

Practical Management of Stroke Prevention in Patients with Atrial Fibrillation and Renal Impairment Receiving Newer Oral Anticoagulants: Focus on Rivaroxaban

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Abstract

Stroke is the most feared risk associated with atrial fibrillation (AF). Both stroke and bleeding risk are independently increased in patients with AF and renal dysfunction. The newer oral anticoagulants show similar or better stroke prevention without further bleeding risk compared with vitamin K antagonist therapy and without its numerous practical challenges. Nonetheless, renal monitoring is an important aspect of newer oral anticoagulant treatment. This paper reviews management of patients with AF and renal impairment receiving newer oral anticoagulants, with a specific focus on rivaroxaban given that it is now prescribed more often than warfarin by cardiologists in the US.

Keywords: Antithrombotic therapy; Arrhythmia; Cardiology; Renal disease; Kidney disease; Hematology

Abbreviations: AF: Atrial Fibrillation; CCS: Canadian Cardiovascular Society; CHADS₂: Congestive Heart Failure, Hypertension, Age \geq 75 Years, Diabetes Mellitus, Stroke or Transient Ischemic Attack (doubled); CHA₂DS₂-VASc: Congestive Heart Failure/Left Ventricular Dysfunction, Hypertension, Age \geq 75 years (Doubled), Diabetes Mellitus, Stroke or Transient Ischemic Attack (Doubled), Vascular Disease, Age 65-74 Years, Sex category (Female); CKD: Chronic Kidney Disease; CrCl: Creatinine Clearance; CYP: Cytochrome P450; eGFR: Estimated Glomerular Filtration Rate; ESC: European Society of Cardiology; EU: European Union; HAS-BLED: Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly (>65 years), Drugs/alcohol; OAC: Oral Anticoagulant; PCC: Prothrombin Complex Concentrate; PD: Pharmacodynamic(s); PK: Pharmacokinetic(s); VKA: Vitamin K Antagonist

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia of clinical significance and is estimated to affect 1-2% of the developed world's population [1-5]. Given that AF involves chaotic atrial activity with consequent deterioration of atrial mechanical function, AF predisposes patients to stasis-related atrial thrombi and is associated with a fivefold increase in the risk of stroke compared with individuals with normal sinus rhythm [6,7].

Although relatively rare in people younger than 40 years of age, the prevalence of AF increases with age [4]. The incidence of AF doubles with each decade of life after 55 years of age such that the lifetime risk for developing AF is approximately 1 in 4 [4,8]. Renal impairment is another age-associated condition and, as such, often manifests concurrently with AF [9-11]. Thus, approximately one in three outpatients with AF have chronic kidney disease (CKD) [12], and patients with CKD are 2- to 3-times more likely to have AF (depending on the stage of CKD) than are patients with normal renal function [13].

Even though vitamin K antagonists (VKAs) continue to be advocated by current guidelines as an efficacious treatment for stroke prevention in most patients with non-valvular AF [14-16], the safety of oral anticoagulant (OAC) therapy in patients with AF and CKD remains unclear. Although CKD is associated with an increased risk of stroke in

patients with AF, CKD also increases the risk of bleeding associated with antithrombotic therapy [17-19]. Patients with severe renal impairment (creatinine clearance [CrCl] \leq 30 mL/min) were generally excluded from randomized controlled trials with anticoagulants, making it difficult to provide evidence-based recommendations for the use of such agents in patients with AF and severe renal impairment (Table 1) [10,14]. Indeed, one national guideline group recommended against any antithrombotic stroke prophylaxis whatsoever, including acetylsalicylic acid, for patients with the most compromised renal function (CrCl < 15 mL/min and on dialysis) [14], given that the bleeding risk is so high and any stroke prophylaxis benefit is moderated by an otherwise limited prognosis. There is currently a large care gap between patients with AF who require OAC therapy and those who actually receive OAC therapy [20], and this gap is further exacerbated in patients with AF and renal impairment despite a higher, and broader, thromboembolic risk [21].

Compared with VKAs, the direct Factor Xa inhibitors (rivaroxaban, apixaban) and the direct thrombin inhibitor (dabigatran) have a quicker onset and offset of action, a more consistent anticoagulant effect, without need for routine coagulation monitoring or dose adjustment, and fewer interactions with food and other drugs [22]. Three of these agents (dabigatran, apixaban and rivaroxaban) now have clinical approval in many parts of the world for stroke prophylaxis in AF. All three agents are renally excreted to different degrees, and dose adjustments are recommended in patients with renal impairment (Table 1) [15]; however, only rivaroxaban has been evaluated at a reduced dose in patients with moderate renal impairment (CrCl 30-49 mL/min) [23]. This paper reviews the evidence with respect to the specific application

