Preventing bleeding and thromboembolic complications in atrial fibrillation patients undergoing surgery

Prevenindo complicações hemorrágicas e tromboembólicas de cirurgias em pacientes anticoagulados por fibrilação atrial

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ABSTRACT

Neurologists feel uneasy when asked about temporary anticoagulant interruption for surgery in patients with atrial fibrillation (AF). Rational decisions can be made based on current scientific evidence. **Method:** Critical review of international guidelines and selected references pertaining to bleeding and thromboembolism during periods of oral anticoagulant interruption. **Results:** Withholding oral anticoagulants leads to an increased risk of perioperative thromboembolism, depending on factors such as age, renal and liver function, previous ischemic events, heart failure etc. Surgeries are associated with a variable risk of bleeding - from minimal to very high. Individualized decisions about preoperative drug suspension, bridging therapy with heparin and time to restart oral anticoagulants after hemostasis can significantly reduce these opposing risks. **Conclusion:** Rational decisions can be made after discussion with all Health care team professionals involved and consideration of patient fears and expectations. Formal written protocols should help managing antithrombotic treatment during this delicate period.

Keywords: atrial fibrillation, oral anticoagulants, surgery, hemorrhage, thromboembolism.

RESUMO

Preocupação com sangramentos em pacientes anticoagulados por fibrilação atrial (FA) expõe os mesmos a riscos tromboembólicos que aumentam ainda mais quando anticoagulantes são suspensos para operações ou outras intervenções invasivas. **Método:** Revisão de Diretrizes internacionais e outras publicações sobre riscos relacionados a cirurgias. **Resultados:** A suspensão dos anticoagulantes aumenta o risco de complicações tromboembólicas na FA, em razão de idade, função renal e hepática, eventos isquêmicos prévios, cardiopatias etc. O risco hemorrágico das intervenções varia de mínimo a extremamente elevado. Decisões individualizadas sobre suspensão das drogas, recurso a anticoagulantes parenterais no preparo dos pacientes para cirurgia, tempo para retomada do anticoagulante oral após hemostasia reduzem significativamente estes riscos. **Conclusão:** Decisões racionais podem ser tomadas após discussão com os profissionais envolvidos – dentistas, anestesistas, cirurgiões; levando em conta inclusive temores e expectativas dos pacientes. Protocolos institucionais favorecem o manejo perioperatório seguro e devem ser discutidos com os pacientes e seus cuidadores.

Palavras-chave: anticoagulantes, cirurgia geral, fibrilação atrial, hemorragia, tromboembolia.

Individuals with atrial fibrillation (AF) - especially older ones or those with previous thromboembolic episodes (cerebral or systemic) - have a high risk of embolic strokes. Except in the presence of specific contraindications, these patients should receive chronic therapy with oral anticoagulant drugs. However, neurologists frequently feel insecure in prescribing anticoagulants to AF patients, despite the publication of many guidelines reinforcing this need, allegedly because of continuing concerns about the risk of bleeding complications, especially intracranial hemorrhage (ICH).

AF patients nowadays live longer with multiple co-morbidities and over time frequently demand medical and surgical interventions associated with a variable risk of bleeding. One quarter of anticoagulated patients need temporary drug suspension in 2 years[1]. Simply withholding anticoagulants however implies in risk of new embolic events. Balancing the opposing risks of bleeding and embolism may seem empiric. The attending physicians are frequently asked by other professionals - surgeons, anesthesiologists, and dentists - authorization to temporarily withhold Warfarin so

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patients can be submitted to various procedures. This conduct would be clearly inadequate in many instances.

The present text reviews the scientific evidences guiding rational antithrombotic management in FA patients who must be submitted to invasive interventions including surgery. The recommendations should also be useful to stroke patients with less common indications for chronic anticoagulation - e.g., atrial flutter or cerebral venous thrombosis. Patients with stroke caused by other mechanisms who are sometimes anticoagulated for other reasons, especially venous thromboembolism [(VTE) - including peripheral vein thrombosis and pulmonary embolism], may also need changes in anticoagulant strategy. It should be remembered however that typical preventive regimens for venous thrombosis exhibit minimal or no efficacy against arterial thromboembolism. The manuscript reviews the vitamin K antagonist Warfarin and the new oral anticoagulants [(NOACs): direct thrombin and factor Xa inhibitors] and is partially based in a number of recently published guidelines from American and European medical societies to which the interested reader is directed for more details[2,3,4,5,6,7,8,9,10].

ATRIAL FIBRILLATION AND STROKE RISK

Chronic or paroxysmal AF is responsible for a large number of thromboembolic events every year. The main affected area (up to 80%) is the brain – 10 to 12% of cerebral infarcts (CI)[4,11]. The frequency increases as age advances: the attributed risk in individuals with 80 years or more reaches 25%[2,5,10,12]. Risk is also greater in women (in all age groups: HR 1.14 [95%CI, 1.07–1.22]: 20.4% of CI in women vs. 15.6% in men)[10,13,14]. Women also tend to develop strokes in later ages, and the risk difference between genders concentrates in older AF patients (≥ 75 years). These two variables - age and gender - are integrated in current predictive models such as the CHA2DS2-VASc (Table 1)[15,16,17,18].

