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Review

Non-Vitamin K Antagonist Oral Anticoagulants in Adult Congenital Heart Disease

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ABSTRACT

Non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) have several advantages over VKAs that render them an attractive option for adults with congenital heart disease (CHD). Efficacy and safety data specific to the adult CHD population are emerging. Herein, we synthesize the growing literature regarding NOACs in adults with CHD and attempt to identify subgroups for which it appears reasonable to extrapolate data from populations without CHD. Small observational studies suggest that NOACs are safe and effective in selected adults with CHD. NOACs are contraindicated in patients with a mechanical

RÉSUMÉ

Les nouveaux anticoagulants administrés par voie orale (NACO) qui ne sont pas des antagonistes de la vitamine K (AVK) présentent plusieurs avantages comparativement aux AVK qui les rendent attrayants pour le traitement des adultes présentant une cardiopathie congénitale. Des données sur l'efficacité et l'innocuité portant précisément sur les adultes atteints de cardiopathie congénitale voient le jour. Nous résumons ici la littérature de plus en plus abondante sur l'administration de NACO chez des adultes atteints de cardiopathie congénitale et tentons d'identifier des

The growing population of adults with congenital heart disease (CHD) face a 10- to 100-fold higher risk of thromboembolic complications than age-matched controls.[1] Thromboembolic and bleeding risks are not uniform across the various forms of CHD such that the indication for anticoagulation and the choice of antithrombotic agent could be influenced by the underlying cardiac pathology.[2,3] Patients with cyanotic CHD are at highest risk for cerebrovascular accidents.[4] Although vitamin K antagonists (VKAs) emerged as the *de facto* oral anticoagulant for lack of rival agents, non-VKA anticoagulants (NOACs) entered the scene with the completion of the first large clinical trial in 2009.[5] They have since usurped VKAs as the agents of choice in patients with nonvalvular atrial fibrillation[6] and venous thromboembolism,[7] with the promise of more predictable pharmacokinetics, fewer drug-drug and food-drug interactions, greater ease of use, and a more attractive risk to benefit profile (Table 1).

It is, therefore, tempting to extrapolate data from large clinical trials to the adult CHD population in the hope of improving outcomes. However, caution is warranted in generalizing the results of clinical trials to a nontarget population. NOACs can be less safe and effective than VKAs in certain conditions[8] and precautions regarding selection of agents and dose adjustments are required on the basis of clinical circumstances. There is no substitute for clinical research in assessing the value of NOACs in the adult CHD population. Ongoing studies, such as the multinational **NO**ACs for Atrial **T**achyarrhythmias in Congenital Heart Disease (NOTE) registry (www.clinicaltrials.gov: NCT02928133), have begun providing reassuring short-term

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valve, in those with mitral or tricuspid valve stenosis with enlarged and diseased atria, with or without a mitral or tricuspid bioprosthesis, and after recent cardiac surgery (< 3 months). There is currently insufficient evidence to recommend NOACs in patients with a Fontan circulation or cyanotic CHD. Growing literature supports the use of NOACs in patients without CHD who have various forms of valvular heart disease. Therefore, when an indication for oral anticoagulation is established, it appears reasonable to consider a NOAC instead of a VKA in adults with CHD lesions analogous to isolated mitral regurgitation, tricuspid regurgitation, or aortic regurgitation or stenosis. The NOAC agent selected and the prescribed dose should be tailored according to bleeding risk, body weight, renal function, and comedications, especially antiepileptic drugs. The decision to initiate a NOAC should be shared between the patient and care provider. Large-scale research studies are required to further assess safety and efficacy in selected patient subgroups.

sous-groupes pour lesquels il apparaît raisonnable d'extrapoler des données provenant de populations ne présentant pas de cardiopathie congénitale. Des études observationnelles de petite taille laissent supposer que les NACO sont sûrs et efficaces chez certains adultes choisis présentant une cardiopathie congénitale. Les NACO sont contre-indiqués chez les patients porteurs d'une prothèse valvulaire mécanique, ceux qui présentent une sténose mitrale ou tricuspide accompagnée d'une hypertrophie auriculaire, avec ou sans bioprothèse mitrale ou tricuspide, et ceux qui ont récemment subi une chirurgie cardiaque (< 3 mois). L'insuffisance des données probantes actuelles ne permet pas de recommander les NACO chez les patients atteints d'une cardiopathie congénitale cyanogène ou associée a une circulation de type Fontan. Des données de plus en plus abondantes corroborent l'usage des NACO chez les patients qui ne sont pas atteints de cardiopathie congénitale mais qui présentent diverses formes de valvulopathies. Par conséquent, lorsque l'anticoagulation par voie orale est indiquée, il semble raisonnable d'envisager un NACO plutôt qu'un AVK chez les adultes présentant des lésions congénitales analogues à une régurgitation mitrale isolée, à une régurgitation tricuspide ou à une régurgitation ou une sténose aortique. Le choix du NACO et de la dose doit se faire en fonction du risque de saignement, du poids corporel, de la fonction rénale et des médicaments administrés en concomitance, particulièrement s'il s'agit d'antiépileptiques. La décision d'amorcer un traitement par un NACO devrait être prise de concert par le professionnel de la santé et le patient. Des études de grande envergure sont nécessaires pour évaluer plus en profondeur l'innocuité et l'efficacité des NACO dans des sous-groupes de patients choisis.

safety data and will no doubt shed light on longer-term outcomes in the future.[9-13] In the interim, a review of present knowledge could help inform current practice regarding subgroups of adults with CHD for whom it might be reasonable to prescribe a NOAC when anticoagulation is indicated. Such an approach has similarly been used to refine indications and contraindications to NOACs in patients with valvular heart disease.[14]

Indications for Anticoagulation in Adults With CHD

Adults with CHD harbor various risk factors for thromboembolism that include CHD complexity, atrial arrhythmias, previous thromboembolic events (including paradoxical emboli), right to left shunts (eg, cyanotic CHD), pulmonary hypertension, Fontan circulation, intrinsic coagulation abnormalities, valvular prosthesis, and pregnancy, along with factors that are captured using standard risk scores such as **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥ 75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female) (CHA_2DS_2-VASc).[15] There are, therefore, numerous reasons as to why an adult with CHD might require systemic anticoagulation.