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Agent (phase II trial)	CrCl (mL/min)	Dose evaluated at phase III trial [23,33,41]	Approved doses		
			Canada [42,54,95]	US [36,56,96]	EU [35,39,55]
Rivaroxaban (ROCKET AF)	≥ 50	20 mg od	20 mg od	20 mg od	20 mg od
	30-49	15 mg od	15 mg od*†	15 mg od (CrCl 30-50 mL/min)	15 mg od
	15-29	Excluded	Not recommended	15 mg od	15 mg od*†
	<15			Not recommended	Contraindicated
Apixaban (ARISTOTLE)	≥ 50	5 mg bid‡	5 mg bid‡	5 mg bid‡	5 mg bid‡
	30-49	5 mg bid‡	5 mg bid‡	5 mg bid‡	5 mg bid‡
	15-29	5 mg or 2.5 mg bid if ≥ 25 mL/min‡ (excluded if <25 mL/min)	5 mg bid if ≥ 25 mL/min‡§ (not recommended if 15-24 mL/min)	No clear recommendation	2.5 mg bid
	<15	Excluded	Not recommended	Not recommended	Contraindicated
	≥ 50	150 mg bid or 110 mg bid	150 mg bid¶§	150 mg bid (CrCl >30 mL/min)	150 mg bid or 110 mg bid (CrCl >50 mL/min)
30-49	150 mg bid or 110 mg bid*¶				
Dabigatran (RE-LY)	15-29	Excluded	Not recommended	75 mg bid (CrCl 15-30 mL/min)	Contraindicated
	<15			Not recommended	

*Use with caution when close to 30 mL/min; †Use with caution; ‡A reduced dose of 2.5 mg bid is recommended with two or more of the following: age ≥ 80 years, body weight ≤ 60 kg or serum creatinine ≥ 1.5 mg/dl; ¶Consider dose adjustment for patients with a high bleeding risk; §Use with caution in patients with a CrCl of 30-49 mL/min, especially in the elderly or those with other risk factors for bleeding, and consider a lower dose of 110 mg bid. bid, twice daily; CrCl, creatinine clearance; od, once daily.

Table 1: Tested and approved doses of newer oral anticoagulants in patients with mild, moderate and severe renal impairment.

of these drugs to patients with AF who have CKD. The paper focuses on the practical use of rivaroxaban in these patients, given that it is now prescribed by cardiologists in the US more often (40%) than warfarin (35%) [24].

Novel Oral Anticoagulants

Unlike VKAs, which acting directly on several components of the coagulation cascade, the newer OACs target specific coagulation factors [22]. These agents have received regulatory approval for the prevention of stroke and systemic embolism in patients with non-valvular AF. All newer OACs, irrespective of their mode of action, have common properties, such as a rapid onset of action [22] and predictable pharmacokinetic (PK) profiles [25-30]; however, these OACs have some notable differences that will be reviewed.

Dabigatran

Dabigatran is administered as dabigatran etexilate, a prodrug. The dissolution and absorption of dabigatran in the stomach and small intestine is dependent on the presence of an acidic environment [31]; therefore, tartaric acid is included in the dabigatran tablet. Bioavailability is relatively low: approximately 6-7% [25]. Dabigatran is primarily eliminated through renal clearance (by ~80%) [32]. Efficacy and safety endpoints between warfarin and dabigatran, at either the 150 mg twice daily or 110 mg twice daily dose, did not differ between the subgroup of 3505 patients in the RE-LY study (19%) with a CrCl of 30-49 mL/min and those with a CrCl of 50 mL/min or more [33,34]. Nonetheless, because exposure to dabigatran increases with the severity of renal impairment [25], a dose reduction is recommended in patients with moderate renal impairment [22]. The European Union (EU) Summary of Product Characteristics recommends that a dose reduction from the standard dose of 150 mg twice daily to 110 mg twice daily should be considered for patients with a CrCl of 30-50 mL/min and a high risk of bleeding (Table 1) [35]. The Prescribing Information recommends 150 mg twice daily for patients with a CrCl above 30 mL/min [36]. In most parts of the world, dabigatran is contraindicated in patients with severe renal

impairment (estimated CrCl ≤ 30 mL/min) [35-37]. In the US, a dose of 75 mg twice daily is given as an option for patients with a CrCl of 15-30 mL/min, although this is based on PK and pharmacodynamic (PD) data rather than clinical trial experience (Table 1). Known interactions of dabigatran with other drugs (e.g. strong inhibitors of the transporter P-glycoprotein) result in higher plasma concentrations; therefore, a dose reduction for patients receiving these drugs is recommended, together with close clinical surveillance, especially in patients with mild-to-moderate renal impairment [35,36]. The importance of regular monitoring of renal function has been highlighted by post-marketing reports of bleeding events during treatment with dabigatran in elderly patients with severe renal impairment [38].

