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REVIEW

When to withhold oral anticoagulation in atrial fibrillation – an overview of frequent clinical discussion topics

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Abstract: Stroke prevention with oral anticoagulants in patients with atrial fibrillation predisposes for bleeding. As a result, in select patient groups anticoagulation is withheld because of a perceived unfavorable risk-benefit ratio. Reasons for withholding anticoagulation can vary greatly between clinicians, often leading to discussion in daily clinical practice on the best approach. To guide clinical decision-making, we have reviewed available evidence on the most frequently reported reasons for withholding anticoagulation: previous bleeding, frailty and age, and an overall high bleeding risk.

Keywords: hemorrhage, frail elderly, age, anticoagulants, atrial fibrillation

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with heart failure, mortality, and ischemic stroke.[1] Stroke prevention with anticoagulants predisposes AF patients for bleeding. As a result, in select patient groups anticoagulation is withheld because of a perceived unfavorable risk-benefit ratio.[2–4] However, these choices cannot always be justified based on available evidence.

With an aging population, AF is becoming even more prevalent. Decision-making concerning withholding or (re-)initiating anticoagulation is a growing challenge for physicians.[5] In parallel, AF patients are likely to have more comorbidities, and consequently are at higher risk of both stroke and bleeding.[6,7] Increasingly common factors such as previous bleeding, frailty, and an overall high bleeding risk are amongst the most frequently reported reasons for withholding anticoagulation.[2,8]

In this review, evidence and gaps in the current knowledge of the benefits and risks of anticoagulation in AF are discussed, with a focus on high bleeding risk, previous bleeding, and frailty.

Anticoagulation and high bleeding risk

Due to an increase in comorbidities, patients with AF will more often be at an increased bleeding risk. Decision-making regarding anticoagulation can be particularly challenging in these patients, especially when both stroke and bleeding risk are high.[2,9] Oral anticoagulants (OAC) used for stroke prevention in AF are vitamin K antagonists (VKA), such as warfarin, or the non-vitamin K oral anticoagulants (NOAC) dabigatran, rivaroxaban, apixaban, and edoxaban.[1] As described below,

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available evidence suggests the clinical benefit of anticoagulation is higher than is often perceived.

In patients with a CHA_2DS_2-VASc stroke risk score of ≥2 (male) or ≥3 (female), anticoagulation is indicated by current AF-guidelines, and it should be considered in patients with a CHA_2DS_2-VASc of one (male) or two (female).[1,10] In the GARFIELD-AF registry, 30% of the patients with CHA_2DS_2-VASc ≥2 were not treated with oral anticoagulation (OAC).[2] The strongest predictors for withholding OAC were concomitant antiplatelet therapy (odds ratio (OR) 15.0 [95% confidence interval (CI) 14.1–15.8]) and a history of bleeding (OR 2.5 [95% CI 2.2–3.0]).[2] Compared to patients on OAC, patients withheld from OAC had an increased risk of all-cause mortality (5.3% vs 3.9%, $p<0.001$), ischemic stroke or systemic embolism (1.6% vs 1.1%, $p<0.001$), but a decreased risk of major bleeding (0.5% vs 0.8%, $p<0.001$). Data from the NCDR PINNACLE, a prospective United States-based registry focusing on quality-improvement, showed an even higher proportion of 42% of the patients with CHA_2DS_2-VASc ≥2 not treated with OAC.[11] In a multivariable model, lower CHA_2DS_2-VASc scores and higher HAS-BLED scores were both associated with OAC non-prescription.[11,12] Similar observations were derived from German insurance databases, where 40.5–48.7% of AF patients were classified as "definite OAC under-use".[13]

A Spanish, prospective, observational study in 1361 AF patients with stable anticoagulation control with VKA observed an annual cessation rate of 1.54%/year.[14] In 80% of them, OAC was stopped because of a major bleeding or at the health care providers' discretion. Cox regression analysis showed that the occurrence of major bleeding, heart failure, cancer, or renal impairment during follow-up was all independently associated with early OAC cessation. The authors conclude that many factors associated with bleeding also predispose to OAC cessation. OAC cessation, however, was associated with an increase in ischemic stroke (Hazard Ratio (HR) 1.85 [95% CI 1.17–2.94]) and all-cause mortality (HR 1.30 [95% CI 1.02–1.67]).

