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ABBREVIATIONS

- CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age (65-74 years 1 point, ≥ 75 years 2 points), Diabetes mellitus, Stroke, transient ischemic attack or thromboembolism (2 points), VAscular disease (history of myocardial infarction, peripheral arterial disease or aortic atherosclerosis), female Sex Category

- $CHADS_2$: Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke, transient ischemic attack or thromboembolism (2 points)

- CHD: Congenital Heart Disease

- HAS-BLED: Hypertension (systolic blood pressure > 160 mmHg), Abnormal liver or renal function, Stroke, Bleeding tendency or predisposition, Labile INR in patients taking a VKA, Elderly (age > 65 years), Drugs (antiplatelet agents or alcohol use)

- INR: International normalized ratio

- NOAC(s): Non-vitamin K antagonist oral anticoagulants

- RR: Relative risk

- VKA: Vitamin K Antagonist(s)

ABSTRACT

Non-vitamin K antagonist oral anticoagulants (NOACs) have several advantages over vitamin K antagonists (VKA) 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 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 co-medications, 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.

KEY WORDS: Adult congenital heart disease; anticoagulation; non-vitamin K antagonist oral anticoagulant; vitamin K antagonist

SUMMARY

It appears reasonable to use a non-vitamin K antagonist oral anticoagulant (NOAC) instead of a vitamin K antagonist in adults with an indication for oral anticoagulation and congenital heart disease (CHD) analogous to structural heart diseases included in NOACs trials. NOACs are contraindicated in patients with mechanical valves, atrioventricular valve stenosis with enlarged and diseased atria with or without a bioprosthesis, or recent cardiac surgery. Insufficient evidence supports the use of NOACs in patients with a Fontan circulation or cyanotic CHD.

INTRODUCTION

The growing population of adults with congenital heart disease (CHD) faces 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]. While vitamin K antagonists (VKA) 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 non-valvular 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 hopes of improving outcomes. However, caution is warranted in generalizing the results of clinical trials to a non-target 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 NOACs for atrial tachyarrhythmias in congenital heart disease (NOTE) registry (www.clinicaltrials.gov NCT02928133), have begun providing reassuring short-term 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 may 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, prior thromboembolic events (including paradoxical emboli), right-to-left shunts (e.g., cyanotic CHD), pulmonary hypertension, Fontan circulation, intrinsic coagulation abnormalities, valvular prosthesis, and pregnancy, along with factors that are captured by standard risk scores such as CHA_2DS_2-VASc[15]. There are, therefore, numerous reasons as to why an adult with CHD may require systemic anticoagulation.

Atrial arrhythmias

Contemporary prevalence estimates for atrial arrhythmias in adults with CHD range from 10 to 15%[16, 17], with projections suggesting that over 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 two-fold higher risk of stroke[17]. Adults with CHD may have important risk factors for stroke that are not captured by 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 Supplementary Table S1 for a classification of CHD complexity)[2, 15] and intra-atrial reentrant 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 1,000 patient-years when antithrombotic therapy is at the physician's discretion[19, 20]. In a multicenter 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, in comparison to study populations included in NOAC trials for non-valvular atrial fibrillation, the on-treatment residual annual rate of stroke or systemic embolism 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 non-linear and rises sharply at two 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), prior 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 prior thromboembolic event[1]. Many patients with an atriopulmonary Fontan circulation harbor thrombotic risk factors that may justify long-term anticoagulation (class IIb, level of

evidence C according to the scientific statement on prevention and treatment of thrombosis in pediatric and congenital heart disease 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 MRI 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 and iron deficiency, as a consequence of inappropriate phlebotomies, also favour the occurrence of stroke[36]. On the other hand, Eisenmenger syndrome carries a substantial bleeding risk due to 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 prior to 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 dependant 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 may overcome the effect of a NOAC, suggesting a mechanism for the reduced occurrence of intracranial haemorrhage[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 may partially account for the more favourable safety profile of NOACs[42].

Dabigatran

Dabigatran (Pradaxa™) is a small hirudin analog that prevents the conversion of fibrinogen to fibrin by inhibiting thrombin (factor IIa)[43]. The effect of dabigatran may be reversed by idarucizumab (Praxbind™), a monoclonal antibody[44].