Apixaban

Apixaban, as with rivaroxaban and other Factor Xa inhibitors that are still in development or under clinical assessment, has no prodrug. It has been shown to have predictable PK [27]. The absolute bioavailability of apixaban is 50% [39]. Apixaban is metabolized mostly via cytochrome P450 (CYP) 3A4 and is a substrate of P-glycoprotein; therefore, drugs that are strong inhibitors of both CYP3A4 and P-glycoprotein may significantly alter apixaban plasma concentrations and are not recommended for concomitant use. Elimination of apixaban is through multiple pathways including metabolism, the kidneys and the biliary system, although total renal clearance accounts for approximately half of the systemically available dose [27,40]. Of the 25% of administered dose excreted in the urine, more than 80% is unchanged drug. In a subgroup analysis of the ARISTOTLE trial, the 3017 patients (15%) with an estimated glomerular filtration rate (eGFR) of 50 mL/min or less achieved efficacy and safety outcomes that were at least equivalent to those in patients who had eGFRs greater than 50 mL/min [19]. However, no specific data have been published for patients treated with apixaban with an eGFR or CrCl of 25 mL/min or less (Table 1). In the ARISTOTLE study, a reduced dose of 2.5 mg twice daily (instead of the standard 5 mg twice-daily dose) was administered in 428 patients (4.7%) in the apixaban group with two of the following: age >80 years,

weight <60 kg and serum creatinine \geq 1.5 mg/dl (133 μ mol/L) [41]. However, it is not clear how many of this relatively small cohort received the lower dose because of renal impairment. In the EU, apixaban is not recommended for use in patients with a CrCl below 15 mL/min (Table 1) because no clinical data are available for these patients [39]. The EU Summary of Product Characteristics states that patients with exclusive criteria of severe renal impairment (defined as CrCl 15-29 mL/min) should receive the lower dose of apixaban 2.5 mg twice daily, whereas the Canadian Monograph specifies that no dosing recommendation can be made in patients with a CrCl of 15-24 mL/min because of "very limited" clinical data [42].

Rivaroxaban

Rivaroxaban has been found to have a predictable clinical pharmacology profile [30,43] and PD that correlates with plasma concentrations [43]. Similar to apixaban, the metabolism of rivaroxaban is via CYP3A4 and rivaroxaban is a substrate of P-glycoprotein; therefore, drugs that are strong inhibitors of both CYP3A4 and P-glycoprotein are not recommended for concomitant use. Rivaroxaban has a dual mode of elimination: two-thirds of the drug undergoes metabolic degradation in the liver, half of which is excreted via the kidneys and the other half via the hepatobiliary route; the remaining one-third of the dose is excreted as unchanged drug in the urine [43]. The use of rivaroxaban in patients with renal impairment is discussed below.

Risk Stratification

Treatment guidelines for AF uniformly recommend that all affected patients are stratified using a predictive index for the risk of stroke (e.g. CHADS₂ [44] or CHA₂DS₂-VASc [45]) and for bleeding (e.g. HAS-BLED [46]) and that most patients should receive antithrombotic therapy to prevent stroke unless the bleeding risk is excessive [14-16]. Although CHADS₂ or CHA₂DS₂-VASc score can only increase (with age or the accumulation of additional risk), bleeding risk can rise but can also be lowered. In the case of HAS-BLED, discontinuation of antiplatelet medication or alcohol, optimization of international normalized ratio control and improvement in renal or hepatic function, where possible, can all reduce bleeding risk. As such, an elevated bleeding risk should not generally lead to avoidance of treatment with OAC, because the risk of bleeding rarely outweighs the elevated risk of stroke; instead, it should prompt the physician to reduce bleeding risk and to increase careful monitoring of the patient for blood loss.

The recommendation to stratify patients according to their stroke and bleeding risk and to consider these relative hazards in subsequent therapeutic decision making applies equally to patients with and without renal impairment [10,47]. However, it should be noted that bleeding risk increases as kidney function worsens [48] such that anticoagulant use, indeed the use of any antithrombotic, becomes controversial in patients with extremely poor renal function, such as those with a CrCl below 15 mL/min, especially those on dialysis [14]. Thus, all patients, but especially those with moderate or severe renal impairment, need careful evaluation and the ultimate decision for use of oral anticoagulation to be based on individual risk stratification. Although not included in the CHADS₂ and CHA₂DS₂-VASc scores, renal impairment increases the risk of stroke in patients with AF [17-19]. Abnormal renal function is included in the bleeding risk scores [46,49]. If the risk of stroke is deemed to outweigh the risk of bleeding, OAC treatment should be considered [10,50]. Furthermore, regular and ongoing monitoring of renal function should become routine in the management of patients with AF. Special attention should be given to the elderly or in patients with borderline renal function at baseline who might be prone to