Table 1. Advantages and disadvantages of NOACs relevant to adults with CHD

Advantages	Disadvantages
• No dose adjustment required on the basis of frequent monitoring of coagulation parameters • Predictable anticoagulant effect • Fewer food and drug interactions than VKAs • Rapid onset of action • Consistently lower risk of intracranial haemorrhage compared with VKAs	• Precautions and contraindications on the basis of renal function • Higher cost than VKAs • Limited experience and availability of reversal agents • Risk of bleeding • Blood levels more difficult to monitor • Paucity of efficacy and safety data specific to adults with CHD • Contraindicated during pregnancy and breastfeeding

CHD, congenital heart disease; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

Atrial arrhythmias

Contemporary prevalence estimates for atrial arrhythmias in adults with CHD range from 10% to 15%,[16,17] with projections suggesting that > 50% of those with complex CHD will develop atrial arrhythmias by 65 years of age.[17] Among adults with CHD, those with atrial arrhythmias have a twofold higher risk of stroke.[17] Adults with CHD might have important risk factors for stroke that are not captured using standard risk scores such that decisions regarding anticoagulation should be made in concert with an adult CHD specialist. For example, practice guidelines recognize that adults with moderate or complex CHD (see Supplemental Table S1 for a classification of CHD complexity)[2,15] and intra-atrial re-entrant tachycardia (atrial flutter) or atrial fibrillation could benefit from anticoagulation despite a CHA_2DS_2-VASc score of 0.[2]

The type and prevalence of arrhythmia depends, in part, on the heart defect, type of repair, surgical incisions, residual hemodynamic lesions, and age.[15] Defects associated with the highest prevalence of atrial arrhythmias include Ebstein

anomaly, transposition of the great arteries with atrial baffles, univentricular hearts, atrial septal defects, and tetralogy of Fallot.[1] Atrial fibrillation is particularly common in patients with residual left-sided lesions or single ventricle physiology.[18] In contemporary cohorts of patients with CHD and atrial arrhythmias, the risk of thromboembolic complications ranges from 11 to 14 per 1000 patient-years when antithrombotic therapy is at the physician's discretion.[19,20] In a multicentre cohort of 482 patients with CHD and atrial arrhythmias, complexity of CHD was the only factor independently associated with thromboembolic events.[20] As shown in Table 2, compared with study populations included in NOAC trials for nonvalvular atrial fibrillation, the residual annual rate of stroke or systemic embolism during treatment is similar in adults with CHD despite their younger age and fewer traditional risk factors.

Fontan circulation

Thromboembolic complications can have devastating consequences in patients with a Fontan circulation and have been associated with mortality in some[21] but not all studies.[22,23] The risk of thromboembolism is nonlinear and rises sharply at 2 different points in time: within 2-3 years and 15 years after Fontan surgery.[21] Many associated factors have been identified including atrial arrhythmias, a fenestration (for systemic thromboembolic events), previous thrombosis, an atriopulmonary connection with atrial flow stasis, a blind pulmonary artery stump or hypoplastic cardiac chambers with flow stasis, bilateral cavopulmonary anastomoses, protein-losing enteropathy, prolonged pleural effusions, ventricular dysfunction, intrinsic coagulation abnormalities, and thrombogenic material.[24-26] Anticoagulation has consistently been recommended for Fontan patients with a residual atrial shunt, atrial thrombus, atrial arrhythmias, or a previous thromboembolic event.[1] Many patients with an atriopulmonary Fontan circulation harbor thrombotic risk factors that might justify long-term anticoagulation (class IIb, level of evidence C according to the scientific statement on prevention and treatment of thrombosis in pediatric and CHD from the American Heart Association).[24]

Eisenmenger syndrome

Pulmonary artery dilatation, stasis, endothelial injury, older age, and biventricular dysfunction favour the formation of mural thrombi in patients with Eisenmenger syndrome,[27-31] which, in turn, can cause artery to artery embolization. By 35 years of age, 13% of patients have had a clinically recognized pulmonary embolism.[32] A VKA can treat pulmonary emboli in the presence of thrombus in the central pulmonary arteries, but routine anticoagulation to prevent thrombus formation is not indicated.[33] Risks and benefits of anticoagulation must be carefully weighed, considering that anticoagulation does not improve survival.[34,35] The prevalence of stroke in patients with Eisenmenger syndrome is 8%-14%[32,36] and increases to 47% if routine cerebral magnetic resonance imaging is performed.[37] Female sex, low oxygen saturation, advanced age, biventricular dysfunction, low functional capacity, and pulmonary artery aneurysm are associated with an increased risk of thrombus.[28,30,33,37,38] Atrial fibrillation, pulmonary hypertension, microcytosis,

Table 2. Comparison of risk factors and annual rates of stroke or systemic embolism in selected studies

	Adults with CHD				Nonvalvular atrial fibrillation									
Study	TACTIC[20]		RE-LY[50]		ROCKET-AF[48]		ARISTOTLE[51]			ENGAGE AF-TIMI 48[49]				
Drug	Aspirin, VKA, or NOAC*		Dabigatran		Rivaroxaban	VKA	Apixaban	VKA		Edoxaban				VKA
Dose		110 mg BID	150 mg BID		20/15 mg QD		5/2.5 mg BID			60 mg QD	30 mg QD			
N	482	6015	6076	6022	7131	7133	9120	9081		7035	7034			7036
$CHADS_2$ 0-1, %	93	33	32	31	0	0	34	34		77†	78†			77†
SSE, % per year	1.14	1.53	1.11	1.69	1.7	2.2	1.27	1.60		1.18	1.61			1.50
Major bleeding, % per year	0.77 OAC 0.07 antiplatelet	2.71	3.11	3.36	3.6	3.4	2.13	3.09		2.75	1.61			3.43
Major bleeding in patients aged younger than 65-75 years, % per year	Same (mean age 32 years)	1.89	2.12‡	3.04‡	2.21	2.16	1.2	1.5		2.02‡	N/A			2.62‡