The RE-ALIGN trial, which was prematurely terminated because of an excess of thromboembolic and bleeding events in patients with mechanical valves on high-dose dabigatran

compared to VKA, raises 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 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, may eventually be reconsidered[46].

Rivaroxaban, apixaban and edoxaban

Rivaroxaban (Xarelto™), apixaban (Eliquis™), and edoxaban (Lixiana™) prevent the conversion of prothrombin to thrombin (factor IIa) by inhibiting coagulation factor Xa[43]. Their effects may be reversed by 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 pre-tricuspid 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 HAS-BLED score ≤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 that had transitioned form 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 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 on a VKA, initiation of therapy in another center, or non-compliance with follow-up. Ten minor bleeding events occurred with no major bleed. During a total of 316 patient-months of therapy, one patient with protein-losing enteropathy and right-to-left shunting through a fenestration had deep vein thrombosis while on dabigatran. Another patient had progression of Fontan circuit thrombosis while on apixaban. Pinto et al also reported the progression of thrombus in a patient with a lateral tunnel Fontan and atrial flutter on 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

Non-valvular atrial fibrillation

The results of four large clinical trials (RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48) in patients with atrial fibrillation were pooled in a meta-analysis that included 42,411 patients randomized to a NOAC versus 29,972 patients on 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], haemorrhagic 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 haemorrhage (RR 0.48, 95% CI 0.39-0.59, p<0.0001)[6]. Considering all NOACs, there was a highly suggestive trend towards 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 / 15 mg daily) were associated with a similar reduction in stroke and systemic embolism compared to 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 / 15 mg edoxaban daily regimen[49, 50]. The effects of NOACs were consistent in subgroup analyses according to age, sex, history of diabetes, prior stroke or transient ischemic attack, creatinine clearance, $CHADS_2$ score, and prior 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 has 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 enrolment 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 in comparison to 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 to a VKA was consistent across trials, with the exception of excess bleeding with rivaroxaban 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 haemorrhage in patients with valve disease, with the exception of rivaroxaban.

Heterogeneity in the definitions of non-valvular and valvular atrial fibrillation

Hetereogeneity 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 by meta-analyses and substudies in patients with atrial fibrillation and bioprosthetic valves or prior valve surgery[52, 54, 58]. However, a concern remains regarding NOAC use in patients with mitral bioprosthetic valves and prior rheumatic mitral valve disease with large and severely diseased atria such that a VKA may 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 may 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. 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 a recent operation (<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 is 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 GALILEO trial tested the hypothesis that a rivaroxaban-based antithrombotic strategy (10 mg daily plus 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 plus 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 due to excess harm (death and bleeding) in the rivaroxaban group.

Venous thromboembolism

NOACs are non-inferior 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 to aspirin, with no excess in major bleeds[7]. These data suggest that NOACs can offer antithrombotic benefits with a risk of bleeding comparable to 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 noted above.

Labile INR

On average, patients with atrial fibrillation on warfarin 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 centers 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 haemorrhages in patients with heart failure[62].