Risk scales help define the best antithrombotic strategy in AF patients. The main scales used are presented in Table 1. Using for instance the CHADS2 model:

• low risk (score 0) - acetylsalicylic acid (ASA) 81-325 mg/day or no treatment (optimizing possible associated risk factors);

• medium risk (score 1) – ASA or Warfarin (consider patient preferences and hemorrhage risk);

• greater risk (score ≥ 2) – Warfarin (International Normalized Ratio (INR) 2-3 [goal INR- 2.5]).

Recommendations are similar using the CHAD2DS2-VASc, with some authors suggesting the use of NOACs from a score of 1 or more[19]. CHAD2DS2-VASc probably better estimates risk in patients classified as low-risk using the CHADS2 model[16,17,18].

The instruments used to stratify the annual risk of stroke recurrence in AF probably underestimate the actual

Table 1. Main scales for arterial thromboembolic risk evaluation in patients with atrial fibrillation.

CHADS2		CHA2DS2-VASc	
Score	Criteria	Score	Criteria
1 point	CHF	1 point	CHF
1 point	Hypertension	1 point	Hypertension
1 point	Age > 75 years	2 points	Age > 75 years
1 point	Diabetes mellitus	1 point	Diabetes mellitus
2 points	Stroke/TIA	2 points	Stroke/TIA/systemic embolism
		1 point	Vascular disease
		1 point	Age 65-74 years
		1 point	Female gender
Total Score	Annual risk (%)	Total Score	Annual risk (%)
0	1.9	0	0
1	2.8	1	1.3
2	4.0	2	2.2
3	5.9	3	3.2
4	8.5	4	4.0
5	12.5	5	6.7
6	18.2	6	9.8
		7	9.6
		8	6.7
		9	15.2

CHF: congestive heart failure – signs and symptoms, confirmation by exams; Hypertension – resting BP > 140/90 mmHg in at least 2 moments or current pharmacological treatment; Diabetes mellitus – fasting glycemia > 125 mg/dL or current pharmacological treatment; Stroke – any type of cerebral ischemia; Vascular disease – myocardial infarct/angina, peripheral arterial disease, aortic plaque... TIA: transient ischemic attack.

risk, most probably around 7 to 10%[20]. Any history of previous thromboembolic event - usually cerebral - is therefore a marker of high risk of recurrence. Except in cases with a strong contraindication such as recent severe hemorrhage or a persistent bleeding tendency these patients should be adequately anticoagulated. Besides the factors usually included in prediction scales such as coronary heart disease, congestive heart failure etc., the risk also increases with rheumatic valve disease; biological heart valves (any position) or aortic mechanical valves; and even more with mechanical mitral valves (the risk is particularly high with caged-ball or tilting disk models).

A difficult area is the diagnosis of paroxysmal AF. Some 10 to 12% of stroke patients will exhibit AF during the initial hospital stay, but at least 10 to 15% more may have paroxysmal episodes only evident after long monitoring periods. A series of methods for paroxysmal AF detection have been prospectively evaluated. Ambulatory monitoring for 30 days in individuals with cryptogenic CI revealed 11% (7.6-15.7%) of episodes persisting for at least 5 seconds (6.7% for episodes > 30 seconds), most frequently asymptomatic[11]. More than half of the episodes were detected only after 10 days of monitoring.

Other methods are being tested. Some researchers suggest teaching patients and family caregivers to evaluate the arterial pulse as to its frequency and regularity; preliminary studies show reasonable sensitivity and specificity in the identification of tachyarrhythmias and its differentiation from sinus rhythm after a brief training[21]. Detection of the

arrhythmia should be followed by formal Electrocardiogram (EKG) exam that can even be done by telemetry[22]. The so-called event-Holter can be triggered by patients whenever they suspect the presence of the arrhythmia. These two techniques however tend to detect only a few episodes. In the study of Flint and cols referred above only 6% of the episodes detected by EKG monitoring were perceived by the patients[11]. Other methods of low availability that are not dependent on patient awareness have been proposed including subcutaneous cardiac monitors used for periods of many months. Using one of these systems in patients with cryptogenic CI, AF episodes of at least 30 seconds were detected 6 times more frequently than in a control group (8.9% vs. 1.4%) after 6 months (12.4% vs. 2% in 12 months)[23].

