dose of 110 mg twice daily. The primary outcome was recurrent stroke. The primary safety outcome was major bleeding. A total of 5390 patients were enrolled at 564 sites and were randomly assigned to receive dabigatran (2695 patients) or aspirin (2695 patients). The mean age of the patients was 64.2 years and 19% were older than 75 years. During a median follow-up of 19 months, dabigatran was not superior to aspirin in preventing recurrent stroke: 177 patients (6.6%) in the dabigatran group (4.1% per year) and in 207 patients (7.7%) in the aspirin group (4.8% per year) (HR 0.85; 95%CI 0.69-1.03). On the other hand, in patients over 75 years old, a benefit was found in favor of dabigatran (HR 0.63; 95%CI 0.43-0.94). The incidence of major

bleeding was not greater in the dabigatran group than in the aspirin group: 77 patients (1.7% per year) in the dabigatran group and in 64 patients (1.4% per year) in the aspirin group (HR 1.19; 95%CI 0.85-1.66). But there were more clinically relevant non major bleeding events in the dabigatran group: 70 patients (1.6% per year) and 41 patients (0.9% per year), respectively (45).

ATTICUS randomized trial is designed to determine whether the factor Xa inhibitor apixaban administered within 7 days after ESUS is superior to acetylsalicylic acid for prevention of new ischemic lesions documented by brain magnetic resonance imaging within 12 months after index stroke. The study is still ongoing (46).

To date, the DOAs should not be used in the ESUS. By against, it is essential to give the means to detect the AF in these situations. Other parameters will probably be important to take into account, such as the size of the left atrium.

Stroke prevention after intracranial hemorrhage (ICH)

Resumption of OAT after ICH?

A relevant proportion of ICH patients are simultaneously at increased risk of ischemic disease including myocardial infarction and stroke. About 15–20% of ICH patients have an indication for long-term anticoagulation, usually because of AF, with 90% of them having a CHA2DS2VASc score of 2 or greater. Management of these patients has to weigh the benefits as well as the risks of prescribing or withholding antithrombotic therapy (47).

Due to low quality of evidence, the 2014's & 2015's guidelines did only provide little help, suggesting a multidisciplinary approach for individual decision making (48,49). While the benefit of OAT for prevention of thromboembolic complications, caused by several indications like AF, artificial heart valves, deep vein thrombosis and pulmonary embolism, or coagulopathies, is generally accepted, OAT resumption after ICH is mainly an issue of safety, i.e. risk of recurrent ICH (50).

Recurrence risk is related to several modifiable and non-modifiable factors. Age and stroke history represent non-modifiable risk factors for both thromboembolic and hemorrhagic complications, reflected by their simultaneous integration into commonly used stratification

models (CHADS2-Score and HAS-BLED-Score) (51). The same holds true for uncontrolled arterial hypertension representing a major and modifiable risk factor especially for recurrence of ICH, increasing HR to 3.5 (95%CI 1.7-7.5, p=0.001) in lobar ICH and to 4.2 (95%CI 1.0-17.5, p<0.05) in non-lobar ICH (52). Distinguishing location of index ICH is of outmost importance because of the strong relation between lobar ICH and cerebral amyloid angiopathy (50). Lobar location increases the risk of recurrent ICH shown by longitudinal data (n=1145) documenting a duplication of the annual recurrence rate compared to non-lobar ICH (7.8% versus 3.4%) (52). In concordance, a meta-analysis of 9 cohort studies including 1552 patients investigated the first ever ICH risk in relation to cerebral microbleed status in patients with ischemic stroke and AF using long-term OAT (53). The annual ICH incidence rate rose from 0.3% in patients without microbleeds to 0.8% in patients with any microbleeds and to 2.5% in patients with more than 5 microbleeds (53). Moreover, a vast number of additional factors – gender, diabetes mellitus, serum lipid levels, smoking, alcohol or drug abuse, and further medication subtly interacting with coagulation and platelet function – have been documented to be associated with ICH recurrence, complicating the decision if, when and how to resume OAT after ICH (50).