Underweight patients

Low body weight (<60 kg) is one of the criteria for a dose reduction with apixaban and edoxaban. Underweight patients taking a NOAC have a 4-fold higher risk of major bleeding compared to normal weight patients[63]. Low body weight patients are underrepresented 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 by the Cockroft and Gault formula and monitored at a frequency corresponding to the creatinine clearance/10 in months[59]. While all NOACs are effective and safe in subgroup analyses of pivotal trials, apixaban and edoxaban may 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 on dialysis suggests that apixaban may be associated with fewer major bleeds and a similar risk of stroke or systemic embolism compared to a VKA[66]. It may, 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 both a thrombotic and haemorrhagic 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 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 breastfeeding[59]. About 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 to warfarin[70]. There is 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 ≥2 g/dL or to transfusion of ≥2 red blood cell units[50]. In the multicenter TACTIC study of CHD patients with atrial arrhythmias, the annualized rate of major bleeding on an oral anticoagulant (predominantly VKA) was 0.77%/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 is younger than patients enrolled in anticoagulation trials, with only 6.8% of patients in TACTIC having a HAS-BLED score ≥ 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 is 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 to 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 impact 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. Non-adherence to a single dose of a VKA can be less consequential owing to the residual anticoagulant effects of prior doses[72]. Switching to a VKA can be considered in patients with poor adherence to a NOAC. Adherence and persistence rates vary between 49-99% depending on setting and definition but are likely better with once daily intake[72]. In comparison, the one-year discontinuation rate with VKAs is 26-35%[72]. The more active lifestyle and geographical 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 may render NOAC therapy more appealing. This may 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 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 VKA TO 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]. While rates of stroke and major bleeding were similar between NOAC and VKA treated patients, the rate of intracranial haemorrhage 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 SAMe-TT_2R_2 score >2 (female sex, age <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 on 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; (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 congenital heart disease although the risk factors for stroke or bleeding that they encompass may 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 ACHD 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 stenosis. Suggested choices of antithrombotic medications for selected clinical situations are summarized in the Figure.
- 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 haemorrhage compared to 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 congenital patients. The intention was to provide practical guidance regarding clinical situations in which it may or may 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. While CHD-specific registries will continue to offer important insights, randomized trials are required to overcome limitations inherent to observational studies, including confounding by indication.

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FIGURE LEGEND

Figure: Suggested choices of antithrombotic medications for selected clinical situations in adults with congenital heart disease. Green indicates that NOAC use is reasonable. Yellow indicates that NOACs should be used with caution. Red indicates that VKAs are strongly preferred over NOACs or that NOACs are contraindicated. CHD, congenital heart disease; AV, atrioventricular; VKA, vitamin K antagonist; NOAC, non-vitamin K antagonist oral anticoagulant; > preferred to; AF/IART, atrial fibrillation/intraatrial reentrant tachycardia; TIA, transient ischemic attack.

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TABLES

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

Advantages	Disadvantages
• No dose adjustment required based on 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 to VKA	• Precautions and contraindications based on 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

VKA denotes vitamin K antagonist; CHD, congenital heart disease

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

	Adults with CHD	Non-valvular atrial fibrillation									
Study	**TACTIC[20]**	**RE-LY[50]**			**ROCKET-AF[48]**		**ARISTOTLE[51]**		**ENGAGE AF-TIMI 48[49]**		
Drugs	Aspirin, VKA or NOAC*	Dabigatran		VKA	Rivaroxaban	VKA	Apixaban	VKA	Edoxaban		VKA
Dose		110 mg bid	150 mg bid		20/15 mg qday		5/2.5 mg bid		60 mg qday	30 mg qday	
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, %/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, %/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 < 65-75, %/year	Same Mean age 32 years	1.89	2.12 (<75)	3.04 (<75)	2.21	2.16	1.2	1.5	2.02 (<75)	N/A	2.62 (<75)

*37.8% on antiplatelet therapy, *54.4% on oral anticoagulants (OAC, 8.3% on NOACs), 7.9% nothing; **$CHADS_2$ ≤3; CHD denotes congenital heart disease; VKA, vitamin K antagonist; NOAC, novel oral anticoagulant; SSE, stroke or systemic embolism; bid, twice daily; qday, once daily

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

Study	Study type	N	Type of VHD	NOAC	Treatment favoured in patients with VHD*		
					Stroke and systemic embolism	Major bleeding	Intracranial bleeding
Caldeira D 2018[54]	Meta-analysis	12,653	Native VHD Valve repair Bioprosthesis	All	NOAC	NOAC	NOAC
Pan KL 2017[56]	Meta-analysis	13,574	Native VHD	All	NOAC	None	NOAC
Renda G 2017[77]	Meta-analysis	13,585	Native VHD Valve surgery	All	NOAC	None	NOAC
Vinereanu D 2018[55]	Substudy of ARISTOTLE	3,382	MR	Apixaban 5 / 2.5 mg bid	None	NOAC	NOAC
Vinereanu D 2018[55]	Substudy of ARISTOTLE	324	AS	Apixaban 5 / 2.5 mg bid	None	None	None
Vinereanu D 2018[55]	Substudy of ARISTOTLE	842	AR	Apixaban 5 / 2.5 mg bid	None	None	None
De Caterina R 2017[52]	Substudy of ENGAGE AF-TIMI 48	2,824	2,250 MR 254 MS 369 AR 165 AS 191 bioprosthesis 123 valve repairs 19 valvuloplasty	Edoxaban 60 mg qday	None	None	None
Carnicelli AP 2017[58]	Substudy of ENGAGE AF-TIMI 48	191	131 MVR 60 AVR	Edoxaban 60 or 30 mg qday	None	Low-dose NOAC	N/A
Ezekovitz MD 2016[53]	Substudy of RE-LY	3,950	3,101 MR 193 MS 1,179 TR 97 AR 471 AS	Dabigatran 150 mg bid	NOAC	None	NOAC
Ezekovitz MD 2016[53]	Substudy of RE-LY			Dabigatran 110 mg bid	None	NOAC	NOAC