ARISTOTLE, **A**pixaban for **R**eduction **i**n **S**troke and **O**ther **T**hromboembolic **E**vents in Atrial Fibrillation; BID, twice per day; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; CHD, congenital heart disease; ENGAGE AF-TIMI 48, **E**ffective **An**ticoa**g**ulation With Factor X**a** Next **Ge**neration in **A**trial **F**ibrillation-**T**hrombolysis in **M**yocardial **I**nfarction 48; NOAC, novel oral anticoagulant; OAC, oral anticoagulant; QD, once daily; RE-LY, **R**andomized **E**valuation of **L**ong-term Anticoagulation Therap**y**; ROCKET-AF, **R**ivaroxaban **O**nce Daily Oral Direct Factor Xa Inhibition **C**ompared With Vitamin **K** Antagonist for Prevention of Stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation; SSE, stroke or systemic embolism; TACTIC, **T**he **A**nticoagulation **T**herapy in **C**ongenital Heart Disease; VKA, vitamin K antagonist.

* Antiplatelet therapy was received by 37.8%. OACs were received by 54.4% (8.8% of those on NOACs), 7.9% received no OAC.

† $CHADS_2 \leq 3$.

‡ Younger than 75 years.

and iron deficiency, as a consequence of inappropriate phlebotomies, also favour the occurrence of stroke.[36] However, Eisenmenger syndrome carries a substantial bleeding risk because of reduced levels of coagulation factors (II, V, VII, IX, X) and von Willebrand factor multimers, along with increased fibrinolytic activity.[33]

Right to left shunt

In general, patients with a probable embolic stroke and patent foramen ovale who do not undergo closure should receive antithrombotic therapy. A recent expert panel issued a weak recommendation in favour of oral anticoagulants over antiplatelet therapy.[39] Although a NOAC is not considered contraindicated in this setting, the current experience is largely with VKAs.[39] In patients with intracardiac shunts, shunt closure is generally recommended before intra-cardiac lead implantation, barring a contraindication.[40,41] If the shunt is not closed, oral anticoagulation should be considered in light of the increased thromboembolic risk.

Mechanism of Action of NOACs

NOACs are small molecules that bind to the active site of a single protease in the coagulation cascade.[42] In contrast, VKAs reduce the production of active proteases by interfering with the gamma-carboxylation of vitamin K-dependent coagulation (II, VII, IX, X) and antithrombotic (protein C, S, and Z) factors.[42] NOAC binding is reversible such that their effect can be overcome by increasing the thrombogenic substrate or by a strong procoagulant stimulus.[42] For example, the brain contains very high levels of tissue factor, the main initiator of coagulation. Exposure of blood to brain tissue might overcome the effect of a NOAC, suggesting a mechanism for the reduced occurrence of intracranial hemorrhage.[42] The dose relationship between NOAC level and intensity of coagulation is more linear than with VKA because the inhibition of a single protease is more predictable than inhibition of multiple steps of the coagulation cascade.[42] This might partially account for the more favourable safety profile of NOACs.[42]

Dabigatran

Dabigatran is a small hirudin analogue that prevents the conversion of fibrinogen to fibrin by inhibiting thrombin (factor IIa).[43] The effect of dabigatran and be reversed by idarucizumab (Praxbind; Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT), a monoclonal antibody.[44]

The **R**andomized, Phase II Study to **E**valuate the Sa**f**ety and Pharmacokinetics of Ora**l** Dab**ig**atran Etexilate in Patients After Heart Valve Replacemen**t** (RE-ALIGN) trial, which was prematurely terminated because of an excess of thromboembolic and bleeding events in patients with mechanical valves who received high-dose dabigatran compared with VKAs, raised concerns about the role of NOACs in the setting of prosthetic material.[8] Mechanical valves appear to induce sufficient thrombin generation to overcome the effect of dabigatran at clinically relevant concentrations.[45] The semicircular leaflets and Dacron or Teflon sewing ring promote thrombin generation by activating factor XII and the intrinsic coagulation pathway more than metallic leaflets.[45] To achieve a therapeutic effect similar to an international normalized ratio (INR) between 2 and 3.5, considerably higher concentrations of dabigatran ($>$ 200 ng/mL) than tested in RE-ALIGN ($>$ 50 ng/mL)[8] are required, with prohibitive bleeding risks.[45] Importantly, bioprosthetic heart valves also have Dacron sewing rings such that an initial 3-month course of VKA can be helpful in reducing the risk of thrombosis while the ring undergoes endothelialization.[45] These concepts are relevant to CHD patients with similar prosthetic material. The use of NOACs in patients with mechanical valves, particularly factor Xa inhibitors, might eventually be reconsidered.[46]

Rivaroxaban, apixaban, and edoxaban

Rivaroxaban, apixaban, and edoxaban prevent the conversion of prothrombin to thrombin (factor IIa) by inhibiting coagulation factor Xa.[43] Their effects might be reversed by use of andexanet alpha, a modified recombinant factor Xa molecule that binds NOACs.[47]

Evidence Specific to CHD

Evidence for the use of NOACs in adults with CHD is emerging in the form of observational studies. In a series of 75 adults with CHD on NOACs by Pujol et al., 31 had a pretricuspid shunt, 16 complex CHD, 5 cyanosis, and 3 a Fontan circulation.[12] Most were anticoagulated for atrial arrhythmias (76%) or history of stroke/transient ischemic attack (20%) and were predominantly treated with rivaroxaban (73%).[12] The population had a low bleeding risk, with a **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly ($>$ 65 Years), **D**rugs/Alcohol Concomitantly (HAS-BLED) score $\leq$ 1 in 72% of patients.[12] No thrombotic or major bleeding event occurred during a mean follow-up of 12 months.[12] Similarly, Yang et al. reported an early international experience on 99 adults with CHD (56% moderate CHD, 29% complex CHD, 33% with a history of heart failure, 11% with Fontan palliation), all of whom had atrial arrhythmias.[13] Apixaban was the most commonly prescribed agent (62%) and the median HAS-BLED score was 0. After 30 days of therapy, 8 minor events (5 minor bleeds, 3 side effects) occurred in the 54 patients who had transitioned from a VKA to a NOAC. These findings were considered reassuring, particularly in patients with moderate or complex CHD.[13] Cheng et al. reported 13 patients with CHD treated with a NOAC for a median of 570 days.[9] More gastrointestinal side effects were observed with dabigatran.[9]