sudden drops in CrCl or eGFR with dehydration or acute illness. Thus, the Canadian Cardiovascular Society (CCS) guidelines recommend annually assessing renal function in patients with AF who are receiving OAC therapy [14]. More frequent measurements should be considered in patients who require a reduced OAC dose, such as those with a CrCl less than 60 mL/min or with conditions that may transiently reduce eGFR [51]. This is especially true in patients older than 75 years [14,52]. In the European Society of Cardiology (ESC) 2012 guidelines update, assessment of renal function (by CrCl) is considered mandatory with use of all newer OACs and should be performed annually in patients with normal (CrCl \geq 80 mL/min) or mild (CrCl 50-79 mL/min) renal impairment and perhaps 2-3 times a year in patients with moderate renal impairment (CrCl 30-49 mL/min) [15].

Rivaroxaban in Patients with Renal Impairment

When considering rivaroxaban for long-term management, renal function should be estimated by determining CrCl using the Cockcroft-Gault formula before initiating therapy and then as often as needed thereafter [52]. One-third of the rivaroxaban dose is eliminated as unchanged drug in the urine [43]. A moderate increase in plasma exposure and PD effects were observed with rivaroxaban 10 mg when given to patients with increasing renal impairment [53]. However, this is expected for a drug with partial renal excretion. The more important finding was that the influence of renal function on rivaroxaban clearance was moderate; thus, the extent of increased plasma exposure is unlikely to be of clinical relevance [53], even in patients with severe renal impairment. As such, no dose adjustments are necessary for mild renal impairment (CrCl 50-80 mL/min) [54-56].

Use of rivaroxaban in patients with atrial fibrillation and moderate renal impairment

Because rivaroxaban clearance is influenced by renal function [57], the daily dose of rivaroxaban in the ROCKET AF trial was reduced from 20 mg once daily to 15 mg once daily in patients with moderate renal impairment (CrCl 30-49 mL/min) at baseline [23]. A PK/PD analysis of simulated patients with AF supported this dose reduction, suggesting that the reduced dose would result in similar rivaroxaban exposure in patients with moderate impairment as with the 20 mg once-daily dose in patients with healthy renal function [57]. A sub analysis of 2950 (20.7%) patients with moderate renal impairment who were treated as part of the ROCKETAF trial found that the rivaroxaban dose adjustment yielded efficacy and safety results consistent with the overall trial in comparison with dose-adjusted warfarin [18]. The dose adjustment in patients with moderate renal impairment meant that the treatment effect for rivaroxaban versus warfarin in these patients was similar to that observed in patients with a CrCl \geq 50 mL/min for both the primary efficacy endpoint and principal safety outcome. Compared with warfarin treatment in patients with moderate renal impairment, fatal bleeding (hazard ratio: 0.39; 95% confidence interval: 0.15-0.99) and critical organ bleeding (hazard ratio: 0.55; 95% confidence interval: 0.30-1.00) were less frequent with rivaroxaban 15 mg once daily. Therefore, a dose reduction from 20 mg once daily to 15 mg once daily is recommended for patients with moderate renal impairment in both the EU (CrCl 30-49 mL/min) [55] and US labels (CrCl 30-50 mL/min) [56]. Rivaroxaban should be used with caution in patients with moderate renal impairment who are concomitantly receiving drugs known to alter rivaroxaban plasma concentrations (e.g. potent inhibitors of CYP3A4) [55] or drugs that might worsen renal function (e.g. diuretics or angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers).

Use of rivaroxaban in patients with atrial fibrillation and severe renal impairment

Both the CCS and the ESC 2012 guideline updates recommend against the use of the newer OACs in patients with a CrCl below 30 mL/min [14,15] given that patients with this severity of renal impairment were excluded from phase III trials. However, there may be some flexibility for physicians regarding these patients. Limited data in patients with a CrCl of 15-29 mL/min indicate that rivaroxaban plasma concentrations are increased significantly at this level of renal dysfunction [53], but the extent of therapeutic effect may not be of clinical relevance. Therefore, the EU Summary of Product Characteristics [55] states that rivaroxaban 15 mg once daily should be used with caution in patients with a CrCl of 15-29 mL/min (Table 1), but only after a careful and considered benefit-risk assessment is undertaken before and during treatment [52]. No dose adjustment is necessary for elderly patients [55], although experts suggest that the renal function of patients aged >75 years should be monitored regularly [52].

When should a possible decline in renal function be considered?