Breithard G 2014[57]	Substudy of ROCKET-AF	1,992 for efficacy 1,999 for safety	1,756 MR 486 AR 215 AS 15 congenital VHD 106 valve procedures 11 other	Rivaroxaban 20 / 15 mg qday	None	Warfarin	None
Avezum A 2015[78]	Substudy of ARISTOTLE	4,808	3,526 MR 131 MS 887 AR 384 AS 2,124 TR 251 previous valve surgery	Apixaban 5 / 2.5 mg bid	NOAC	None	NOAC
Noseworthy PA 2016[79]	Administrative database review	20,158	19,351 AS, AI or MR 654 MS 74 rheumatic MS 55 valve repairs 24 bioprosthesis	Dabigatran Rivaroxaban Apixaban	NOAC for AS, AI or MR None for MS	None NOAC for AS, AI or MR	N/A

*If no treatment is favoured (none), there is no significant difference in effectiveness or safety between the non-vitamin K antagonist oral anticoagulant (NOAC) and warfarin. Patients may have multiple types of valvular heart disease (VHD). Types of VHD included moderate or severe mitral regurgitation (MR), mild mitral stenosis (MS), moderate or severe aortic stenosis (AS) or regurgitation (AR), moderate or severe tricuspid regurgitation (TR) and valve surgery (other than mechanical prosthetic heart valves). AVR denotes bioprosthetic aortic valve replacement; MVR, bioprosthetic mitral valve replacement; bid, twice daily; qday, once daily; N/A: not available

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 co-medications (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 • Asses if patient is likely not to fare well on a VKA (e.g., SAMe-TT_2R_2 score > 2)
Initiation of treatment

• Baseline blood tests: haemoglobin, renal and liver function, full coagulation panel
• Choose NOAC and correct dose
  o Improved adherence with once daily regimen
• If switching from a VKA:
  o If INR <2: start NOAC
  o If INR 2-2.5: start NOAC the next day
  o If INR >2.5: repeat INR in 1-3 days
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  o Rivaroxaban intake with food
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  o Yearly for all
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  o Tailored if decreased renal function: creatinine clearance/10 in months
• Assess adherence and use adherence aids as needed
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Adapted from Steffel et al with permission [59].
NOAC denotes non-vitamin K antagonist oral anticoagulant; CHD, congenital heart disease; VKA, vitamin K antagonist; SAMe-TT_2R_2: female sex, age <60 years, medical history, treatment with VKA interacting drugs, tobacco use, non Caucasian race; NSAID, non steroidal anti-inflammatory drug

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

Advantages	Disadvantages
• No dose adjustment required based on 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 to VKA	• Precautions and contraindications based on 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

VKA denotes vitamin K antagonist; CHD, congenital heart disease

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

	Adults with CHD	Non-valvular atrial fibrillation									
Study	**TACTIC[20]**	**RE-LY[50]**			**ROCKET-AF[48]**		**ARISTOTLE[51]**		**ENGAGE AF-TIMI 48[49]**		
Drugs	Aspirin, VKA or NOAC*	Dabigatran		VKA	Rivaroxaban	VKA	Apixaban	VKA	Edoxaban		VKA
Dose		110 mg bid	150 mg bid		20/15 mg qday		5/2.5 mg bid		60 mg qday	30 mg qday	
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, %/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, %/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 < 65-75, %/year	Same Mean age 32 years	1.89	2.12 (<75)	3.04 (<75)	2.21	2.16	1.2	1.5	2.02 (<75)	N/A	2.62 (<75)

