Review

Arrhythmias in Adults With Congenital Heart Disease: What the Practicing Cardiologist Needs to Know

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ABSTRACT

The expanding population of adults with congenital heart disease (CHD) combined with the pervasiveness of arrhythmias has resulted in the rapid growth of a dedicated sector of cardiology at the intersection between 2 subspecialties: electrophysiology and adult CHD. Herein, practical considerations are offered regarding urgent referral for catheter ablation of atrial arrhythmias, anticoagulation, and primary prevention implantable cardioverter-defibrillators (ICDs). Patients with Ebstein anomaly and ventricular pre-excitation should be referred promptly due to the high prevalence of multiple accessory pathways and increased incidence of atrial tachyarrhythmias, which may be poorly tolerated. In patients with transposition of the great arteries and atrial switch surgery, atrial arrhythmias should be managed without delay because they could provoke ventricular arrhythmias and sudden death. Other settings in which atrial arrhythmias can be poorly

RÉSUMÉ

L'augmentation de la population d'adultes présentant une cardiopathie congénitale jumelée à l'omniprésence des troubles d'arythmie a entraîné la croissance rapide d'un domaine spécialisé de la cardiologie, qui recoupe deux sous-spécialités : l'électrophysiologie et la cardiopathie congénitale chez l'adulte. Les auteurs présentent des considérations pratiques au sujet de l'aiguillage urgent des patients en vue d'une ablation par cathéter afin d'éliminer les arythmies auriculaires, de l'instauration d'une anticoagulothérapie et de la mise en place d'un défibrillateur cardioverteur implantable (DCI) en prévention primaire. Les patients atteints de la maladie d'Ebstein ou présentant une préexcitation ventriculaire doivent être aiguillés sans tarder vers un spécialiste, en raison de la forte prévalence de multiples voies accessoires et de l'incidence accrue de tachyarythmies auriculaires susceptibles d'être mal tolérées. Chez les patients présentant une

What does the practicing cardiologist need to know about arrhythmias in adults with congenital heart disease (CHD)? Prominent societies with a vested interest in this focused area of medicine convened an international panel to elaborate an evidence-based expert consensus statement on the recognition and management of arrhythmias in adults with CHD.[1] The result was a comprehensive document containing recommendations that span topics from delivery of care, to noninvasive monitoring, pharmacologic therapy, electrophysiological studies, catheter ablation, surgical options, and indications for pacemakers, cardiac resynchronization therapy, and implantable cardioverter-defibrillators (ICDs). Moreover, several contemporary review articles have addressed this issue.[2,3] It is not the objective of this article to provide an all-encompassing overview of this growing field of cardiology at the intersection between electrophysiology and adult CHD. Rather, the intention is to offer practical guidance on common questions

that arise. As such, the article expands on a presentation at the Symposium of the *Canadian Journal of Cardiology* dedicated to emerging themes in adults with CHD. In particular, 3 key questions relevant to the practicing cardiologist are addressed:

1. Who to refer urgently for catheter ablation of atrial arrhythmias?
2. Who to anticoagulate for atrial arrhythmias?
3. When to consider a primary prevention ICD?

Who to Refer Urgently for Catheter Ablation of Atrial Arrhythmias?

Arrhythmogenesis in adults with CHD can be influenced by a confluence of variables that may include native anatomical defects, surgical scarring, hypoxemia, hemodynamic sequelae, neurohormonal abnormalities, and genetic factors.[4] In general, any new-onset or worsening arrhythmia should be of concern and prompt hemodynamic assessment to exclude and address potential contributory factors such as obstructive or regurgitant lesions, intracardiac shunts, myocardial ischemia, and ventricular dysfunction.[1] Nevertheless, certain clinical circumstances are of greater concern

tolerated include single ventricle physiology and Eisenmenger syndrome. Long-term anticoagulation is generally indicated in patients with sustained intra-atrial reentrant tachycardia or atrial fibrillation and a mechanical valve, moderate or severe systemic atrioventricular valve stenosis, traditional risk factors for stroke, and/or moderate or complex CHD. The only class I indication for a primary prevention ICD is a systemic left ventricular ejection fraction $\leq$ 35%, with biventricular physiology, and New York Heart Association class II or III symptoms. ICD therapy is reasonable in selected adults with tetralogy of Fallot and multiple risk factors for sudden death identified by observational studies. Indications for ICDs in patients with systemic right ventricles and univentricular hearts are less well established, underscoring the need for future research to inform risk stratification.