Georgekutty et al. reviewed their experience with NOACs in 21 patients with a Fontan circulation anticoagulated because of arrhythmias (12), thrombosis (8), or persistent right-to-left shunt (2).[10] A NOAC was prescribed on the basis of patient or provider preference, labile INR during treatment with a VKA, initiation of therapy in another centre, or noncompliance with follow-up. Ten minor bleeding events occurred with no major bleed. During a total of 316 patient-months of therapy, 1 patient with protein-losing enteropathy and right to left shunting through a fenestration had deep vein thrombosis during treatment with dabigatran. Another patient had progression of Fontan circuit thrombosis during treatment with apixaban. Pinto et al. also reported the progression of thrombus in a patient with a lateral tunnel Fontan and atrial flutter during treatment with apixaban.[11] The NOTE registry included 74

patients with a Fontan circulation. During a median follow-up of 1.2 years, 3 (4.1%) thromboembolic events and 3 (4.1%) major bleeds occurred. Although adverse event rates were not statistically significantly higher than with VKAs during a brief follow-up period (personal communication from Barbara J.M. Mulder), the limited experience precludes definitive endorsement of NOAC use in Fontan patients until further evidence becomes available.

Evidence About NOACs Relevant to CHD

Nonvalvular atrial fibrillation

The results of 4 large clinical trials (**R**andomized **E**valuation of **L**ong-term Anticoagulation Therap**y** [RE-LY], **R**ivaroxaban **O**nce Daily Oral Direct Factor Xa Inhibition **C**ompared With Vitamin **K** Antagonist for Prevention of Stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation [ROCKET-AF], **A**pixaban for **R**eduction **i**n **S**troke and **O**ther **T**hromboembol**i**c **E**vents in Atrial Fibrillation [ARISTOTLE], **E**ffective A**n**ticoa**g**ulation With Factor X**a** Next **Ge**neration in **A**trial **F**ibrillation-**T**hrombolysis **i**n **M**yocardial **I**nfarction 48 [ENGAGE AF-TIMI 48]) in patients with atrial fibrillation were pooled in a meta-analysis that included 42,411 patients randomized to a NOAC vs 29,972 patients randomized to warfarin.[6] NOACs significantly reduced stroke and systemic embolism (relative risk [RR] 0.81; 95% confidence interval [CI], 0.73-0.91; $P < 0.0001$), hemorrhagic stroke (RR, 0.49; 95% CI, 0.38-0.64; $P < 0.0001$), all-cause mortality (RR, 0.90; 95% CI, 0.85-0.95; $P = 0.0003$), and intracranial hemorrhage (RR, 0.48; 95% CI, 0.39-0.59; $P < 0.0001$).[6] Considering all NOACs, there was a highly suggestive trend toward a reduction in major bleeding (RR, 0.86; 95% CI, 0.73-1.00; $P = 0.06$). The trend was consistent for all agents except rivaroxaban (RR, 1.03; 95% CI, 0.90-1.18; $P = 0.72$).[6,48] Lower-dose NOACs (dabigatran 110 mg twice daily or edoxaban 30 mg or 15 mg daily) were associated with a similar reduction in stroke and systemic embolism compared with warfarin (RR, 1.03; 95% CI, 0.84-1.27; $P = 0.74$), fewer major bleeds (RR, 0.65; 95% CI, 0.43-1.00; $P = 0.05$), and intracranial haemorrhages (RR, 0.31; 95% CI, 0.24-0.41; $P < 0.0001$), but more ischemic strokes (RR, 1.28; 95% CI, 1.02-1.60; $P = 0.045$).[6] The increased risk of ischemic stroke appears to be driven by results with the 30 mg or 15 mg edoxaban daily regimen.[49,50] The effects of NOACs were consistent in subgroup analyses according to age, sex, history of diabetes, previous stroke or transient ischemic attack, creatinine clearance, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack [$CHADS_2$] score, and previous use of a VKA.[6]

Subgroups of patients with atrial fibrillation and valvular heart disease

Patients with atrial fibrillation and valvular heart disease have more adverse events. None of the NOAC trials have specifically targeted patients with valvular heart disease. All trials excluded patients with mechanical valves or severe mitral stenosis, and only ENGAGE AF-TIMI 48 (edoxaban) allowed enrolling subjects with bioprosthetic valves. In addition, ROCKET-AF (rivaroxaban) excluded patients with "hemodynamically relevant valve disease"[48] and patients with moderate or severe mitral stenosis did not qualify for enrollment in ARISTOTLE (apixaban)[51] or ENGAGE AF-TIMI 48 (edoxaban).[49] Nevertheless, 13%-26% of patients included in the major NOAC trials had some form of valve disease,[52,53] allowing for substudies and meta-analyses summarized in Table 3. Patients with valvular heart disease were older, more often female, had more comorbidities, more permanent or persistent atrial fibrillation, and had higher $CHADS_2$ and HAS-BLED scores.[53-56] Overall, higher adverse event rates were observed in patients with valve disease.[14] In the RE-LY trial (dabigatran), the presence of exclusive right-sided valve disease (tricuspid or pulmonary regurgitation) was associated with excess major bleeding compared with patients without valvular heart disease regardless of treatment assignment.[53]

Stroke, systemic embolism, and bleeds in patients with atrial fibrillation and valve disease. NOACs appear to be as effective or superior to VKAs for the prevention of stroke or systemic embolism in patients with valvular heart disease, barring the types of valve disease excluded from the trials (Table 3). A lower incidence of major bleeding with a NOAC compared with a VKA was consistent across trials, with the exception of excess bleeding with rivaroxaban use in patients with valve disease in ROCKET-AF.[57] The patients with valvular heart disease in ROCKET-AF were older and had more comorbidities.[57] Likewise, a consistent advantage of NOACs over VKAs was observed in reducing the incidence of intracranial hemorrhage in patients with valve disease, with the exception of rivaroxaban.