Although it may be challenging to predict declining renal function, there are conditions and circumstances whose presence should at least heighten concern about this possibility. Many risk factors for acute kidney injury have been identified [58], including patient age [59], sepsis [60], previous cardiac surgery [61,62], contrast dye [63], diabetes [64,65], rhabdomyolysis [66], pre-existing renal disease [67,68], hypovolemia [69] and shock [69]. From a more practical perspective, renal failure can result from pre-renal, intra-renal or post-renal causes, with pre-renal etiologies accounting for 60-70% of cases [70]. Intravascular volume depletion, often manifesting subsequent to fever, vomiting and diarrhoea, is the most common cause of pre-renal failure. When serious, it can lead to decreased kidney perfusion; however, dehydration from any cause, including diuretics, can lead to acute renal failure [70]. The initial assessment should include the patients' history to identify systemic illnesses or the use of nephrotoxic medications that might cause poor renal perfusion or directly impair renal function. Older patients, who often have a preceding age-related decline in renal function, have a higher risk of developing acute renal insufficiency or experiencing a worsening of any pre-existing renal impairment, and therefore require the most careful surveillance.

Even in the absence of any acute kidney injury, inappropriate dosing in patients with CKD can cause ineffective therapy. By itself, CKD can affect glomerular blood flow and filtration, tubular secretion and re-absorption, and renal bioactivation and metabolism. As a result, drug absorption, bioavailability, protein binding, distribution volume and non-renal clearance (metabolism) can be altered in these patients. Physicians should pay careful attention when considering drug therapies with active or toxic metabolites that can accumulate and contribute to exaggerated pharmacological effects or adverse drug reactions in patients with CKD.

The simple monitoring of serum creatinine levels is routine in practice and is used in the HAS-BLED bleeding risk score [46]. However, because the elderly tend to have decreased muscle mass, this method of assessment can be an inadequate measure of renal function. Up to 40% of patients aged 65 years or older have at least modest renal insufficiency, defined as an eGFR below 60 mL/min using the Cockcroft-Gault formula [71]. Thus, assessment of renal function needs to take both age and weight into account rather than just serum

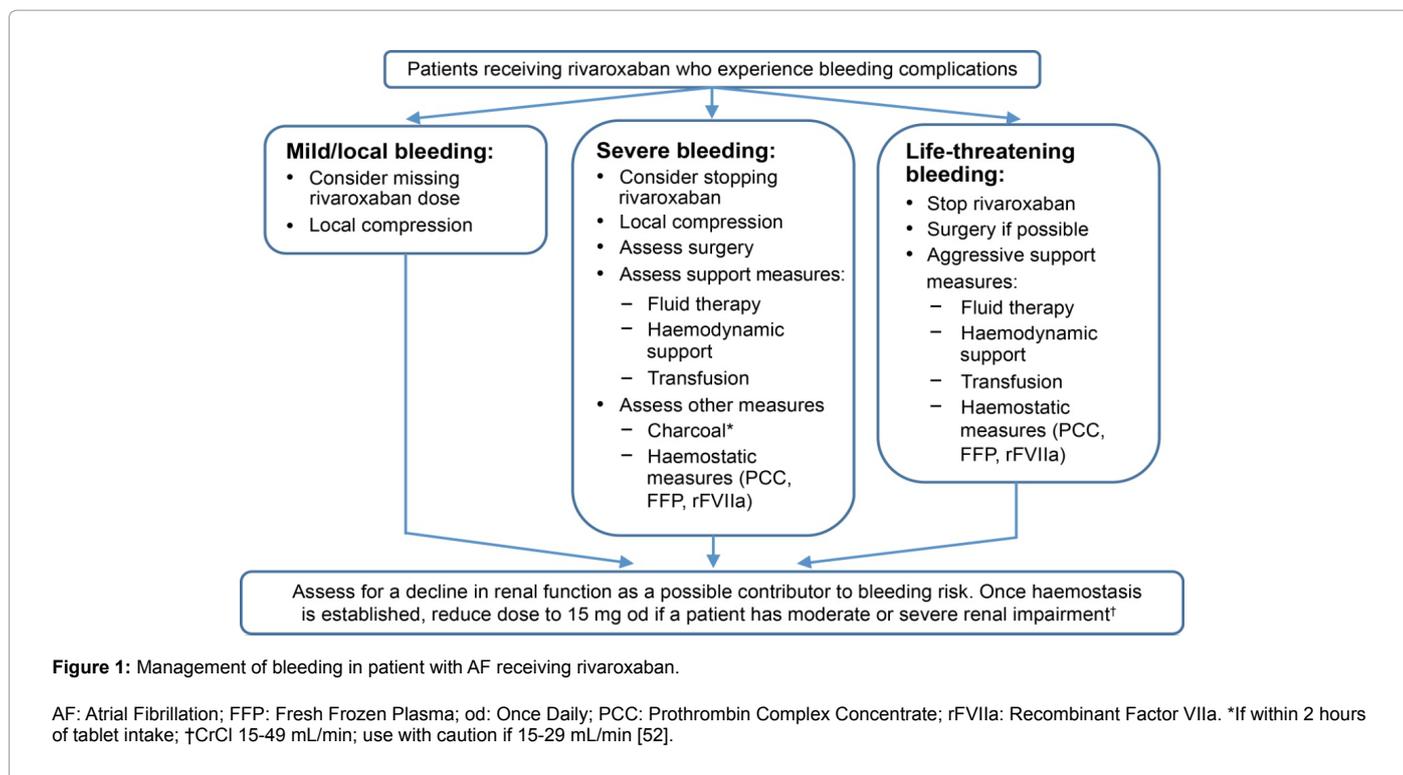
creatinine alone. Unfortunately, this is not often performed despite the fact that many medications (including antibiotics, antihypertensives, fibrates, sedatives/hypnotics and anxiolytics) are cleared through the kidneys and dosing guidelines require dosage adjustments in patients with decreased CrCl [72]. Aggravating matters is the fact that older patients tend to be taking multiple drugs at any given time, making assessment difficult. A national survey from the US reported that the average nursing home resident used seven to eight different medications each month whereas approximately one in three patients used nine or more different medications [73]. In a study in Canada, 62% of patients older than 65 years of age on public drug programmes had claims for five or more drugs and 5.5% had claims for 15 or more [74]. Furthermore, the number of drug classes used increased with age, such that 28.6% of patients aged 85 years or older had claims for 10 or more drug classes versus 16.8% for those aged between 65 and 74 years [74].