From the year 2015 onwards there was growing evidence. The observational RETRACE study included patients with OAT-associated ICH and investigated thromboembolic and hemorrhagic complication rates according to OAT exposure during one year of follow-up (54). Among 719 survivors with AF, resumption of OAT significantly reduced thromboembolic events (OAT: 9/172 [5.2%] versus no-OAT: 82/547 [15.0%]; p<0.001) without leading to increased rates of re-bleeding (OAT: 14/172 [8.1%] versus no-OAT: 36/547 [6.6%]; p=0.48). Furthermore, OAT resumption was associated with a decreased long-term mortality risk among patients included in a propensity-matched survival analysis (HR 0.258; 95%CI 0.125-0.534; p<0.001); i.e. 9 patients with OAT of 108 died (8.3%) compared to 47 patients without OAT of 153 (30.7%; p<0.001) (54). The same year, a large Danish registry including 1752 patients reported data strongly supporting these results (55). The authors found a significantly decreased adjusted HR (0.55; 95%CI 0.39–0.78) for all-cause mortality, stroke, and systemic embolism in patients on oral anticoagulant treatment in comparison with no

treatment during 1-year follow-up. The annual incidence rate of ischemic stroke and systemic embolism among patients using OAT was halved (5.3; 95%CI 3.3-8.5 per 100 patient years) compared with patients without antithrombotic treatment or on antiplatelet therapy. For recurrent ICH, rates of 8.0 for OAT treated patients again did not significantly differ from 8.6 for patients with no antithrombotic treatment (adjusted HR 0.91; 95%CI 0.56-1.49), and 5.3 for patients using antiplatelet therapy (adjusted HR 0.60; 95%CI 0.37-1.03). Another Danish population-based cohort study (n=2978) confirmed these results, showing a significant lower risk of death (adjusted HR 0.59; 95%CI 0.43-0.82) and thromboembolic events (adjusted HR 0.58; 95%CI 0.35-0.97) in ICH patients with post-discharge use of OAT, again without significantly increasing risks for major bleedings or recurrent ICH (adjusted HR 0.65; 95%CI 0.41-1.029) (56). These results favoring resumption of OAT were further reproduced by several subsequent observational and registry studies (57-59).

Several meta-analyses of reported data have been conducted until now, all of them showing a significant reduction of thromboembolic complications without leading to increased risk of ICH recurrence (60-63). Furthermore, antiplatelet agents – sometimes considered as a safer alternative approach – were not beneficial neither for thromboembolism prophylaxis nor prevention of ICH recurrence (61). One recent meta-analysis of individual patient data (n=1012) did also address the association of OAT resumption with functional outcome, documenting that OAT resumption increases chances for a favorable outcome after 12 months (modified Rankin Scale 0–3) by 4-fold in both non-lobar and lobar ICH patients (64).

Even in the absence of recurrent clinically apparent stroke, patients resuming OAT seem to benefit with respect to better functional recovery, hypothetically due to prevention from micro- embolism cumulating to significant central nervous system damage influencing post-ICH recovery associated with cardioembolic stroke risk (65).

Of note, all of these observational studies harbor important limitations due to confounding by indication and selection bias (50). Physicians individually weigh patient's risk for ischemic versus hemorrhagic complications which results in selected patients with favorable risk-benefit-profiles restarting OAT. This might also be reflected by their younger age, less severe ICH, and better functional outcome in observational studies (54, 66).

In general, withholding therapy in severely affected patients is frequent in ICH care possibly further affecting post-discharge drug prescription (66, 67). As statistical adjustment is to a large extent possible for quantifiable parameters, additional unmeasured variables likely introduce residual bias influencing the reported associations (61, 66). Further, many investigations included heterogeneous patient cohorts combining different intracranial pathologies – mostly ICH, but also patients with subarachnoid hemorrhage, epidural or subdural hematomas – as well as OAT indications AF, mechanical heart valves, deep vein thrombosis – each strongly influencing patients individual risk for recurrent hemorrhage or thromboembolism (50).

Randomized controlled trials (RCTs) have not been performed to address this treatment dilemma: resumption or not after ICH? Recently, RESTART Study (REstart or STop Antithrombotics Randomised Trial) estimated the relative and absolute effects of antithrombotic drug on recurrent ICH and whether this risk might exceed any reduction of occlusive vascular events. In this study, the risk of recurrent ICH is probably too small to exceed the established benefits of antiplatelet therapy for secondary prevention. Only effects of antiplatelet therapy were studied, patients with long-term anticoagulation indication were excluded (38).Randomized controlled trials (RCTs) have not been performed to address this treatment dilemma. Recently, RESTART Study (REstart or STop Antithrombotics Randomised Trial) estimated the relative and absolute effects of antithrombotic drug on recurrent ICH and whether this risk might exceed any reduction of occlusive vascular events. In this study, the risk of recurrent ICH is probably too small to exceed the established benefits of antiplatelet therapy for secondary prevention. Only effects of antiplatelet therapy were studied, patients with long-term anticoagulation indication were excluded (68).