Heterogeneity in the definitions of nonvalvular and valvular atrial fibrillation. Heterogeneity in the definitions of valvular atrial fibrillation with variable exclusion criteria in the anticoagulation trials prompted a new Evaluated Heart Valves Rheumatic or Artificial (EHRA) classification system.[14] According to the expert consensus statement, EHRA type 1 patients have atrial fibrillation in the setting of a mechanical valve or rheumatic or moderate to severe mitral stenosis and should receive a VKA as an anticoagulant.[14] EHRA type 2 patients have atrial fibrillation and other forms of valve disease such that a NOAC or VKA is considered acceptable, while taking the CHA_2DS_2-VASc score into consideration.[14] To date, no alarming signal regarding excess strokes or major bleeding events with apixaban or edoxaban has been detected in meta-analyses and substudies in patients with atrial fibrillation and bioprosthetic valves or previous valve surgery.[52,54,58] However, a concern remains regarding NOAC use in patients with mitral bioprosthetic valves and previous rheumatic mitral valve disease with large and severely diseased atria such that a VKA might remain the better option in this scenario.[59]

Implications for adults with CHD. Valve disease is common in adults with CHD. In the absence of CHD-specific evidence, it might be reasonable to prescribe a NOAC instead of a VKA to patients with atrial arrhythmias and categories of valve disease that are similar to those with reassuring efficacy and safety data from large NOAC trials.

Table 3. Summary of outcomes in patients with atrial fibrillation and valvular heart disease treated with a NOAC vs VKA

					Treatment favoured in patients with VHD*		
Reference	Study type	N	Type of VHD	NOAC	Stroke and systemic embolism	Major bleeding	Intracranial bleeding
Caldeira et al.[54]	Meta-analysis	12,653	Native VHD Valve repair Bioprosthesis	All	NOAC	NOAC	NOAC
Pan et al.[56]	Meta-analysis	13,574	Native VHD	All	NOAC	None	NOAC
Renda et al.[77]	Meta-analysis	13,585	Native VHD Valve surgery	All	NOAC	None	NOAC
Vinereanu et al.[55]	Substudy of ARISTOTLE	3382	MR	Apixaban 5 or 2.5 mg BID	None	NOAC	NOAC
Vinereanu et al.[55]	Substudy of ARISTOTLE	324	AS	Apixaban 5 or 2.5 mg BID	None	None	None
Vinereanu et al.[55]	Substudy of ARISTOTLE	842	AR	Apixaban 5 or 2.5 mg BID	None	None	None
De Caterina et al.[52]	Substudy of ENGAGE AF-TIMI 48	2824	2250 MR 254 MS 369 AR 165 AS 191 Bioprosthesis 123 Valve repairs 19 Valvuloplasty	Edoxaban 60 mg QD	None	None	None
Carnicelli et al.[58]	Substudy of ENGAGE AF-TIMI 48	191	131 MVR 60 AVR	Edoxaban 60 or 30 mg QD	None	Low-dose NOAC	N/A
Ezekowitz et al.[53]	Substudy of RE-LY	3950	3101 MR 193 MS 1179 TR 97 AR 471 AS	Dabigatran 150 mg BID	NOAC	None	NOAC
Ezekowitz et al.[53]	Substudy of RE-LY			Dabigatran 110 mg BID	None	NOAC	NOAC
Breithard et al.[57]	Substudy of ROCKET-AF	1992 for efficacy 1999 for safety	1756 MR 486 AR 215 AS 15 Congenital VHD 106 Valve procedures 11 Other	Rivaroxaban 20 or 15 mg QD	None	Warfarin	None
Avezum et al.[78]	Substudy of ARISTOTLE	4808	3526 MR 131 MS 887 AR 384 AS 2124 TR 251 Previous valve surgery	Apixaban 5 or 2.5 mg BID	NOAC	None	NOAC
Noseworthy et al.[79]	Administrative database review	20,158	19,351 AS, AR, or MR 654 MS 74 Rheumatic MS 55 Valve repairs 24 Bioprosthesis	Dabigatran Rivaroxaban Apixaban	NOAC for AS, AR or MR None for MS	None NOAC for AS, AR, or MR	N/A

AR, aortic regurgitation; ARISTOTLE, **A**pixaban for **R**eduction **i**n S**t**roke and **O**ther **T**hromboembol**i**c **E**vents in Atrial Fibrillation; AS, aortic stenosis; AVR, aortic valve replacement; BID, twice daily; ENGAGE AF-TIMI 48, **E**ffective A**n**ticoa**g**ulation With Factor X**a** Next **Ge**neration in **A**trial **F**ibrillation-**T**hrombolysis **i**n **M**yocardial **I**nfarction 48; MR, mitral regurgitation; MS, mitral stenosis; MVR, bioprosthetic mitral valve replacement; N/A, not available; NOAC, novel oral anticoagulant; QD, once daily; RE-LY, **R**andomized **E**valuation of **L**ong-term Anticoagulation Therap**y**; ROCKET-AF, **R**ivaroxaban **O**nce Daily Oral Direct Factor Xa Inhibition **C**ompared With Vitamin **K** Antagonist for Prevention of Stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation; TR, tricuspid regurgitation; VHD, valvular heart disease; VKA, vitamin K antagonist.

*If no treatment is favoured (none), there is no significant difference in effectiveness or safety between the NOAC and warfarin. Patients might have multiple types of VHD.