Given that renal impairment becomes more prevalent with increasing age, it is unsurprising that failure to adjust properly for renal insufficiency is a common cause of dose-related adverse events among the elderly [75]. Adverse events relating to warfarin, specifically bleeding, have been especially common [76]. Thus, not only should CrCl or eGFR be monitored more frequently, dose adjustment (generally lowering the dose) should follow as necessary, with the potential for resumption of the regular dose if and when renal function recovers.

Management of bleeding events

In cases of bleeding, rivaroxaban (as with any OAC) should be discontinued or the next dose delayed, according to established bleeding management protocols (Figure 1) [77]. If bleeding is mild, missing only a single dose will quickly reverse the anticoagulant effect because of the short half-life of rivaroxaban (5-13 hours) [43,55, 78]. If bleeding continues, then the local cause of bleeding must be investigated. If possible, any concomitant antiplatelet drugs should be stopped. If bleeding continues, then drug accumulation should be considered. Patients receiving rivaroxaban should have their prothrombin time measured [78]. The prothrombin time shows a linear dose-response to rivaroxaban and is prolonged; however, this is assay dependent [43,79]. Thus, an elevated prothrombin time is a useful qualitative indicator of drug presence, but does not provide precise information on drug level and hence the anticoagulant effect. A normal prothrombin time in the setting of rivaroxaban use would suggest that hemostatic function is not impaired because of the drug. Renal function should also be assessed, via CrCl or eGFR, as a potential contributor to an increased risk of bleeding. In patients with impaired renal function and bleeding, dose reduction or drug discontinuation should be considered as appropriate [55].

With moderate or severe bleeding, it is imperative to halt anticoagulation treatment and investigate the source of bleeding (Figure 1). Every effort should be taken to control bleeding with pressure or surgical hemostasis. Again, measurement of prothrombin time will indicate if rivaroxaban was taken, but will not provide insight into the anticoagulant effect. Although there is very little clinical evidence (e.g. randomized trials), consideration should be given to the administration of whole blood, fresh frozen plasma or platelet concentrates (in the setting of thrombocytopenia or if antiplatelet drugs had been taken) [55]. Prothrombin complex concentrates (PCCs), activated PCCs, recombinant Factor VIIa, or concentrates of Factors II, IX or X might also be considered, although again there is insufficient clinical experience with such approaches [51,78]. There is no literature either supporting or contraindicating the use of such treatment in patients



with markedly impaired renal function. Note that hemodialysis or hemofiltration should not be considered because rivaroxaban is highly protein bound and, as such, is unlikely to be dialyzable [79,80].