In a Dutch retrospective study, 45 out of 89 patients (51%) with a history of AF and admitted with a first ischemic stroke were insufficiently anticoagulated prior to their stroke.[15] Taken into consideration the increased occurrence of intracranial hemorrhage (ICH) as a result of increased OAC use, strict adherence to AF-guidelines could have prevented an estimated 20 out of 89 (22%) ischemic strokes. In the Registry of the Canadian Stroke Network, 90% of the 597 patients admitted with ischemic stroke and known AF with increased stroke risk were not therapeutically anticoagulated, or not anticoagulated at all.[16] These data demonstrate the perceived difficulties of real-world anticoagulation management, and the importance of good anticoagulation control. Thus, it is of utmost importance to know in which high-risk patient OAC can still safely be prescribed.

To reduce AF-related events, more frequent monitoring of high bleeding risk patients for presence of lower hemoglobin levels and/or active (minor) bleeding, changes in renal function, therapy adherence, and modifiable stroke and/or bleeding risk factors, such as hypertension or alcohol abuse, are likely to result in safer OAC use.[1] The use of accurate bleeding prediction models could diminish under- or overtreatment with OAC in AF. Unfortunately, bleeding prediction has been shown difficult. Over the years, multiple bleeding risk scores, such as the HAS-BLED, ATRIA, GARFIELD-AF risk tool, or $HEMORR_2HAGES$, have been developed to help clinical decision-making.[12,17–19] However, these risk scores have only moderate predictive accuracy, especially in the elderly.[20] Further complicating matters is the fact that an increased bleeding risk is correlated with an increased stroke risk, since strong bleeding risk factors such as increasing age, vascular disease, or prior stroke are the most important risk factors for ischemic stroke.[21–23]

In an effort to improve the prediction of bleeding, the ABC-bleeding risk score (Age, Biomarkers (high-sensitive troponin T, GDF-15, and hemoglobin), Clinical history) has been developed, which had a only slightly higher c-statistic (0.68 [95% CI 0.66–0.70]) than the HAS-BLED (0.61 [95% CI 0.59–0.63]) or the ORBIT score (0.65 [95% CI 0.62–0.67]).[24,25] Since the ABC-bleeding risk scores require the assessment of GDF-15, a cytokine which is upregulated in conditions of systemic inflammation or oxidative stress, the score is currently not implemented in daily clinical practice.[26] An interesting aspect of GDF-15 is that increased levels are not associated with an increased risk of stroke, while it is strongly predictive of bleeding.[27] It will be interesting to see if GDF-15, and perhaps other biomarkers, can guide clinicians with decision-making on anticoagulation (re-)initiation.

Management of patients with a high bleeding risk

Several studies have focused on the question whether AF patients with a high bleeding risk are better off when OAC is withheld. However, based on current literature,

anticoagulation is especially important in patients at a very high stroke risk, regardless of HAS-BLED scores.

To assess the benefit of OAC in AF, a net clinical benefit (NCB) using the method of Singer et al, is often calculated: NCB = (ischemic stroke$_{\text{off OAC}}$ – ischemic stroke$_{\text{on OAC}}$) – 1.5 * (intracranial hemorrhage rate$_{\text{on OAC}}$ – intracranial hemorrhage$_{\text{off OAC}}$), in which the factor −1.5 is to compensate for the often greater clinical impact of intracranial bleeding.[28] A NCB >0 indicates that the benefit of less ischemic stroke with OAC outweighs the risk of ICH. A NCB for warfarin was calculated for each CHA_2DS_2-VASc score in a large Swedish study of 182,678 patients with AF.[29] For CHA_2DS_2-VASc 0 (ie, male without risk factor), there was no NCB of warfarin treatment (NCB 0.0 [95% CI −0.1–0.1]). In patients with CHA_2DS_2-VASc ≥1, a positive NCB was observed. The NCB was highest in the patients at the highest risk of stroke, regardless of HAS-BLED scores. Similar results were seen in a large Danish study, where VKA (with or without aspirin) vs no antithrombotic treatment had a positive NCB in patients with a CHA_2DS_2-VASc ≥2.[30] The NCB with VKA was greater in patients with HAS-BLED ≥3 vs HAS-BLED <3 on VKA (NCB 2.21 [95% CI 1.93–2.50] vs NCB 1.19 [95% CI 1.07–1.32]), and VKA + aspirin (NCB 1.97 [95% CI 1.62–2.32] vs 0.81 [95% CI 0.56–1.07]), respectively.[30] High bleeding risk and high ischemic stroke risk are positively correlated. In individuals with a high bleeding risk, the risk reduction of ischemic stroke with OAC supersedes the small increase in the risk of ICH.[30] In a different Danish study, the NCB was calculated for warfarin, dabigatran, rivaroxaban, and apixaban vs no anticoagulation.[31] A positive NCB was observed in both VKA or NOAC treated patients with CHA_2DS_2-VASc ≥2. The NCB was even greater in the subgroup of patients with HAS-BLED ≥3, irrespective of treatment with VKA or NOAC.