Wich OAT after ICH?

Although data from observational studies in the vast majority solely cover resumption of OAC using vitamin-K antagonists (VKA), it seems apparent that DOAs (50). In general, DOAs were associated with a significant 54% relative risk reduction compared with warfarin (Odds Ratio [OR] 0.46; 95%CI 0.35-0.59; $p<0.001$). However, this analysis referred to drug safety

only and did not focus on inter-class effects regarding prevention of thromboembolic events (69). In fact, no guideline for DOA therapy after acute ICH in patients with AF who were treated with DOA has yet been established. No studies to date have evaluated specifically the safety or effectiveness of resumption of DOA therapy in patients with acute ICH. One recent prospective study investigated 43 patients with ICH who were treated with DOA for nonvalvular AF before ICH onset. In half of patients, DOA therapy was resumed relatively early after ICH onset. Early resumption of DOA therapy for ICH in patients with nonvalvular AF (at a median of 11 days, IR: 5-21 days) is considered to be safe. The functional outcome was associated with not only resumption of DOA therapy but also the timing of resumption. A further rigorous analysis may warrant the adequate indications for and timing of DOA therapy resumption in patients with ICH (70).

When start OAT after ICH?

The described observational studies documented a median starting point in between 4 to 6 weeks after ICH. Studies more specifically addressing this question reported a broad range of supposed optimal time points ranging from 72 h to 10–30 weeks (71-72). One large Swedish registry study (n=2619) suggested an optimal time window within 7–8 weeks for resuming OAT after COX regression-based balancing between observed risk of ischemic and hemorrhagic complications (73). Although having used sound statistical approaches, limitations of that study comprise censoring the first 4 weeks after ICH, narrow information on patient and ICH characteristics as well as treatment allocation gathered by outpatient dispensed drug registry. A meta-analysis from the Kings College in London, UK, assessed the associations of resuming VKA six weeks after ICH with occurrence of both thromboembolic and hemorrhagic complications over a one-year follow-up time frame (61). In essence, VKA-resumption was verified to be safe without increasing hemorrhagic complications over comparator treatments with platelet inhibitors (risk ratio [RR] 1.34; 95%CI 0.79-2.30, p=0.28), or no antithrombotic treatment respectively (RR 0.93; 95%CI 0.45-1.90, p=0.84) (61). As yet, it remains unclear when to optimally resume OAT after ICH but ongoing randomized trials might provide further evidence. Current expert opinion would suggest a timeframe between 4 to 8 weeks after index ICH depending on patient's individual risk

profile (50). Application of a shorter time period to resumption may only be considered in life-threatening situations and compelling indications, such as symptomatic intracardiac thrombus formation or acute pulmonary embolism, and only after confirmation of hematoma stability by control imaging and strict blood pressure control.

Left atrial appendage occlusion (LAAO)

Alternatives to restarting antithrombotic drugs, such as LAAO could be an alternative for managing patients in AF with a high risk of cardioembolic stroke after acute ICH.

LAAO can effectively reduce the risk of stroke in patients with non-valvular AF, which is non-inferior to oral anticoagulation treatment with warfarin (74,75).

LAAO might potentially represent an alternative strategy to chronic OAT in high-risk ICH patients, provided its successful evaluation in ongoing randomized-controlled trials – especially compared with DOAs as a safer and potentially more effective comparator than VKA (14,76). Today, according to FDA approval, interventional LAAO is formally contraindicated in patients with high-bleeding risk such as ICH patients and its off-label use should be preceded by a critical and interdisciplinary decision making process (77).

In summary of this last section, figure 1 presents a suggested flow chart on resumption or withholding of OAT intracranial bleeding.

Conclusion

Anticoagulation decision in an elderly patient with stroke is a frequent situation but may be complex in clinical practice. Management of this condition in the geriatric population is riddled with clinical dilemmas. They are accompanied by a high thromboembolic risk but also a concomitant high bleeding risk, requiring clinicians to balance the net clinical benefice. Indeed, these require deliberation to prevent harm to patients but often, clinical situations are complicated by the under-estimation of the thromboembolic risk and overestimation of the bleeding risk. Consequently, OAT continue to be under-used in older individuals.