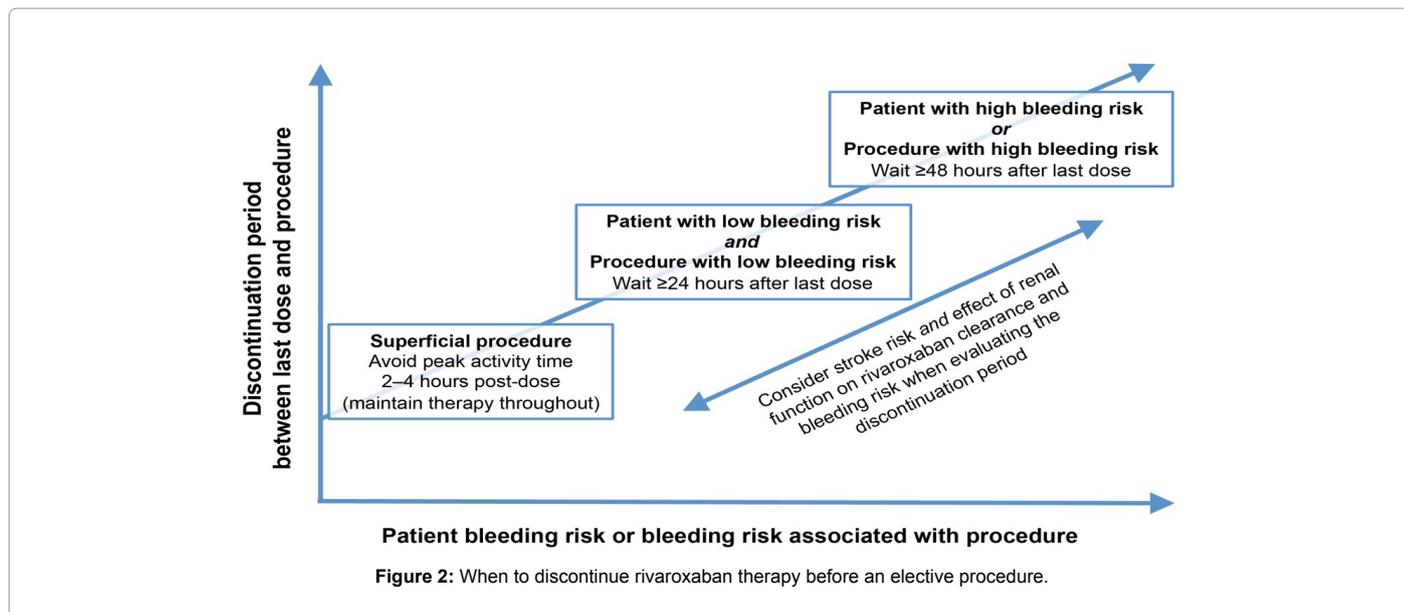
An advantage of rivaroxaban, as with the other newer OACs, is its short half-life so that supportive measures will only be required for a short time; in contrast, the half-life of warfarin is 20-60 hours [22]. There is currently no antidote for rivaroxaban or the other newer OACs; however, there is also no rapidly-acting antidote for warfarin. Administration of vitamin K will reverse the anticoagulant effect of warfarin, but this takes a long time to work (>6 hours in 54% of patients with intravenous administration [81]); far too long if the patient is presenting with an intracranial hemorrhage, for example. After vitamin K administration, increased synthesis of coagulation factors begins within 1-3 hours; however, the clinical effect is not detected until after 4-6 hours, with the maximum effect only seen after 24-36 hours [82]. Although PCCs rapidly correct international normalized ratio in most patients receiving warfarin, this insufficiently impacts prognosis, at least in patients with intracranial hemorrhage for whom mortality and morbidity rates remain high [83]. It has also been suggested that there is a risk of thromboembolic complications with PCC use in VKA-treated patients [84]. There is considerable effort being made to develop reversal agents for both the direct Factor Xa and direct thrombin inhibitor drugs and the expectation is that such products will soon become available. One possible Factor Xa inhibitor antidote, PRT064445 (r-Antidote), has demonstrated dose-dependent reversal of Factor Xa inhibition by rivaroxaban and apixaban (and a third agent, betrixaban) in Factor Xa enzyme assays. In this study, PRT064445 alleviated blood loss resulting from rivaroxaban-induced anticoagulation in a rabbit liver laceration model [85]. PRT064445 is currently being evaluated in a phase II trial in healthy volunteers who have been administered one of four direct/indirect Factor Xa inhibitors, including rivaroxaban [86,87].

Perioperative management

Alteration of the OAC regimen may not be necessary for most patients undergoing low-risk procedures, such as dental procedures (including extractions of up to four teeth), joint and soft tissue injections, arthrocentesis, cataract surgery, upper endoscopy or colonoscopy with or without biopsy [88,89]. For other invasive and surgical procedures, oral anticoagulation needs to be withheld and a clinical decision reached on whether to pursue an aggressive strategy of perioperative administration of intravenous heparin or subcutaneous low molecular weight heparin. This decision should be individualized based on an estimation of the patient's risks of thromboembolism and bleeding [88,89].