However, there are some limitations to these studies. Confounding by indication could have played an important role in these analyses, as patients on different anticoagulation strategies may differ in terms of stroke and bleeding risk, possibly overestimating NCB counts.[29,30,32] Furthermore, non-intracranial major or non-major clinically relevant bleeding is not a part of the used NCB formula, although they often play an important role in clinical decision-making. However, despite these limitations, the evidence for prescribing OAC despite high bleeding risk remains strong.

The treatment of high-risk patients should not only focus on the antithrombotic strategy, but also on reducing the risk of bleeding. A flowchart to help reduce bleeding risk is shown in Table 1. Although many important bleeding risk factors are non-modifiable, treatment should focus on currently known modifiable risk factors for bleeding, including hypertension, labile international normalized ratio (INR), concomitant drug-use, including over the counter drugs like non-steroidal anti-inflammatory drugs (NSAID), and alcohol abuse.[1] A systolic blood pressure of >140 mmHg is associated with an increased bleeding risk, and adequate blood pressure control is therefore recommended to reduce bleeding risk.[1,33] In patients with labile INR, switching to a NOAC should be considered.[1] The concomitant use of antiplatelet drugs, NSAIDs, and drugs inhibiting OAC metabolism can strongly increase bleeding risk, and therefore their use should be avoided if possible.[34–39] Drugs affecting metabolism and increasing bleeding risk in NOACs are primarily *P*-gp and CYP3A4 inhibitors, and in VKA primarily CYP2C9 and CYP3A4 inhibitors.[40] Alcohol abuse (ie, ≥8 units/week) shows conflicting results regarding bleeding risk.[12,21,41] However, suspected heavy drinking is an important reason for clinicians to withhold OAC.[2] Since alcohol abuse is also associated with an increased risk of stroke in AF patients and medication non-adherence, addressing a patients' alcohol usage is nonetheless an important element of the management of AF patients.[21,33,42] However, there is no substantial evidence to withhold OAC in alcohol abusers without significant hepatic impairment.

In patients at risk for gastrointestinal (GI) bleeding, proton pump inhibitors (PPI) can be prescribed to reduce bleeding risk. In a retrospective cohort study in Medicare beneficiaries treated with either apixaban, rivaroxaban, dabigatran, or warfarin, PPI co-therapy was associated with a lower risk of hospitalization for upper GI-bleeding.[43,44] Only in patients categorized in the lowest GI-bleeding risk decile, no protective effect of PPI therapy was observed.[44] Current guidelines recommend that in patients with an elevated GI-bleeding risk PPI should be considered, specifically in patients with a history of GI-bleeding or ulcer, malignancy, or concomitant antiplatelet therapy.[9]

Combined use of antiplatelet drugs and anticoagulants strongly increases bleeding risk, and is a frequently observed reason for withholding OAC.[2,11,38,39] In comparison to VKA monotherapy, single antiplatelet therapy in addition to VKA or NOAC had a HR for major bleeding of 1.82 (95% CI 1.76–1.89) and 1.28 (95% CI 1.13–1.44), respectively.[39] Concomitant dual antiplatelet therapy with a NOAC or VKA was associated with a 1.2–3.9-fold and 2.4–5.4-fold higher risk of major bleeding, respectively.[39] In a meta-analysis only including patients on low-dose