Risk factor modification, identification of barriers to treatment and involvement of patients and their family members are crucial to the initiation of OAT and improvement of treatment adherence. In the absence of contraindications and as allowed by patients' risk factor

profiles, clinicians should explore DOAs as an alternative to conventional VKAs, particularly as they have been shown to reduce the risk of ICH. This is clearly demonstrated for elderly AF patients, even if real-life data remains remain debatable and will need to be confirmed by specifically geriatric observational studies.

References

1- Carandang R, Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Kannel WB, et al. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. *JAMA* 2006;296:2939-46

2- Saposnik G, Cote R, Phillips S, Gubitz G, Bayer N, Minuk J, et al. Stroke outcome in those over 80: a multicenter cohort study across Canada. *Stroke* 2008;39:2310-7

3- Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008;117:e25-e146

4- Leyden JM, Kleinig TJ, Newbury J, Castle S, Cranefield J, Anderson CS, et al. Adelaide stroke incidence study: declining stroke rates but many preventable cardioembolic strokes. *Stroke* 2013;44:1226-31

5- Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. *Circulation* 2018;138:37-47

6- Hanon O, Assayag P, Belmin J, Collet JP, Emeriau JP, Fauchier L, et al. Expert consensus of the French Society of Geriatrics and Gerontology and the French Society of Cardiology on the management of atrial fibrillation in elderly people. *Arch Cardiovasc Dis* 2013;106:303-23

7- Heeringa J, Van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;27:949-53

8- Hijazi Z, Lindbäck J, Alexander JH, Hanna M, Held C, Hylek EM, et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J* 2016;37:1582-90

9- Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med* 1999;159:677-85

10- Donze J, Clair C, Hug B, Rodondi N, Waeber G, Cornuz J, et al. Risk of falls and major bleeds in patients on oral anticoagulation therapy. *Am J Med* 2012;125:773-8

11- Andreotti F, Rocca B, Husted S, Ajjan RA, ten Berg J, Cattaneo M, et al. Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis. *Eur Heart J* 2015;36:3238-49

12- Bo M, Li Puma F, Badinella Martini M, Falcone Y, Iacovino M, et al. Health status, geriatric syndromes and prescription of oral anticoagulant therapy in elderly medical in-patients with atrial fibrillation: a prospective observational study. *Int J Cardiol* 2015;187:123-5

13- Patti G, Lucerna M, Pecen L, Siller-Matula JM, Cavallari I, Kirchhof P, et al. Thromboembolic risk, bleeding outcomes and effect of different antithrombotic strategies in very elderly patients with atrial fibrillation: a sub-analysis from the PREFER in AF (PREvention oF thromboembolic events-European Registry in Atrial Fibrillation). *J Am Heart Assoc* 2017;6(7)

14- Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893-962

15- Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest* 2018;154:1121-201

16- Lindley RI. Stroke prevention in the very elderly. *Stroke* 2018;49:796-802

17- Bo M, Grisoglio E, Brunetti E, Falcone Y, Marchionni N. Oral anticoagulant therapy for older patients with atrial fibrillation: a review of current evidence. *Eur J Intern Med* 2017;41:18-27

18- Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51

19- Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91

20- Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92

21- Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955-62

22- Bai Y, Guo SD, Deng H, Shantsila A, Fauchier L, Ma CS, et al. Effectiveness and safety of oral anticoagulants in older patients with atrial fibrillation: a systematic review and meta-regression analysis. *Age Ageing* 2018;47:9-17

23- Kim IS, Kim HJ, Kim TH, Uhm JS, Joung B, Lee MH, et al. Non-vitamin K antagonist oral anticoagulants have better efficacy and equivalent safety compared to warfarin in elderly patients with atrial fibrillation: A systematic review and meta-analysis. *J Cardiol* 2018;72:105-12

24- Caldeira D, Nunes-Ferreira A, Rodrigues R, Vicente E, Pinto FJ, Ferreira JJ. Non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: A systematic review with meta-analysis and trial sequential analysis. *Arch Gerontol Geriatr* 2019;81:209-14. Corrigendum *Arch Gerontol Geriatr* 2019;83:338

25- Zhu J, Alexander GC, Nazarian S, Segal JB, Wu AW. Trends and variation in oral anticoagulant choice in patients with atrial fibrillation, 2010-2017. *Pharmacotherapy* 2018;38:907-20

26- Loo SY, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. *Br J Clin Pharmacol* 2017;83:2096-106

27- Mitchell A, Watson MC, Welsh T, McGrogan A. Effectiveness and safety of direct oral anticoagulants versus vitamin K antagonists for people aged 75 years and over with atrial fibrillation: a systematic review and meta-analyses of observational studies. *J Clin Med* 2019;8:554. doi: 10.3390/jcm8040554

28- Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, et al. Off-label dosing of non-vitamin K antagonist oral anticoagulants and adverse outcomes: the ORBIT-AF II registry. *J Am Coll Cardiol* 2016;68:2595-604

29- Barra ME, Fanikos J, Connors JM, Sylvester KW, Piazza C, Goldhaber SZ. Evaluation of dose-reduced direct oral anticoagulant therapy. *Am J Med* 2016;129:1198-204

30- Nielsen PB, Skjoth F, Sogaard M, Kjaelgaard JN, Lip GYH, Larsen TB. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ* 2017;356:j510

31- Jørgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. *Stroke 1996*;27:1765-9

32- Mozzafarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics – 2015 update: a report from the American Heart Association. *Circulation 2015*;131: e29–e322

33- Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke 2014*;45: 2160-236

34- International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19,435 patients with acute ischemic stroke. *Lancet 1997*;349:1569-81

35- Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke 2018*;49:e46-e110

36- Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J 2018*;39:1330-93

37- Ford I, Norrie J. Pragmatic trials. *N Engl J Med 2016*;375:454-63

38- King BT, Lawrence PD, Milling TJ, Warach SJ. Optimal delay time to initiate anticoagulation after ischemic stroke in atrial fibrillation (START): Methodology of a pragmatic, response-adaptive, prospective randomized clinical trial. *Int J Stroke 2019* Aug 18 : 1747493019870651

39- Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials. *Stroke 2007*;38:423-30

40- Whiteley WN, Adams HP Jr, Bath PM, Berge E, Sandset PM, Dennis M, et al. Targeted use of heparin, heparinoids, or low-molecular-weight heparin to improve outcome after acute ischemic stroke: an individual patient data meta-analysis of randomised controlled trials. *Lancet Neurol 2013*;12:539-45

41- Al-Sadat A, Sunbulli M, Chaturvedi S. Use of intravenous heparin by North American neurologists: do the data matter? *Stroke 2002*;33:1574-7

42- Caplan LR. Resolved: heparin may be useful in selected patients with brain ischemia. *Stroke 2003*;34:230-1

43- Altavilla R, Caso V, Bandini F, Agnelli G, Tsivgoulis G, Yaghi S, et al. Anticoagulation after stroke in patients with atrial fibrillation. *Stroke 2019*;50:2093-100

44- Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med 2018*;378:2191-201

45- Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med 2019;*16;380:1906-17

46- Geisler T, Poli S, Meisner C, Schreieck J, Zuern CS, Nägele T, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): Rationale and study design. *Int J Stroke 2017*;12:985-90

47- Veltkamp R, Purrucker J. Management of spontaneous intracerebral hemorrhage. *Curr Neurol Neurosci Rep 2017*;17:80

48- Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke 2014*;9:840-55

49- Hemphill JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke 2015*;46:2032-60

50- Kuramatsu JB, Huttner HB. Management of oral anticoagulation after intracerebral hemorrhage. *Int J Stroke 2019*;14:238-46

51- Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The euro heart survey. *Chest 2010*;138:1093-100

52- Biffi A, Anderson CD, Battey TW, Ayres AM, Greenberg SM, Viswanathan A, et al. Association between blood pressure control and risk of recurrent intracerebral hemorrhage. *JAMA 2015*;314:904-12

53- Charidimou A, Karayiannis C, Song TJ, Orken DN, Thijs V, Lemmens R, et al. Brain microbleeds, anticoagulation, and hemorrhage risk: Metaanalysis in stroke patients with AF. *Neurology* 2017; 89:2317-26

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

55- Nielsen PB, Larsen TB, Skjoth F, Gorst-Rasmussen A, Rasmussen LH, Lip GY. Restarting anticoagulant treatment after intracranial hemorrhage in patients with atrial fibrillation and the impact on recurrent stroke, mortality, and bleeding: A Nationwide cohort study. *Circulation 2015*;132 :517-25

56- Ottosen TP, Grijota M, Hansen ML, Brandes A, Damgaard D, Husted SE, et al. Use of antithrombotic therapy and long-term clinical outcome among patients surviving intracerebral hemorrhage. *Stroke 2016*;47:1837-43

57- Park YA, Uhm JS, Pak HN, Lee MH, Joung B. Anticoagulation therapy in atrial fibrillation after intracranial hemorrhage. *Heart Rhythm 2016*;13:1794-802