A table including AF patients and other risk groups for thromboembolic complications has been developed (Table 2)[7,8]. It can be used in surgical patients, although it is based on annual risk in clinical settings[7]. The risk of hemorrhage in anticoagulated patients can also be reasonably estimated using scales such as HAS-BLED (Table 3)[24, 25]. It should be highlighted that the same factors may increase the risks of both thromboembolism and hemorrhage[26]. Hence, therapeutic decisions should always be individualized and patients and relatives or caregivers should receive adequate instruction on the necessary care to help reduce bleeding risks – diet habits, scheduled laboratory controls, risks related to drug interactions and falls etc.

EFFICACY AND USE OF ORAL ANTICOAGULANTS

Warfarin

The efficacy of Warfarin in AF as compared to placebo is undisputable. In primary prevention, the risk reduction (RR) reaches 68% (annual risk 1.4% vs. 4.5%)[27]. ASA is also efficacious but much less so[28]. The differences between Warfarin and ASA are small only in young patients with non-rheumatic AF and without other risk factors[29,30]. After a thromboembolic event, the annual stroke risk falls with Warfarin from 12% to 4% (vs. placebo)[31]. This same study showed a clear advantage of Warfarin over ASA in patients eligible for anticoagulation.

The INR-goal for most patients is 2.5 (2.0-3.0). The first main studies accepted higher levels of anticoagulation[27,28,29,30], but there is a strong consensus nowadays that the risk of bleeding complications increases disproportionally in patients with INR of 4 or more[3,7,8].

NOACs

In the last decade large studies comparing NOACs (inhibitors of thrombin– dabigatran – and of Factor Xa – apixaban, rivaroxaban, edoxaban) and Warfarin in non-valvular AF were published. They are briefly summarized here. The comparison between dabigatran and Warfarin (RELY study: one third of patients with paroxysmal AF) showed non-inferiority of the new drug (combined outcome including systemic embolism and stroke: 1.69%/year in the Warfarin group) of lower doses (110 mg b.i.d.: 1.53%/year) and superiority of the higher doses tested (150 mg b.i.d.: 1.11%/year), despite a very small increase in myocardial infarct rates and some increase in the risk of gastrointestinal hemorrhage[19]. The rates of major bleeding complications were similar in patients on Warfarin or on the higher doses of dabigatran but were lower in those on lower doses. Mortality was slightly less in those using the higher doses (3.64%/year vs. 4.13% for Warfarin – p = 0.051). Some methodological difficulties of the study should however be mentioned: some 40% of both groups used ASA together with the anticoagulants; there was no blinding in the adjustment of Warfarin doses; in patients with stroke/transient ischemic attack (TIA) the risk reduction with dabigatran was not statistically significant even in higher doses (only non-inferiority was demonstrated).

Table 2. Risk stratification for perioperative thromboembolism (adapted from refs. 7 and 8).

	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism (VTE)
High (> 10%/year)*	Any mitral valve prosthesis Any caged-ball or tilting disc aortic valve prosthesis Recent (within 6 months) stroke or transient ischemic attack	CHADS 2 score of 5 or 6 Recent (within 3 months) stroke or transient ischemic attack Rheumatic valvular heart disease	Recent (within 3 months) VTE Severe thrombophilia (e.g., deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate (5-10%/year)	Bileaflet aortic valve prosthesis and one or more of the following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age > 75 y	CHADS 2 score of 3 or 4 VTE within the past 3-12 months Non-severe thrombophilia (e.g., heterozygous factor V Leiden or prothrombin gene mutation)	Recurrent VTE Active cancer (treated within 6 months or palliative)
Low (< 5%/year)	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	CHADS 2 score of 0 to 2 (assuming no prior stroke or transient ischemic attack)	VTE > 12 months previous and no other risk factors

† Annual risks derived from clinical cohort studies and adapted for surgical patients. * Some patients otherwise included in other groups may be seen as having a very high risk. Examples include patients with lower CHADS2 scores but with a recent (< 3 months) stroke, remote VTE with serious consequences (pulmonary hypertension), or undergoing operations with specially high thromboembolic risk (carotid endarterectomy, coronary bypass or open heart surgery, vascular surgery)

Table 3. HAS-BLED Score for annual risk of hemorrhage using oral anticoagulants.

Criteria	Points
H (Hypertension)	1
A (Altered function)	
renal	1
liver	1
S (previous Stroke)	1
B (previous Bleed)	1
L (Labile INR)	1
E (Elderly – age > 65 years)	1
D (Drugs predisposing to hemorrhage)	
medicines	1
alcohol	1
Total Score	Annual risk of bleeding under anticoagulation, %
0 (low risk)	0.6-1.1%
1-2 (medium risk)	1.9-3.2%
≥ 3 (high risk)	4.9-19.6%

Definitions: Hypertension – uncontrolled, SBP > 160 mm Hg; A - chronic renal failure (dialysis, renal transplant, Cr > 2 mg/dL); chronic liver disease or laboratory abnormalities (bilirubin > 2 x normal, AST or ALT or gama-GT or alkaline phosphatase > 3 x normal); B - Bleeding episodes or predisposition; L- elevated INR or INR values out of therapeutic levels > 40% of time; E - age > 65 years; D – medicines (platelet antiaggregants, anti-inflammatory drugs), alcohol (weekly consume ≥ 8 doses).