Examples include patients with bicuspid aortic valves and aortic stenosis or regurgitation, repaired tetralogy of Fallot with pulmonary regurgitation, Ebstein anomaly with tricuspid regurgitation, and congenital valve disease with a bioprosthetic valve that is not in the systemic atrioventricular valve position, with normal or nearly normal atrial size. In contrast, NOACs should be avoided in adults with CHD who have a mechanical valve or recent surgery (< 3 months) as suggested by Jaffer et al.[45] It would also be prudent to avoid NOACs in patients with congenital mitral or tricuspid stenosis who have enlarged and severely diseased atria. There are no definitive data regarding NOACs in patients with a percutaneous valve prosthesis who require anticoagulation for another indication (such as atrial fibrillation). However, patients with transcatheter aortic valve replacement are classified as EHRA type 2, such that a NOAC is not considered contraindicated. The

Table 4. Practical tips for using NOACs relevant to adults with CHD

Baseline information to decide on NOAC eligibility
- Knowledge of congenital cardiac anatomy and pathophysiology
- Knowledge of kidney function, age, and weight
- Knowledge of comedications (notably antiarrhythmic and antiepileptic drugs); consult a pharmacist to assess drug interactions
- Knowledge of history of bleeding, especially gastrointestinal bleeding
- Assess bleeding risk (HAS-BLED score)
- Establish that NOAC use is acceptable in light of the underlying CHD; if in doubt, favour VKA
- Assess if patient is likely not to fare well using a VKA (eg, SAMe-TT_2R_2 score > 2)

Initiation of treatment
- Baseline blood tests: hemoglobin, renal and liver function, full coagulation panel
- Choose NOAC and correct dose
  - Improved adherence with once daily regimen
- If switching from a VKA:
  - If INR < 2: start NOAC
  - If INR 2-2.5: start NOAC the next day
  - If INR > 2.5: repeat INR in 1-3 days
- Decide on need for proton pump inhibitor (limited data)
- Educate patient about anticoagulation and medication intake
  - Rivaroxaban intake with food
  - Strict adherence to prescribed regimen
  - How to deal with missed doses and suspected overdose
- Patient should carry information about anticoagulant therapy
- Organize and ensure follow-up

Follow-up
- Initial follow-up at 1 month then every 3-6 months
- Involve specialized nurses in adult CHD during patient follow-up
- Check for thromboembolic and bleeding events
- Assess comedications
- Assess modifiable risk factors: hypertension, aspirin use, NSAID use, alcohol intake
- Assess that choice and dosing of NOAC remain optimal
- Determine need for blood tests (hemoglobin, renal and liver function, full coagulation panel):
  - Yearly for all
  - Every 6 months if age older than 75 years or frail patient
  - Tailored if decreased renal function: creatinine clearance divided by 10 (in months)
- Assess adherence and use adherence aids as needed
- Reinforce education
- Bridging generally not recommended if temporary interruption is needed

CHD, congenital heart disease; HAS-BLED, **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (> 65 Years), **D**rugs/Alcohol Concomitantly; INR, international normalized ratio; NOAC, novel oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; SAMe-TT_2R_2, **S**ex, **A**ge, **M**edical History, **T**reatment, **T**obacco Use, **R**ace; VKA, vitamin K antagonist.

Modified from Steffel et al.[59] with permission from Oxford University Press.

Global Study Comparing a Riv**a**roxaban-Based Antithrombotic Strategy to an Antip**l**atelet-Based Strategy After Transcatheter Aort**i**c Va**l**ve R**e**placement to **O**ptimize Clinical **O**utcomes (GALILEO) trial tested the hypothesis that a rivaroxaban-based antithrombotic strategy (10 mg daily with aspirin 75-100 mg daily for 90 days then rivaroxaban alone) would reduce the risk of thromboembolic complications after transcatheter aortic valve replacement with an acceptable risk of bleeding compared with the recommended antiplatelet therapy-based strategy (clopidogrel 75 mg daily with aspirin 75-100 mg daily for 90 days followed by aspirin alone) in subjects without a need for chronic oral anticoagulation.[60] This trial was recently terminated early because of excess harm (death and bleeding) in the rivaroxaban group.

Venous thromboembolism

NOACs are noninferior to the combination of parenteral heparin and VKA for the acute treatment (3 months) of venous thromboembolism, and are associated with fewer bleeds.[7] There is also evidence for extended prevention of venous thromboembolism with dabigatran, apixaban, or rivaroxaban after 3-12 months of initial therapy. Of note, recurrent venous thromboembolism is less frequent with either rivaroxaban 20 mg or 10 mg daily compared with aspirin, with no excess in major bleeds.[7] These data suggest that NOACs can offer antithrombotic benefits with a risk of bleeding comparable with that of aspirin. Even if the Fontan circulation could be considered a venous circuit, data specific to patients with a Fontan circulation are required before extrapolating such results in light of the thrombotic concerns already noted.

Labile INR

On average, patients with atrial fibrillation during warfarin treatment in clinical trials spend 65% of their time in the therapeutic range.[6] A greater reduction in bleeding events associated with NOACs is observed at centres with a time in the therapeutic range below 66%,[6] suggesting a larger benefit in patients with difficulties maintaining therapeutic INRs.

Heart failure

In patients with atrial fibrillation and a biventricular circulation with a systemic left ventricle, NOACs appear to be as safe and effective in patients with and without heart failure.[61,62] Moreover, NOACs have been associated with fewer intracranial hemorrhages in patients with heart failure.[62]