*37.8% on antiplatelet therapy, *54.4% on oral anticoagulants (OAC, 8.3% on NOACs), 7.9% nothing; **$CHADS_2$ ≤3; CHD denotes congenital heart disease; VKA, vitamin K antagonist; NOAC, novel oral anticoagulant; SSE, stroke or systemic embolism; bid, twice daily; qday, once daily

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

Study	Study type	N	Type of VHD	NOAC	Treatment favoured in patients with VHD*		
					Stroke and systemic embolism	Major bleeding	Intracranial bleeding
Caldeira D 2018[54]	Meta-analysis	12,653	Native VHD Valve repair Bioprosthesis	All	NOAC	NOAC	NOAC
Pan KL 2017[56]	Meta-analysis	13,574	Native VHD	All	NOAC	None	NOAC
Renda G 2017[77]	Meta-analysis	13,585	Native VHD Valve surgery	All	NOAC	None	NOAC
Vinereanu D 2018[55]	Substudy of ARISTOTLE	3,382	MR	Apixaban 5 / 2.5 mg bid	None	NOAC	NOAC
Vinereanu D 2018[55]	Substudy of ARISTOTLE	324	AS	Apixaban 5 / 2.5 mg bid	None	None	None
Vinereanu D 2018[55]	Substudy of ARISTOTLE	842	AR	Apixaban 5 / 2.5 mg bid	None	None	None
De Caterina R 2017[52]	Substudy of ENGAGE AF-TIMI 48	2,824	2,250 MR 254 MS 369 AR 165 AS 191 bioprosthesis 123 valve repairs 19 valvuloplasty	Edoxaban 60 mg qday	None	None	None
Carnicelli AP 2017[58]	Substudy of ENGAGE AF-TIMI 48	191	131 MVR 60 AVR	Edoxaban 60 or 30 mg qday	None	Low-dose NOAC	N/A
Ezekovitz MD 2016[53]	Substudy of RE-LY	3,950	3,101 MR 193 MS 1,179 TR 97 AR 471 AS	Dabigatran 150 mg bid	NOAC	None	NOAC
Ezekovitz MD 2016[53]	Substudy of RE-LY			Dabigatran 110 mg bid	None	NOAC	NOAC

Breithard G 2014[57]	Substudy of ROCKET-AF	1,992 for efficacy 1,999 for safety	1,756 MR 486 AR 215 AS 15 congenital VHD 106 valve procedures 11 other	Rivaroxaban 20 / 15 mg qday	None	Warfarin	None
Avezum A 2015[78]	Substudy of ARISTOTLE	4,808	3,526 MR 131 MS 887 AR 384 AS 2,124 TR 251 previous valve surgery	Apixaban 5 / 2.5 mg bid	NOAC	None	NOAC
Noseworthy PA 2016[79]	Administrative database review	20,158	19,351 AS, AI or MR 654 MS 74 rheumatic MS 55 valve repairs 24 bioprosthesis	Dabigatran Rivaroxaban Apixaban	NOAC for AS, AI or MR None for MS	None NOAC for AS, AI or MR	N/A

*If no treatment is favoured (none), there is no significant difference in effectiveness or safety between the non-vitamin K antagonist oral anticoagulant (NOAC) and warfarin. Patients may have multiple types of valvular heart disease (VHD). Types of VHD included moderate or severe mitral regurgitation (MR), mild mitral stenosis (MS), moderate or severe aortic stenosis (AS) or regurgitation (AR), moderate or severe tricuspid regurgitation (TR) and valve surgery (other than mechanical prosthetic heart valves). AVR denotes bioprosthetic aortic valve replacement; MVR, bioprosthetic mitral valve replacement; bid, twice daily; qday, once daily; N/A: not available

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 co-medications (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 • Asses if patient is likely not to fare well on a VKA (e.g., SAMe-TT_2R_2 score > 2)
Initiation of treatment