Table 1 Flowchart to help reduce bleeding risk in high-risk AF patients

1. Estimate benefit of OAC • Assess stroke risk (e.g. CHA_2DS_2-VASc) • Identify known bleeding risk factors (e.g. anemia, age, previous bleeding, impaired renal function, etc.) 2. Treatment plan • Treat modifiable risk factors • Consider co-treatment with PPI, in: ○ History of GI-bleeding or ulcer ○ Malignancy ○ Concomitant antiplatelet therapy or NSAIDs	
Risk factor	**Treatment option (s)**
Hypertension	Aim for <140 mmHg systolic blood pressure if tolerated
Heavy alcohol use (≥8 units/week) Labile INR (Time in Therapeutic Range (TTR) <60%)	Discourage use of alcohol • Consider switch to NOAC • In case of VKA preference: ○ more frequent monitoring ○ switch to longer acting VKA
NSAIDs, strong *P*-gp inhibitors, or antiplatelet therapy.	Avoid these medications if possible. Consider switch to an alternative treatment. In case of antiplatelet therapy, consider switch from VKA to NOAC.
3. Monitoring plan • Assess hemoglobin levels and renal function at least yearly • Stimulate and monitor therapy adherence • Actively ask for (minor) bleeding	

Abbreviations: AF, atrial fibrillation; OAC, oral anticoagulation; INR, international normalized ratio; NOAC, non-VKA oral anticoagulant; VKA, vitamin K Antagonist; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

aspirin from the pivotal NOAC trials, rates of stroke or systemic embolism were lower with NOACs (HR 0.78 [95% CI 0.67–0.91]), in comparison to VKAs.[45] The rates of major bleeding were similar (HR 0.83 [95% CI 0.69–1.01]). The rates of ICH were lower (HR 0.38 [95% CI 0.26–0.56]). The results from these studies suggest NOACs may be both safer and more effective than VKAs in patients on concomitant antiplatelet therapy. There have only been head-to-head studies between NOAC or VKA and concomitant antiplatelet use in patients after a recent percutaneous coronary intervention (PCI). The WOEST, PIONEER-AF PCI, RE-DUAL PCI, and AUGUSTUS trials all showed less bleeding with dual therapy (NOAC or VKA with a $P2Y_{12}$ inhibitor) compared to triple therapy (dual therapy plus aspirin), with no significant difference in efficacy.[46–49] However, these individual trials were not powered for the efficacy endpoints. A meta-analysis of the WOEST, PIONEER-AF PCI, and RE-DUAL PCI trials suggests the incidence of ischemic events with dual therapy vs triple therapy is equally low.[50] The current guidelines provide a good overview and recommend an individualized approach of triple therapy duration based on bleeding and atherothrombotic risk with the aim to keep triple therapy duration as short as possible.[9] The optimal antithrombotic regimen beyond 1 year remains undefined in these patients, but will also importantly depend on risk factors for bleeding.

Although the far majority of AF patients with increased stroke risk will benefit from OAC, the risks can outweigh the benefits in some patients (e.g. patients with a non-treatable cause of (recurrent) major bleeding).[9] In these patients, a left atrial appendage (LAA) occluding device or surgical LAA occlusion may be considered according to the current guidelines (class of recommendation IIb, level of evidence C).[1] The ASAP study included AF patients with $CHADS_2 \geq 1$ and a contraindication for OAC (in 93%: history or tendency of bleeding), in which a LAA occluding device (Watchman) was implanted.[51] After implantation, patients received 6 months of clopidogrel or ticlopidine, and lifelong aspirin. Ischemic stroke rate (1.7%/year) was significantly lower than expected based on the predicted stroke risk of the cohort (7.3%/year). The