A study comparing rivaroxaban (20 mg/daily [15 mg if Cr Cl 30-49 mL/min]) and Warfarin in patients with slightly greater embolic risk (CHADS2 ≥, with previous embolic events in 55%, congestive heart failure in > 60%) demonstrated non-inferiority but not superiority (even in patients with a previous stroke) in reducing the annual thromboembolic risk: 2.1% vs. 2.4% (ROCKET-AF)[32]. Also, there was no significant difference in annual global risk of hemorrhage (14.9% vs. 14.5%). Patients on rivaroxaban had more gastrointestinal hemorrhages (3.2% vs. 2.2%) and more hemorrhages requiring blood transfusions (1.6% vs. 1.3%/year); and lower rates of ICH (0.5% vs. 0.7%/year) and fatal hemorrhages (0.2% vs. 0.5%/year). An important critic has been made to this study: time spent with adequate levels of anticoagulation (55%) in the Warfarin group (INR monitored by a blinded electronic system) was less than in many other studies.

Apixaban (5 mg b.i.d.; patients with Cr levels > 2.5 mg/dL excluded) has been compared to ASA (AVERROES – see ahead) and with Warfarin. In this case (ARISTOTLE), the annual risk of the composite outcome (hemorrhagic or ischemic stroke and systemic embolism) was significantly lower with apixaban (1.27% vs. 1.60%) even in patients with a previous stroke/TIA[33]. There were also lower rates of severe hemorrhages (2.1 vs. 3.1%), CH (0.24% vs. 0.47%) and a slight reduction in global mortality (3.52% vs. 3.94%), with no differences in rates of gastrointestinal hemorrhage.

A large trial (ENGAGE-AF) suggests similar results (non-inferiority for cerebral or systemic embolism and lower rates of major bleeding vs. Warfarin) using a novel anti-Xa drug, edoxaban, in two regimens (30 or 60 mg once daily)[34]. Whatever the dose used it was halved if the patient's weight fell below 60 Kg or if Cr Cl was reduced (30-50 mL/min). In the intention-to-treat analysis, there was a trend for superiority using larger doses (HR ratio, 0.87; 97.5%CI: 0.73-1.04; p = 0.08) and an opposite trend for inferiority with the lower doses (HR 1.13; 97.5%CI: 0.96 to 1.34; p = 0.10). Both regimens were associated however with lower rates of severe hemorrhages, ICH and slightly lower mortality (significant difference with the higher dose regimen).

In summary, NOACs should be considered as an option on a par with Warfarin in most recently diagnosed non-valvular AF patients, taking into account clinical particulars (e.g., renal function [should be checked regularly during treatment], previous gastrointestinal hemorrhage) and patient preferences (inconvenience of multiple INR tests, cost etc.). Patients adequately anticoagulated with Warfarin (absence of bleeding or recurrent thromboembolism) should not routinely be switched to NOACs. Those with less than 60% of the time with an INR within therapeutic levels are probably at increased risk of thromboembolic or hemorrhagic events and constitute a group in which opting for a NOAC would probably be advantageous.

Special situations

Contraindication to anticoagulant treatment: there is no doubt about the efficacy of Warfarin or NOACs and their superiority over ASA (generally 100 mg/day). Warfarin is also superior (annual rate of composite outcome - 3.9% vs. 5.6%) to the combination of aspirin and clopidogrel in primary prevention (ACTIVE W: AF plus at least one risk factor)[35].

More recently, two studies evaluated strategies for AF patients with contraindications to Warfarin. In the first study (ACTIVE-A) double antiaggregation (ASA + clopidogrel) was compared to ASA only[36] : the additional reduction in ischemic events with double therapy was basically neutralized by an increased risk of severe hemorrhages (RR 0.97; 95%CI: 0.89–1.06; p = 0.54 for the composite outcome). It is therefore difficult to accept the IIa level AHA recommendation for double antiaggregation in patients with a contraindication to Warfarin treatment. Especially as another study with apixaban (5 mg b.i.d.) vs. ASA (AVERROES: patients with Cr > 2.5 mg/dL excluded) showed superiority of apixaban (stroke or systemic embolism: annual rate 1.6% vs. 3.7%) and absence of significant differences in adverse effects (severe hemorrhages, gastrointestinal bleedings, mortality)[37]. The best strategy in this important group of patients remains under scrutiny. The availability of antagonists for both thrombin and Factor Xa inhibitors in the near future[38,39] could possibly make the decision to start a NOAC the most appropriate in many cases.