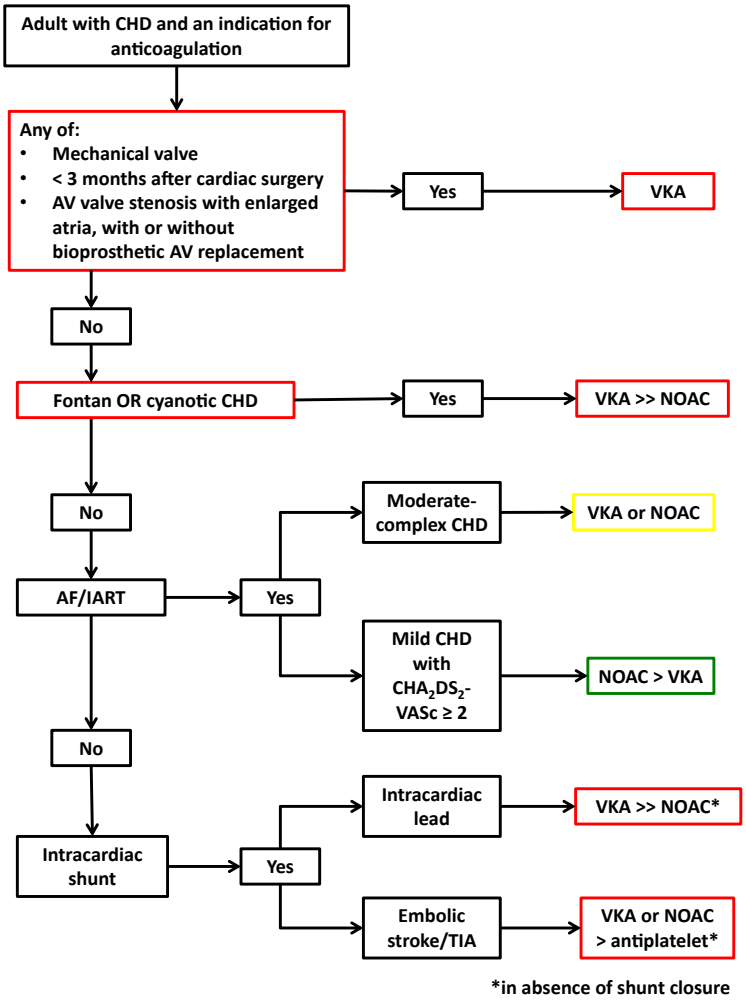

Figure 1. Suggested choices of antithrombotic medications for selected clinical situations in adults with congenital heart disease. **Green** indicates that non-vitamin K antagonist oral anticoagulant (NOAC) use is reasonable. **Yellow** indicates that NOACs should be used with caution. **Red** indicates that vitamin K antagonists (VKAs) are strongly preferred over NOACs or that NOACs are contraindicated. >, preferred to; AF/IART, atrial fibrillation/intra-atrial reentrant tachycardia; AV, atrioventricular; CHA_2DS_2-VASc, Congestive Heart Failure, Hypertension, Age (≥75 years), Diabetes, Stroke/Transient Ischemic Attack, Vascular Disease, Age (65-74 years), Sex (Female); CHD, congenital heart disease; TIA, transient ischemic attack.

Underweight patients

Low body weight (< 60 kg) is one of the criteria for a dose reduction of apixaban and edoxaban. Underweight patients taking a NOAC have a fourfold higher risk of major bleeding compared with normal weight patients.[63] Low body weight patients are under-represented in large outcome trials but no difference in the efficacy of NOACs was detected in patients with a lower body weight.[59]

Renal insufficiency

In a large series of adults with CHD, 50% had some degree of renal dysfunction.[64] All NOACs are partially eliminated by the kidney (dabigatran 80%, edoxaban 50%, rivaroxaban 35%, apixaban 27%) and should be dose-adjusted accordingly.[59] Creatinine clearance should be estimated using the Cockroft-Gault formula and monitored at a frequency corresponding to the creatinine clearance/10 in months.[59] Although all NOACs are effective and safe in subgroup analyses of pivotal trials, apixaban and edoxaban might have the best safety profile in patients with reduced renal function.[59] The dose of rivaroxaban should be reduced to 15 mg daily if the creatinine clearance is 30-49 mL/min. Edoxaban and apixaban also have specific dose reduction criteria in the presence of renal insufficiency.[65] Data from randomized controlled trials on NOAC use in patients with a creatinine clearance < 30 mL/min are very limited. A large retrospective study of patients with atrial fibrillation who were receiving dialysis suggests that apixaban might be associated with fewer major bleeds and a similar risk of stroke or systemic embolism compared with a VKA.[66] It might, therefore, be acceptable to use apixaban in some patients with end-stage renal disease and atrial fibrillation.[67]

Liver disease

The prevalence of liver disease in adults with CHD is uncertain but is particularly high in patients with a Fontan circulation.[68] Liver disease is a thrombotic and hemorrhagic condition that interferes with drug metabolism. Patients with liver disease were excluded from pivotal NOAC trials.[59] As such, NOACs should be used with caution in patients with

Child-Turcotte-Pugh B cirrhosis and avoided in patients with class C cirrhosis.[59] Rivaroxaban should not be used in patients with liver dysfunction.[59] NOACs do not appear to cause hepatotoxicity.

Women of reproductive age

NOACs are contraindicated during pregnancy and breast-feeding.[59] Approximately 32% of women of reproductive age taking a factor Xa inhibitor experience heavy menstrual bleeding.[69] Rivaroxaban is associated with prolonged menstrual bleeding, increased need for menorrhagia-related interventions, and more interruptions of anticoagulant therapy compared with warfarin.[70] There are no data to suggest that these undesirable effects are limited to rivaroxaban. Women of childbearing age taking a NOAC should be counselled about the need for reliable contraception. If pregnancy is planned or occurs unexpectedly, a strategy should be in place to replace the NOAC with low molecular-weight heparin under the supervision of a provider experienced in pregnancy and CHD.

Bleeding Risk

Major bleeding is defined by the International Society on Thrombosis and Haemostasis as symptomatic bleeding in a critical area or organ, or bleeding leading to a drop in hemoglobin $\geq$2 g/dL or to transfusion of $\geq$2 red blood cell units[50]. In the multicentre **T**he **A**nti**c**oagulation **T**herapy **i**n **C**ongenital Heart Disease (TACTIC) study of CHD patients with atrial arrhythmias, the annualized rate of major bleeding with use of an oral anticoagulant (predominantly VKAs) was 0.77% per year,[20] which is substantially lower than the rates reported in clinical trials of NOACs or VKAs (Table 2). In general, the CHD population requiring anticoagulation was younger than patients enrolled in anticoagulation trials, with only 6.8% of patients in TACTIC having a HAS-BLED score $\geq$ 2.[20] The HAS-BLED score was associated with major bleeds independent of CHD complexity.[20] Thus, despite the presence of risk factors such as Eisenmenger syndrome, pulmonary hypertension, acquired von Willebrand disease, thrombocytopenia, and hepatic dysfunction,[15] on the whole the bleeding risk in CHD patients who require anticoagulation is generally low. There are no data to suggest that risk is higher with a NOAC. On the contrary, NOACs have consistently been associated with a lower risk of intracranial hemorrhage (odds ratio, 0.49; 95% CI, 0.36-0.45) compared with VKA or aspirin in a meta-analysis that included 57,491 patients.[71]