• Baseline blood tests: haemoglobin, renal and liver function, full coagulation panel
• Choose NOAC and correct dose
  o Improved adherence with once daily regimen
• If switching from a VKA:
  o If INR <2: start NOAC
  o If INR 2-2.5: start NOAC the next day
  o If INR >2.5: repeat INR in 1-3 days
• Decide on need for proton pump inhibitor (limited data)
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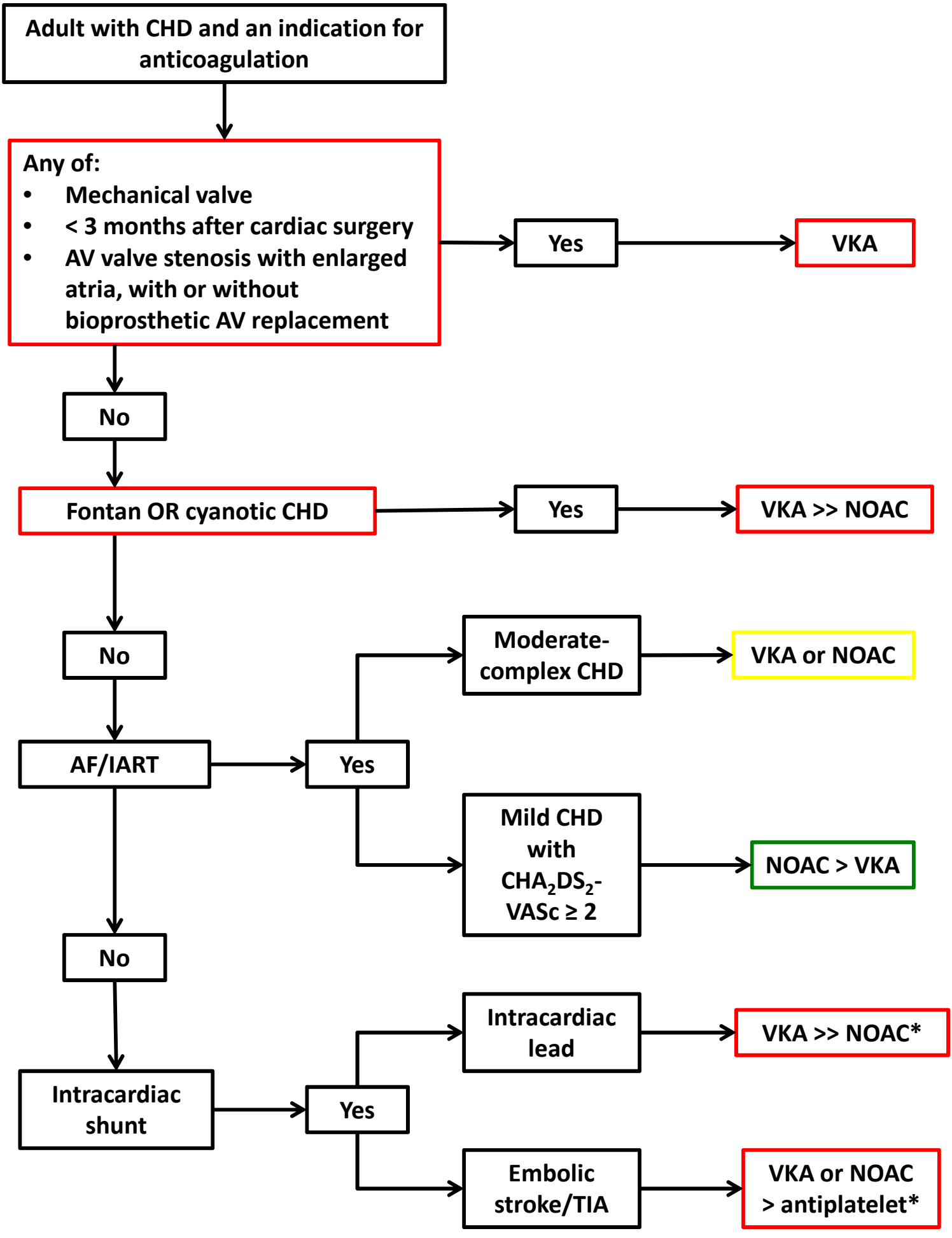

*in absence of shunt closure