Anticoagulants associated with platelet antiaggregants: an also much discussed question regards patients

with coronary heart disease and stents with indication for anticoagulation because of AF (with or without previous stroke/TIA). Some 20% of patients with AF and stroke have symptomatic coronary disease (and many more will develop it in the future). The risks of the simultaneous use of Warfarin and antiplatelet drugs are well known and generally contraindicate their routine association. Triple therapy (double antiaggregant and anticoagulation) is associated with increased mortality and major bleeding risk and no additional reduction of thromboembolic events when compared to single antiaggregation with clopidogrel plus Warfarin treatment[40]. Some medical societies suggest, based in somewhat limited evidence, the concomitant use of Warfarin and ASA or clopidogrel/prasugrel in special situations for 12 months (CHADS2 ≥ 2) or for an undefined time (acute coronary syndromes); and triple therapy for 12 months after pharmacological stent placement[3,7,8,40,41]. In AF anticoagulated patients undergoing angioplasty/stent placement, the antiplatelet drugs should be used in low doses; whenever possible, non-pharmacological stents should be preferred in anticoagulated patients (minimizing time on triple therapy).

There are fewer data on antiaggregation in patients using NOACs. Concomitant exposure to antiaggregants and NOACs markedly increases the risk of bleeding[6]. One third of patients included in large studies comparing Warfarin and theses drugs were receiving antiplatelet drugs, usually ASA in low doses. Specific trials comparing different strategies for double or triple therapy following percutaneous coronary interventions are under way (RE-DUAL-PCI, PIONEER AF-PCI). Even recognizing the empiric nature of this suggestion, the same strategy considering coronary risks and the time since the coronary events or stent implantation (and the differences between pharmacological and non-pharmacological stents) is recommended (see ref. 6 for further discussion).

Recurrence while on treatment with Warfarin: The ideal strategy here is still undefined. Increasing the INR (e.g., to 3) or adding antiplatelet drugs are strategies that do not seem to reduce the risk of recurrence but clearly add to the risk of severe hemorrhages. The use of NOACs in this setting has not been studied.

When to start treatment: the golden rule– *primum non nocere* – should prevail when deciding when to start the anticoagulant treatment after a stroke related to AF. The AHA/ASA Guidelines on secondary stroke prevention suggest that it is safe to postpone treatment up to two weeks in most patients[3]. Data pointing to a high risk of early recurrence of embolism in patients with AF-related stroke - up to 8.5% in 14 days -would suggest a need to start anticoagulation in a shorter time[42]. These data contrast however with a much lower risk indicated in very large prospective studies (CAST, IST) which found daily rates not exceeding 0.5%[43,44]. The recommendation to withhold early anticoagulation is strongly based on results of a study including 449 patients with AF treated up to 30 hours after stroke onset[42]. Treatment

with a LMWH - dalteparin - was not superior to that with ASA, with a low risk of ICH in both groups. Studies like the IST also indicate that the reduction in the risk of early recurrence (first 14 days) obtained by treatment with full doses of UFH is counterbalanced by an increased risk of ICH[44]. A meta-analysis of patients with cardioembolic stroke confirmed this idea[45]. In the IST, UFH treatment starting in the first 48 hours was also useless in the subgroup of patients with AF[46].

Oral anticoagulation should probably be started earlier (first week) in individuals without an increased risk of symptomatic hemorrhage - large lesions, initial hemorrhagic transformation, general bleeding tendency, uncontrolled hypertension. The risk of early recurrence is greater for instance in patients with CHF or an acute anterior myocardial infarct, and this should also be considered in making the best individualized decision. In stroke patients with AF starting oral anticoagulants, there is a tendency to avoid initial bridging with UFH or LMWH. The bridging strategy does not confer obvious benefits (or increased risks) and prolongs hospital stay[47].

BLEEDING RISK AND MANAGEMENT OF ANTICOAGULATED PATIENTS UNDERGOING SURGERY

Temporary withholding of anticoagulants is necessary in up to one quarter of patients in the first two years of use, most frequently because of fear of hemorrhage during surgery or invasive procedures[1]. Any period without anticoagulant poses an increased risk of thromboembolic events in AF patients[48]. Opposing risks vary according to age, associated cardiac disease, bleeding history and other patient factors (cancer, renal failure etc.). In patients with AF-related strokes the risk of recurrence is inversely related to the time elapsed since the ischemic event[7,48]. The intrinsic bleeding risk of the surgery or endoscopic procedure should also be carefully evaluated (Tables 4 and 5). Major surgeries and endoscopic procedures with mucosal or submucosal lesion resections are associated with a high bleeding risk[7,9]. These patients should have anticoagulants (and clopidogrel) withheld. Superficial interventions (skin, teeth) or ophthalmological surgeries in sites without vascularization (such as cataract surgery with or without lens implantation) have a minimal risk and should be made without changes in the antithrombotic regimen. This last recommendation is especially relevant in individuals with a recent stroke/TIA (i.e., in the last 3-6 months).