From a practical perspective, any patient taking an OAC and requiring surgery should have their renal function assessed, in conjunction with a consideration of the half-life of their anticoagulant agent, and the relative risk of stroke versus bleeding [51]. Together, these matters will inform decisions around the timing of any temporary drug discontinuation, the need for bridging therapy, and when therapy should be resumed and, potentially, at what dose.

For rivaroxaban in particular, the recommendation is to withhold the drug for at least 24 hours before the procedure in patients with a low risk of bleeding and then to restart it once hemostasis is established [51,55]. For patients with a CrCl of 15-30 mL/min, it has been recommended that the delay is at least 36 hours, even when there is a low risk of bleeding [51]. For procedures associated with a high risk of bleeding (or for patients at high risk of bleeding) it has also been recommended that the procedure be delayed by at least 48 hours after the last dose (Figure 2) [51,77]. Again, a patient's renal function and stroke risk should also be considered, as well as their bleeding risk (Figure 2). As mentioned at the beginning of this section, for non-invasive or superficial procedures, treatment with rivaroxaban may be maintained,



avoiding times of rivaroxaban peak activity (2-4 hours post dose) [52]. For urgent procedures, physicians should consider the increased risk of bleeding against the urgency of the procedure and delay at least 24 hours if possible [51,54-56]. The physician should again consider the patient's renal function and the effect this may have on rivaroxaban clearance. Patients with a CrCl of 15-49 mL/min after the procedure should be switched to the 15 mg dose (if not already on this dose) [55] or switched to warfarin for at least a while after the procedure. This is in contrast to dabigatran, which may need to be stopped at least 4 or 5 days before a procedure in patients with poor renal function and high bleeding risk because of its greater dependence on renal clearance and the consequent effect this has in terms of prolonging drug half-life [35,51,90].

Measuring Rivaroxaban in Patients

Because of their predictable pharmacology, routine coagulation monitoring of newer OACs is not required [22, 91]. In patients with renal impairment, advanced age and clinically relevant drug-drug interactions, periodic laboratory drug measurement may be appropriate [92]. Under such circumstances, quantitative measurements of rivaroxaban can be taken using an anti-Factor Xa chromogenic assay; rivaroxaban-specific calibrators and controls (commercially available, e.g. from Technoclon or Hyphen-BioMed) should be used for calibration, with results expressed as ng/mL of rivaroxaban [52]. However, these measurements are expensive and not readily available. In the meantime, routine monitoring of rivaroxaban and the other anticoagulants is not available and, although not required for therapeutic efficacy, this would facilitate monitoring of patient adherence. Until readily available and affordable monitoring tools become available, prescribers should take the time to educate patients with regard to the therapeutic intent of these drugs, specifically the aim to prevent severe, often disabling stroke in patients with AF, and to underline that this benefit is only to be achieved if the drugs are taken as prescribed. For patients for whom there is adherence concern, once-daily dosing may be preferable because this has been shown to improve patient adherence to therapy versus twice-daily dosing [93, 94]. Once-daily dosing is therefore expected to promote compliance with newer OAC therapy in patients with AF [51].

Discussion

AF is an increasingly prevalent condition whose most feared complication is a major ischemic stroke. Available OACs are all highly effective at reducing the risk of stroke, albeit with a potential slight increase in bleeding, compared with no treatment. Although bleeding risk must be respected, it should not be overestimated or overemphasized. As with every aspect of care, clinical judgement of risk versus benefit needs to be considered, and bleeding risk is rarely sufficiently high as to outweigh the benefit of stroke risk reduction. Renal impairment is intimately associated with AF, being very common in the older patient cohorts most likely to develop AF. However, CKD is independently associated with increased stroke risk and increased bleeding risk [17-19]. Accordingly, in the subgroup of patients with AF and CKD, greater attention to the benefit-risk assessment of antithrombotic treatment is warranted, especially when drugs have some renal-dependent clearance. With appropriate monitoring of renal function and dose adjustment, rivaroxaban is an important option for preventing stroke in patients with AF and impaired renal function (with a reduced dose available for these patients), while placing them at similar or less risk of bleeding than with VKA or other established antithrombotic therapies.

Conflict of Interest

Dr. Cox has served on advisory boards for AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Pfizer and Sanofi-Aventis; has participated in research funded by Bayer, Merck, Pfizer and Sanofi-Aventis; has served as/is a consultant to the Nova Scotia Department of Health, the New Brunswick Department of Health and the Public Health Agency of Canada; was an external expert to the Canadian Agency for Drugs and Technologies in Health in their reviews of antithrombotic therapies in atrial fibrillation; and is a member of the Canadian Cardiovascular Society's Atrial Fibrillation Guidelines Panel and Chair of its Atrial Fibrillation Quality Indicator Subcommittee.

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