Patient Preference and Adherence to Therapy

The choice of oral anticoagulant must balance risks, benefits, and patient expectations in relation to underlying CHD and other comorbidities.[14] Decisions should, as much as possible, be shared between the patient and care provider and require the willingness and ability to take an oral anticoagulant, acceptance of the effect of anticoagulation on potential lifestyle changes, and an understanding of the consequences of thrombosis and risks of bleeding.[14]

It is crucial for patients to understand that a NOAC must be taken as prescribed to maintain protection against thromboembolism because therapeutic effects disappear within 12-24 hours. Nonadherence to a single dose of a VKA can be less consequential because of the residual anticoagulant effects of previous doses.[72] Switching to a VKA can be considered in patients with poor adherence to a NOAC. Adherence and persistence rates vary between 49% and 99% depending on setting and definition but are likely better with once-daily intake.[72] In comparison, the 1-year discontinuation rate with VKAs is 26%-35%.[72] The more active lifestyle and geographic mobility of the population of adults with CHD contribute to lesser adherence to medication intake.[15] Obviating the need for INR monitoring and follow-up at anticoagulation clinics might render NOAC therapy more appealing. This might also be the case for patients with INR self-monitoring considering the cost of the device and need for periodic calibration.

Drug Interactions

Potential drug interactions with NOACs must be considered. Chang et al. identified an increase in major bleeds in patients taking amiodarone, fluconazole, rifampin, and phenytoin in association with a NOAC.[73] Amiodarone, diltiazem, and verapamil increase the serum concentration of dabigatran, edoxaban, and apixaban via P glycoprotein competition.[59] In addition, diltiazem and verapamil are cytochrome P450 3A4 (CYP3A4) inhibitors, resulting in a further increase in NOAC levels.[59] For adults with CHD who have epilepsy, additional relevant drug interactions with NOACs include carbamazepine, levetiracetam, phenobarbital, valproic acid, and topiramate.[59] Consultation with a clinical pharmacist is suggested to minimize drug interactions.

Switching From a VKA to a NOAC

Denas et al. used administrative data with propensity score matching to address the question of whether switching to a NOAC is advantageous for a patient with atrial fibrillation if a high proportion of time spent in the therapeutic range can be achieved with a VKA.[74] Although rates of stroke and major bleeding were similar between NOAC- and VKA-treated patients, the rate of intracranial hemorrhage was significantly lower with a NOAC.[74] In a substudy of ROCKET-AF, rivaroxaban was associated with fewer bleeds in VKA-naive patients and similar bleeding in VKA-experienced patients after 30 days of therapy.[75] A **S**ex, **A**ge, **Me**dical History, **T**reatment, **T**obacco Use, **R**ace (SAMe-TT_2R_2) score $>$ 2 (female sex, age younger than 60 years, medical history, treatment with VKA-interacting drugs, tobacco use, non-Caucasian race) can help identify patients who are less likely to fare well using a VKA[76] but has not been validated in adults with CHD.

Practical Tips

Key practical tips on using NOACs in adults with CHD, as adapted from recommendations from the European Heart Rhythm Association,[59] are summarized in Table 4.

Summary and Recommendations for NOAC Use in Adults With CHD

- Efficacy and safety data for NOACs in adults with CHD are limited to small observational studies that provide encouraging information.
- NOACs are contraindicated in adults with CHD and: (1) a mechanical heart valve; and (2) history of mitral

or tricuspid valve stenosis with enlarged and diseased atria with or without a mitral or tricuspid bioprosthesis.

- VKAs are recommended over NOACs within 3 months after cardiac surgery.
- It would be premature to endorse the use of NOACs in patients with cyanotic CHD or Fontan physiology. Several cases of thrombus have been described in a small number of Fontan patients receiving NOACs. Larger series with longer follow-up are required.
- CHA_2DS_2-VASc and HAS-BLED scores have not been validated in patients with CHD although the risk factors for stroke or bleeding that they encompass might be relevant to adults with CHD and atrial arrhythmias. The indication for anticoagulation in a patient with CHD of moderate or great complexity should preferably be discussed with an adult CHD cardiologist.
- A NOAC can be considered in adults with CHD and anticoagulation indications for atrial arrhythmias when the CHD lesions are analogous to isolated mitral regurgitation, tricuspid regurgitation, aortic regurgitation, or aortic stenosis. Suggested choices of antithrombotic medications for selected clinical situations are summarized in Figure 1.
- NOAC use should not replace the recommended antiplatelet regimen after implantation of a transcatheter valve prosthesis.
- NOACs have consistently been associated with a decreased risk of intracranial hemorrhage compared with adjusted-dose VKAs.
- The dose of rivaroxaban should be adjusted to creatinine clearance. The dose of edoxaban should be adjusted to body weight and creatinine clearance. The dose of apixaban should be adjusted to serum creatinine, age, and body weight. Drug interactions, especially with antiepileptic drugs, should be taken into account.
- The decision to initiate a NOAC should be shared between the patient and care provider. The patient should be made aware of the paucity of data specific to adults with CHD.

Conclusion

Herein, we attempted to summarize current knowledge regarding NOAC use in adults with CHD as well as studies in the general population of relevance to patients with CHD. The intention was to provide practical guidance regarding clinical situations in which it might or might not be reasonable to extrapolate data from large clinical trials to subgroups of the adult CHD population on the basis of similar anatomic and pathophysiological considerations. We acknowledge that there is no substitute for sound clinical research and that recommendations can change on the basis of new research findings. Robust studies are required to provide definitive evidence regarding the safety and efficacy of NOACs in the heterogeneous subgroups of adults with CHD. Although CHD-specific registries will continue to offer important insights, randomized trials are required to overcome limitations inherent to observational studies, including confounding by indication.

Disclosures

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.06.022.