Some principles should be kept in mind:

• The disappearance of antithrombotic effects (and hence the reversal of bleeding risk) depends on the time without the drug - this is greater with platelet antiaggregants (because of the expected platelet turnover) - around 7-10 days; and lower with NOACs (beware of renal insufficiency - see ahead). Warfarin has a half-life of 36 to 42 hours,

and after 3 half-lives the expected residual anticoagulant activity is 12.5% (sometimes slower reduction in older patients). The INR is normal in almost all patients after 5 days without the drug. Some 7% of patients will have an INR over 1.5 on the day before surgery. In surgeries associated with a high bleeding risk they should receive oral vitamin K (1-2.5 mg), and have another test confirming INR normalization on the day of surgery[49,50]. Low risk procedures can be performed with an INR between 1.5 and 1.8, allowing for a shorter time without anticoagulation[51].

• Bridging therapy with UFH or LMWH when oral antithrombotic treatment is withheld increase the risk of hemorrhages. This risk varies with the doses used (therapeutic doses > VTE prophylactic doses); and the time since the last preoperative dose or from surgery to treatment return. Postponing this return and reducing the doses used can minimize the bleeding risks but increase the time with a high risk of thromboembolic events. Bridging with heparin is considered in patients with a high risk of arterial thromboembolism (> 10%/year) but not in those with low risk (< 5%). Decisions should be highly individualized in individuals with an intermediate risk (see Table 2).

• Bridging for the prevention of arterial thromboembolism only makes sense with full doses of heparin (UFH or LWH); studies using intermediate or "subtherapeutic" doses (e.g., enoxaparin 40 mg b.i.d.) are scarce[52]. Table 6 summarizes the suggested conduct.

• Typical therapeutic and prophylactic doses: Unfractionated heparin (UFH) – continuous IV infusion to reach aPTT 1.5-2 times the control values, 5,000 IU SC every 8 or 12 hours; enoxaparin – 1 mg/Kg b.i.d., 40 mg/daily dose.

• Time to effective antithrombotic action should be remembered when restarting treatment – minutes after UFH or ASA, many hours after Low molecular-weight heparin (LMWH) or NOACs, and many days after clopidogrel maintenance doses or Warfarin.

Warfarin

The scenario is somewhat more complicated for patients on Warfarin than those on NOACs, as the time to full disappearance of the anticoagulant effects is significantly longer - usually several days. Patients with a high risk of recurrent thromboembolism - such as those with a CHADS2 score of 5 or 6, stroke/TIA in the last 3 months, severe CHF, rheumatic valvular disease or mechanical valves - usually receive bridging therapy with full doses of LMWH. An ambulatory strategy can reduce costs[50,53]. Heparin bridging is started when the INR is below 2.0, with the last dose given 24 hours before surgery; treatment is again started after assessment indicates full hemostasis, usually 48 hours

Table 4. Bleeding risk in diverse procedures (modified from references 6, 7, 9).

Minimal risk (no change in anticoagulant regimen)	Dental interventions * Extraction of 1-3 teeth Periodontal surgery Drainage of abscess Implants Cataract Endoscopy without intervention/biopsy Superficial interventions ^
Low bleeding risk	Glaucoma ** Endoscopy with biopsy Prostate or bladder biopsy Catheter ablation or electrophysiological study Angiography Pacemaker or ICD implantation ***
High bleeding risk****	Complex radiofrequency ablation Epidural or spinal anesthesia / diagnostic spinal tap Thoracic surgery Abdominal surgery Major orthopedic surgery Hepatic or renal biopsy Transurethral prostate resection

* Mouth-washing/oral administration of tranexamic acid (Transamin ®) or epsilon-aminocaproic acid may reduce bleeding. An option in more extensive surgeries is to withhold Warfarin for 2-3 days. ^ Drainage of abscesses, excision of small skin lesions etc. ** Considered as minimal risk surgery by some authors, others suggest high risk (> 30%) in anticoagulated patients (see text). *** Can be associated with hematomas from deep infraclavicular fascial dissection/squeezing without suture; risk may be higher in complex anatomic settings (e.g., cardiac congenital malformations). **** Very high-risk surgery involves genitourinary system (transurethral resection, bladder tumor resection, nephrectomy and renal biopsy); resection of intestine (anastomosis bleeding) or large and sessile colonic polyps (late stalk bleeding - may be lessened with stalk clipping); highly vascularized organs (thyroid, spleen, liver); large areas of tissue lesion (cancer surgery, arthroplasty, reconstructive plastic surgery); and cardiac, intracranial or spinal surgery (small bleeding may have severe consequences).

Table 5. Bleeding risk in gastrointestinal endoscopic procedures (from ref. 9).