EWOLUTION trial was a nonrandomized, prospective cohort study in which 1020 patients with a Watchman device were enrolled.[52] In this study, 72.2% of the patients had a reported contraindication for OAC. The observed ischemic stroke rate was 1.3 (95% CI 0.8–1.9) per 100 patient-years, which was 83% lower than predicted based on historical data using the CHA_2DS_2-VASc score. In patients with a previous major bleeding specifically, the risk reduction was similar at 85% (observed risk: 1.2 [95% CI 0.4–2.5]). Unfortunately, there are no randomized data available on LAA occlusion in patients with a contraindication for OAC. However, based on available evidence, LAA occlusion seems to be a safe and effective strategy in patients with a contraindication for OAC.[53]

(Re-)initiation of anticoagulation after bleeding

One of the most frequently reported reasons to withhold anticoagulation is a history of bleeding, especially a history of ICH.[2,3,14,54] Nevertheless, available data indicate a benefit of OAC resumption in patients with AF and a prior major bleeding.

Recently, a meta-analysis was published comprising 5685 AF patients that experienced a major bleeding.[55] In comparison with the withholding of OAC after the index bleeding, OAC restarters had a 46% relative risk (RR) reduction of any thromboembolic event, and a 10.8% absolute risk reduction for all-cause mortality.[55] Restarting OAC was associated with an increased risk of a recurrent major bleeding (OR 1.85), although no increased risk of recurrence of the index bleeding event (ie, ICH or GI-bleeding) was observed. NCB analysis, including thromboembolic events, major bleeding, and all-cause mortality, demonstrated that restarting OAC was associated with a clinical advantage (NCB 0.11 [95% CI 0.09–0.14]).[55] An important limitation, however, is that all included studies were observational, and selection bias in these studies is possible.[56] Furthermore, only one study included patients with a history of "any major bleeding", whereas the other six studies solely focused on either ICH or GI-bleeding. Therefore, these results should be interpreted with caution.

A retrospective analysis of insurance data showed a lower combined risk of ischemic stroke and all-cause mortality with the resumption of warfarin (HR 0.76 [95% CI 0.59–0.97]) or dabigatran (HR 0.66 [95% CI 0.44–0.99]).[57] In comparison to no re-initiation, warfarin resumption had an increased risk of major bleeding (HR 1.56 [95% CI 1.10–2.22]), whereas dabigatran resumption was not significantly associated with major bleeding (HR 0.65 [95% CI 0.32–1.33]). The risk-benefit ratio was, therefore, higher for dabigatran than for warfarin. Careful interpretation of these results is warranted, as differences in time to resumption, dosing (75 mg dose was initiated in 9.6% of the dabigatran users), switching, and discontinuation between warfarin or dabigatran treated patients could have strongly influenced outcomes.[56]

In patients with a history of ICH and AF, an increasing body of evidence shows the benefits of OAC resumption. However, there is substantial controversy regarding the optimal time period for re-initiation.[58–60] A pooled analysis of the retrospective AF studies of Kuramatsu et al, and Nielsen et al, showed that OAC restarters had a lower rate of any thromboembolic event (HR 0.45 [95% CI 0.26–0.78]), and that OAC resumption was not significantly associated with recurrent major bleeding (HR 1.65 [95% CI 0.97–2.79]).[55,61,62] In a model with any thromboembolic event, major bleeding, and all-cause mortality, OAC resumption after ICH resulted in a positive NCB.[55] A meta-analysis from eight studies with a retrospective design comprised of 5306 patients hospitalized for anticoagulation-associated ICH for any indication.[63] The re-initiation of OAC resulted in a lower risk of thromboembolic events (RR 0.34 [95% CI 0.25–0.45]), without an increase in recurrent ICH (RR 1.01 [95% CI 0.58–1.77]).[63] Not only a lower risk of thromboembolism has been observed, but also an improvement in functional recovery of OAC resumption in ICH survivors. A pooled analysis of three prospective studies in 941 AF patients showed that anticoagulation resumption was associated with improved functional recovery at 1-year post-ICH (OR 1.89 [95% CI 1.32–2.70]).[64] Although there is good evidence in favor of VKA resumption from observational studies, data on NOAC resumption after recent ICH are very limited.[65,66] Data from randomized controlled trials are not available. APACHE-AF is an ongoing trial focusing on the safety and efficacy of full-dose apixaban vs antiplatelet drugs or no antithrombotic therapy after recent ICH in AF.[67] SoSTART is an ongoing trial with a similar design, but the choice of OAC is left to the physician: dabigatran, rivaroxaban, apixaban, edoxaban, warfarin, phenindione, or acenocoumarol.[68]