58- Pennlert J, Overholser R, Asplund K, Carlberg B, Van Rompaye B, Wiklund PG, et al. Optimal timing of anticoagulant treatment after intracerebral hemorrhage in patients with atrial fibrillation. *Stroke 2017*;48:314-20

59- Vestergaard AS, Skjoth F, Lip GY, Larsen TB. Effect of anticoagulation on hospitalization costs after intracranial hemorrhage in atrial fibrillation: A registry study. *Stroke 2016*;47:979-85

60- Chai-Adisaksopha C, Iorio A, Hillis C, Siegal D, Witt DM, Schulman S, et al. Warfarin resumption following anticoagulant-associated intracranial hemorrhage: A systematic review and meta-analysis. *Thromb Res 2017*;160:97-104

61- Korompoki E, Filippidis FT, Nielsen PB, Del Giudice A, Lip GYH, Kuramatsu JB, et al. Long-term antithrombotic treatment in intracranial hemorrhage survivors with atrial fibrillation. *Neurology 2017*;89:687-96

62- Murthy SB, Gupta A, Merkler AE, Navi BB, Mandava P, Iadecola C, et al. Restarting anticoagulant therapy after intracranial hemorrhage: A systematic review and meta-analysis. *Stroke 2017*;48:1594-600

63- Zhou Z, Yu J, Carcel C, Delcourt C, Shan J, Lindley RI, et al. Resuming anticoagulants after anticoagulation-associated intracranial haemorrhage: systematic review and meta-analysis. *BMJ Open 2018;*8:e019672

64- Biffi A, Kuramatsu JB, Leasure A, Kamel H, Kourkoulis C, Schwab K, et al. Oral anticoagulation and functional outcome after intracerebral hemorrhage. *Ann Neurol 2017*;82:755-65

65- Murphy MP, Kuramatsu JB, Leasure A, Falcone GJ, Kamel H, Sansing LH, et al. Cardioembolic stroke risk and recovery after anticoagulation-related intracerebral hemorrhage. *Stroke 2018*;49:2652-8

66- Sembill JA, Wieser CY, Sprugel MI, Gerner ST, Giede-Jeppe A, Reindl C, et al. Initiating anticoagulant therapy after ICH is associated with patient characteristics and treatment recommendations. *J Neurol 2018*;265:2404-14

67- Sembill JA, Gerner ST, Volbers B, Bobinger T, Lucking H, Kloska SP, et al. Severity assessment in maximally treated ICH patients: the max-ICH score. *Neurology 2017;*89:423-31

68- RESTART Collaboration. Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial. *Lancet 2019*;393:2613-23

69- Wolfe Z, Khan SU, Nasir F, Raghu Subramanian C, Lash B. A systematic review and Bayesian network meta-analysis of risk of intracranial hemorrhage with direct oral anticoagulants. *J Thromb Haemost 2018*;16:1296-306

70- Kato Y, Hayashi T, Suzuki K, Maruyama H, Kikkawa Y, Kurita H, Takao M. Resumption of Direct Oral Anticoagulants in Patients with Acute Spontaneous Intracerebral Hemorrhage. *J Stroke Cerebrovasc Dis 2019*;28:104292

71- Hawryluk GW, Austin JW, Furlan JC, Lee JB, O'Kelly C, Fehlings MG. Management of anticoagulation following central nervous system hemorrhage in patients with high thromboembolic risk. *J Thromb Haemost 2010*;8 :1500-8

72- Majeed A, Kim YK, Roberts RS, Holmstrom M, Schulman S. Optimal timing of resumption of warfarin after intracranial hemorrhage. *Stroke 2010*;41:2860-6

73- Pennlert J, Overholser R, Asplund K, Carlberg B, Van Rompaye B, Wiklund PG, et al. Optimal timing of anticoagulant treatment after intracerebral hemorrhage in patients with atrial fibrillation. *Stroke 2017*;48:314-20

74- Holmes DR, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: The PREVAIL trial. *J Am Coll Cardiol 2014*;64:1-12

75- Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: A randomized clinical trial. *JAMA 2014*;312:1988-98

76- Holmes DR, Redd VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in

patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet 2009*;374:534-42

77- Schellinger PD, Tsivgoulis G, Steiner T, Kohrmann M. Percutaneous left atrial appendage occlusion for the prevention of stroke in patients with atrial fibrillation: review and critical appraisal. *J Stroke 2018*;20:281-91

Figure

Figure 1: Re-starting of anticoagulation post intracranial bleeding. Issue of European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation 2018.