Low risk*	Higher risk
Diagnostic endoscopy (upper GI tract, colonoscopy, flexible sigmoidoscopy), even with biopsy	Polipectomy
Endoscopic retrograde cholangiopancreatograhy without sphincterotomy	Biliary or pancreatic sphincterotomy
Endoscopic ultrasound without fine needle aspiration	Pneumatic or bougie dilation
Enteroscopy and diagnostic balloon-assisted enteroscopy	Percutaneous gastrostomy placement
Capsule endoscopy	Therapeutic balloon-assisted enteroscopy
Enteric stent deployment (without dilation)	Endoscopic ultrasound with fine needle aspiration
	Endoscopic hemostasis
	Tumor ablation (any technique)
	Cystogastrostomy
	Treatment of varices

* Most patients using ASA only should not withhold the drug (exception– mucosal/submucosal resections). Tienopiridines (clopidogrel, prasugrel etc.) are usually withheld electively, especially in complex procedures involving more than simple biopsies.

Table 6. Bridging strategy for Warfarin treated patients according to hemorrhagic risk of surgery.

High-risk	Minimal/low-risk
Withhold Warfarin for 5-7 days and start full-dose LMWH or UFH	Continue oral treatment (minimal-risk procedures) or withhold Warfarin with heparin bridging (consider shorter periods of drug suspension – e.g. 2-3 days)
Last dose of UFH (half-life 30-120 min) 4-6 hours before procedure; 24 hours for LMWH (residual anti-Xa activity in most patients after 12 h)	Last dose of UFH (half-life 30-120 min) 4-6 hours before procedure; 24 hours for LMWH (residual anti-Xa activity in most patients after 12 h)
Restart UFH or LMWH in 48-72 hours (after confirming full hemostasis)*	Return UFH or LMWH after 24 hours
Restart Warfarin as soon as possible to shorten period under heparin treatment.	

* If bleeding continues after 72 hours, consider low dose UFH or LMWH (only useful in VTE prevention) or restarting Warfarin treatment without bridging therapy.

after major interventions (24 hours after low-risk procedures)[3,7]. Similar recommendations apply to patients anticoagulated for recent VTE (i.e., < 3 months) or with severe thrombophilias (e.g., antiphospholipid syndrome). Patients with an intermediate CHADS2 score (3 to 4) should have individualized decisions as to the use of LMWH after careful assessment of the specific surgery-related bleeding risks. The thromboembolic risk is probably similar in patients with VTE occurring 3 to 12 months before, more benign thrombophilias, or recent oncologic treatment. In most patients with an even lower risk (CHADS2 = 0 to 2 without stroke/TIA, VTE > 12 months before, and no other risk factors) it is probably safe to simply withhold Warfarin for 4 or 5 days. An INR is obtained on the day before planned surgery to assess the eventual need of oral vitamin K (usually 1-2.5 mg); and in the next morning just before surgery (fresh plasma given if necessary).

Surgical urgencies with a high bleeding risk should be postponed whenever possible for one or two days, giving fresh plasma and oral or intravenous Vitamin K to obtain reversal of anticoagulation. A normal point of care INR test - as suggested nowadays for the urgent evaluation of possible thrombolysis in hyperacute CI patients using Warfarin) probably suffices to assure that coagulation has returned to basal conditions. The point of care test tends to overestimate the INR when compared to standard INR analysis[54].

Treatment with Warfarin after surgeries with a high bleeding risk should be reinitiated in patients with a medium to high risk of recurrent thromboembolic events as soon as a full hemostasis is secured, usually after 12 to 24 hours (not later)[7]. In very high-risk patients full doses of UFH or LMWH should be given while waiting for the INR to reach therapeutic levels. The first two weeks following any procedure here discussed are associated with an increased risk of both thromboembolic and hemorrhagic events, and frequent contact is always indicated after hospital discharge.

Minimal risk surgeries: these include a number of dental, skin and ocular interventions. Dental extraction and root canal treatment should be done without interruption of the anticoagulant (some patients may be more fearful of the hemorrhages than the thromboembolic risks and may prefer to withhold the drug for 2 to 3 days instead [INR around 1.6-1.9]). Suturing and the use of fibrinolytics (e.g., mouth-washing/oral tranexamic acid [Transamin®] 5 mL 10 minutes before and 3-4 times a day for 1-2 days) reduce even further the bleeding risk[55,56,57]. Patients should be warned that some gingival oozing may persist for a few days, during which local compression and tranexamic acid should be continued. Simple skin biopsies should be done without any change in anticoagulant use. Excision of lesions (nevi, keratosis, carcinomas) are frequently associated with minor bleedings but rarely (< 5%) major ones, and optimization of local hemostasis should generally suffice[58,59]. Cataract extraction is an avascular surgery usually done nowadays with phacoemulsion and topical anesthetics - retrobulbar anesthesia is rarely associated with significant bleeding in anticoagulated patients but this could mandate urgent decompression[60]. Minor bleeding (subconjuntival hemorrhage or dot hyphemas) without any vision loss may occur in up to 10 percent of patients but is not a reason for changing the anticoagulant regimen[61].