Overall, (re-)initiation of OAC in AF patients after a major bleeding seems to be beneficial. However, it is unclear what the optimal moment for (re-)starting OAC

therapy is. In a retrospective assessment of insurance data, 1329 patients with AF, a major GI-bleeding, and an interruption of warfarin for 48 hrs were included.[69] Warfarin restarters had a reduced risk of thromboembolism (HR 0.71 [95% CI 0.54–0.93]) and all-cause mortality (HR 0.67 [95% CI 0.56–0.81]), compared to non-restarters. Both groups had a comparable risk of recurrent GI-bleeding. Compared to restarting warfarin after 30 days after GI-bleeding, an early restart within 7, 7–15, 15–21, or 21–30 days was not associated with a decreased thromboembolic risk. In contrast, restarting warfarin within 7, 7–15, or 15–21 days was associated with a decreased all-cause mortality risk. Careful interpretation of these results is warranted, as it is likely that the different groups analyzed had different risks of rebleeding and thromboembolism, given the high probability of selection bias. Moreover, in this study, restarting warfarin within 7 days was associated with an increased risk of recurrent GI-bleeding, compared to restarting after 30 days.[69] A retrospective study using administrative and clinical databases showed that a restart of warfarin, which was after a median of 4 days (95% CI 2–9), was not related with a recurrence of GI-bleeding.[70] However, when a restart within 1–7 days was compared with >7 days, the rate of recurrent GI-bleeding was increased significantly (12.4% and 6.23%, respectively).[70] In a prospective study of 197 patients hospitalized for GI-bleeding, it was observed that warfarin resumption after a median of 5 days resulted in lower thromboembolic events (HR 0.12 [95% CI 0.006–0.81]), without increasing the risk of GI-bleeding recurrence (HR 2.17 [95% CI 0.86–6.67]).[71,72] All-cause mortality within 90 days after hospital discharge was similar between restarters and non-restarters (HR 0.63 [95% CI 0.22–1.89]). Therefore, it has previously been suggested that warfarin resumption can be considered as early as 7–14 days after GI-bleeding.[73] Since data are lacking on the timing of NOAC resumption after GI-bleeding, the authors advised to apply data for warfarin resumption with caution, because of the faster therapeutic onset of NOACs.[73]

In patients with ICH, "early resumption" (within 2 weeks) of OAC therapy in patients with a high risk of thromboembolism, and "late resumption" (after 4 weeks) in patients with a high risk of ICH, has been suggested.[60] The most recent European Heart Rhythm Association guidelines recommend that OAC may be restarted after 4–8 weeks after ICH, if the risk of thromboembolism is high and the risk of recurrent ICH is low.[9] In general, the optimal timing of resumption after ICH is still largely unknown, and is dependent on many factors. OAC should not be restarted in patients with cerebral amyloid angiopathy, because of the high recurrent ICH risk.[9] In other situations, decision-making is more difficult and should, therefore, be decided in a multidisciplinary team.[1,60] For example, lobar bleeding, cerebral microbleeds, a non-traumatic origin, cerebral aneurysm, or lacunar infarcts are associated with an increased risk of recurrent ICH, while a deep cortical bleed has a relatively low recurrence risk.[60] As data are limited, further research from preferably randomized controlled trials is essential.

Anticoagulation and frailty

Frailty has been defined as a syndrome of increased aging-associated vulnerability, resulting in a compromised ability to cope with stressors.[74] With aging of the population, the incidence of both frailty and AF increases drastically, and is likely to result in an increased incidence of ischemic stroke.[9] It is however problematic that multiple reports have shown a 50% lower prescription rate in frail AF patients, compared to non-frail patients.[75,76] In a questionnaire distributed amongst treating physicians of AF patients from nursing homes in France, recurrent falls (47%) and cognitive impairment (22%) were the most common reasons for withholding OAC.[4] Other studies also found an (excessive) fall risk as an important reason for OAC non-prescription.[8,77] However, an increasing body of evidence suggests that OAC should not be withheld based on frailty solely.