NOACs indication

NOACs have the general advantage over Warfarin of a shorter effect. A typical difficulty with these drugs however is knowing whether or not there is residual anticoagulant activity. Metabolism is slowed in the elderly and with renal insufficiency. Contrary to widespread view, a large number of drugs interact and either increase or reduce the activity or the half-life for elimination of NOACs including:
- antiarrhythmic drugs (quinidine, amiodarone, verapamil);
- calcium channel blockers (diltiazem, verapamil);
- antibiotics, antifungal and antiretroviral drugs (erythromycin and clarithromycin, all iazolics, rifampicin, protease inhibitors [ritonavir etc.]);
- antiepileptics (phenobarbital, carbamazepin, phenytoin);
- antineoplastics (cyclosporin, tacrolimus);
- antacids and proton or hydrogen pump inhibitors.

The first step is trying to know exactly when the last dose was given. Some tests indicate the persistence of anticoagulant effects including increased activated thromboplastin time (aTPT) for dabigatran; or the prothrombin time/INR (point of

care tests not recommended) for Xa factor inhibitors. Direct measurements of thrombin time (dabigatran) and of Xa activity (other drugs) can help but are far less available or fast and have ill-defined cut-off values to ensure a safe surgery.

The hemorrhagic risk of the proposed intervention should be evaluated. Urgent operations should if at all possible be postponed for 12 or ideally 24 hours. Hopefully specific antagonists/antibodies against thrombin and Xa factor inhibitors will be available in the near future[38,39]. In contrast to Warfarin, preoperative bridging with heparins is not indicated in NOAC treated patients[1,62].

Any intervention should be made off the last dose peak anticoagulant effect[6]. In minimal risk interventions - dental extractions, cataracts upper or lower endoscopy without biopsies etc. - an interval of 18 to 24 hours after the last dose is suggested, treatment being reinitiated after 6 hours (this corresponds to skipping one dose of NOACs that are given twice daily). Oral tranexamic acid is suggested in dental surgeries.

In low-risk procedures, withholding NOACs for 24 hours in patients with normal renal function is adequate; 48 hours are suggested for higher-risk surgeries. The degree of renal insufficiency should be carefully assessed. In dabigatran treated patients, even small decreases in renal function (Cr Cl 50-80 mL/min) mandate suspension for 36 hours (low-risk surgeries) or 72 hours (high-risk surgeries); for patients with Cr Cl 30-50 mL/min the corresponding time is 48 hours (low-risk) and up to 96 hours (high-risk). For both rivaroxaban and apixaban, the only suggested change is increasing the interval without the drug in patients with Cr Cl 15-30 mL/min undergoing low risk surgeries to 36 hours. Current data do not allow a precise recommendation for edoxaban treated patients. NOACs should not be used in individuals with Cr Cl below 15 mL/min (including those on hemodialysis).

Of special interest to neurologists is the question of surgeries involving the neuraxis - NOACs are not recommended in these patients[6]. Diagnostic lumbar puncture and spinal or peridural anesthesia should only be done after hemostasis has been fully secured (high-risk surgery protocol).

Time to resume drug after surgery should also consider the risks associated with the specific procedure: 6 to 8 hours in low-risk interventions (also for lumbar puncture and spinal and peridural anesthesia), but 48-72 hours in high-risk surgeries. In patients with a high risk of developing VTE, prophylactic or intermediate doses of LMWH after 6 to 8 hours should be given if hemostasis has been adequately obtained (there are no dependable data evaluating the use of small postoperative doses of NOACs in AF patients with this goal)[6,62]. LMWH should be withheld soon after restarting NOACs, which exhibit full effect after 2 hours.

Final remarks

Neurologists should play an active role in the discussion with cardiologists, surgeons, anesthesiologists, and dentists to reach the best individualized decision regarding antithrombotic perioperative management in AF patients. Decisions should be made considering the objective evaluation of the contrasting risks of thromboembolic recurrence and surgery-related bleeding when withholding anticoagulants or antiplatelet drugs. Uniform care should be pursued and greatly depends on the development of formal institutional protocols. Patients should be evaluated one week before the planned intervention; receive written instructions about anticoagulant suspension, INR testing the day before surgery, the use of parenteral drugs as bridging therapy should follow individualized regimens according to age, renal function and other variables; careful evaluation of hemostasis on days 0 and 1 after surgery; and orientations and regular contact with the Health care team in the following two weeks. In the next few years, further clarification of a number of topics is expected from many studies concerning general surgery (PERIOP-2, BRIDGE) or pacemaker and defibrillation implantation (PACEBRIDGE, BRUISECONTROL) in anticoagulated patients.

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