A recent prospective study in hospitalized, elderly AF patients in Spain showed that amongst patients with anticoagulation, the incidence of ischemic stroke (2.7% vs 3.2%, p=0.79) and major bleeding (7.5% vs 8.1%, p=0.84) was similar between frail and non-frail patients at 1-year follow-up, respectively.[78]

Fall risk is an important parameter of frailty. A history of falls or an increased fall risk is associated with all-cause mortality, ischemic stroke, and bleeding.[79–81] However, conflicting results have been published on the risk of the most feared complication of anticoagulation in patients with frailty: (traumatic) ICH.[79–82] In a retrospective study in AF patients anticoagulated with warfarin, the incidence rate per 100 patient-years of traumatic ICH was 2.0 (95% CI 1.3–3.1)) in high fall risk AF patients, and 0.34 (95% CI 0.27–0.45) in other patients.[82] In a post

hoc analysis of the ARISTOTLE trial, a history of fall(s) was associated with an increased ICH risk (HR 1.96 [95% CI 1.06–3.61]).[80] However, in the ENGAGE-AF TIMI-48 trial and in the Loire Valley AF Project, the presence or absence of fall risk or a history of fall(s), did not increase the incidence of ICH.[79,81] The reason for these contradictory results is uncertain. Nevertheless, using a Markov model, it was estimated that patients with AF taking warfarin have to fall more than 295 times in 1 year for the risks of warfarin to outweigh its benefits.[83] Also, for both edoxaban and apixaban the relative safety and efficacy profile compared with warfarin were consistent in high fall risk patients.[80,81] Fall risk alone should therefore not be a reason to withhold anticoagulation.[9]

Dementia is another often cited reason for OAC non-prescription in AF.[4] However, like fall risk, dementia should not be a general contraindication for OAC.[9] Anticoagulation initiation and monitoring in dementia can be challenging, as therapy adherence and a patients' ability to make decisions are often suboptimal.[9] Nonetheless, OAC treatment is correlated with lower ischemic stroke and all-cause mortality rates in these patients.[84] Moreover, AF is linked to dementia and cognitive decline, and OAC in AF has been associated with a lower risk of dementia.[85,86] Anticoagulation treatment is therefore encouraged, but attention to therapy adherence is especially important.

Table 2 Summary of recommendations

Discussion topic	Recommendations
High bleeding risk	
	High bleeding risk is often not a contraindication, as stroke risk generally outweighs bleeding risk. A detailed recommendation can be found in Table 1.
Recent major bleeding	
Overall	OAC resumption after major bleeding seems to be beneficial. The optimal timing of resumption is not extensively researched.
GI-bleeding	Resumption of OAC is generally recommended. Resumption of OAC can be considered as early as within 7–14 days after GI-bleeding.
ICH	Resumption of OAC is often beneficial, but should be decided in a multidisciplinary team as the benefits and risks are dependent on many factors. The optimal timing of resumption is unknown. If OAC is resumed, restarting after 4 weeks is deemed safe.
Frailty and age	
Overall	Frailty and age are no general contraindications for OAC.
High fall risk	A high risk of falls, or a history of falls, are no general contraindications for OAC.
Cognitive decline	OAC should not generally be withheld in patients with cognitive decline. Feasibility of OAC treatment in terms of medication adherence should always be checked and monitored.

Abbreviations: OAC, oral anticoagulation; GI, gastrointestinal; ICH, intracranial hemorrhage.

Conclusion

Anticoagulation management remains an important discussion topic, especially in an aging AF population with progressively more comorbidities. Often, the perceived unfavorable risk-benefit ratio of anticoagulation is overestimated in these patients. Although a careful assessment of risks and benefits is warranted, the benefits of stroke prevention generally outweigh bleeding risk. This holds true specifically in patients with commonly reported reasons for anticoagulation withholding previous bleeding, frailty and age, and high bleeding risk (Table 2). After major bleeding, the optimal timing of anticoagulation resumption is largely unknown, and often requires multidisciplinary assessment.

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