transposition des gros vaisseaux et ayant subi une détransposition auriculaire, les arythmies auriculaires doivent être prises en charge sans délai, car elles peuvent provoquer des arythmies ventriculaires et la mort subite. Les arythmies auriculaires sont également susceptibles d'être mal tolérées en présence d'une physiologie univentriculaire ou d'un syndrome d'Eisenmenger. Une anticoagulothérapie de longue durée est généralement indiquée chez les patients présentant une tachycardie réentrante intra-auriculaire soutenue ou une fibrillation auriculaire et une valve mécanique, une sténose de la valve auriculoventriculaire systémique modérée ou grave, des facteurs de risque d'accident vasculaire cérébral classiques et/ou une cardiopathie congénitale modérée ou complexe. La seule indication de classe I pour la mise en place d'un DCI en prévention primaire est une fraction d'éjection ventriculaire gauche $\leq$ 35 % avec physiologie biventriculaire et symptômes de classe II ou III selon la New York Heart Association. La mise en place d'un DCI est justifiable chez certains adultes présentant une tétralogie de Fallot et plusieurs facteurs de risque de mort subite relevés dans le cadre d'études d'observation. Les indications relatives à un DCI chez les patients ayant un ventricule droit systémique ou un cœur univentriculaire sont moins bien établies, ce qui fait ressortir la nécessité d'autres recherches pour éclairer la stratification du risque.

than others and merit more urgent referral for consideration of catheter ablation.

Ebstein anomaly with ventricular pre-excitation

Ebstein anomaly accounts for < 1% of congenital heart defects, with an estimated prevalence of approximately 1 per 200,000 live births. It is characterized by adherence of posterior and septal tricuspid valve leaflets to the myocardium, apical displacement of the functional tricuspid annulus, dilation of the right atrioventricular (AV) junction, a portion of the right ventricle that is "atrialized," and a redundant, tethered, and fenestrated anterior tricuspid valve leaflet.[5] The association between Ebstein anomaly and accessory pathways is well established. The pathways, which are predominantly right-sided, are typically located along the lower half of the anatomical tricuspid annulus and are thought to be coupled embryologically to abnormal valve development.[6] It has been estimated that 15% to 25% of patients with Ebstein anomaly have accessory pathways.

Importantly, if ventricular pre-excitation is noted electrocardiographically, more than 30% of patients with Ebstein anomaly will have multiple accessory pathways.[7] Having more than one AV accessory pathway is associated with a high risk for sudden cardiac death.[8] Even if each accessory pathway taken individually is incapable of rapid conduciton, when one pathway is refractory, conduction can course along another thereby permitting rapid ventricular rates in the setting of atrial arrhythmias. Moreover, atrial arrhythmias, including intra-atrial reentrant tachycardia (IART) and atrial fibrillation (Fig.1), are highly prevalent in patients with Ebstein anomaly. In addition, a fast heart rate can result in an increase in right atrial pressure leading to worsening cyanosis due to increased right-to-left shunting across a patent foramen ovale or atrial septal defect.[9]

In short, patients with Ebstein anomaly and ventricular pre-excitation should be referred promptly for consideration of catheter ablation, even if asymptomatic, due to the high probability of multiple pathways, increased incidence of atrial tachyarrhythmias, and potential hemodynamic instability in the event of an atrial arrhythmia.

Dextro-transposition of the great arteries with a Mustard or Senning baffle

In patients with dextro-transposition of the great arteries (D-TGA) and atrial switch surgery (ie, Mustard or Senning baffle), a physiological circulation is restored at the expense of a morphologic systemic right ventricle. In the context of atrial reconstructive surgery with extensive suture lines, patients with D-TGA and Mustard or Senning baffles are predisposed to developing macro- and microreentrant atrial tachyarrhythmias. Sudden death is the leading cause of mortality, with an estimated incidence of 4 to 5 per 1000 patient-years.[1,10] Factors most consistently associated with sudden death are exercise and atrial arrhythmias.[11] Although causality cannot be inferred from observational studies, growing evidence suggests that atrial arrhythmias can trigger sudden deaths in this population. Atrial arrhythmias have been observed to degenerate into ventricular fibrillation during exercise and in the electrophysiology laboratory.[12] In addition, ICD tracings have documented atrial arrhythmias preceding or coexisting with ventricular arrhythmias.[13]

It has been hypothesized that rapid heart rates lead to sudden death by provoking ischemia-related ventricular arrhythmias (Fig. 2).[14] An abnormal hemodynamic response to increased heart rates is well characterized in patients with D-TGA and atrial switch surgery. Stroke volume decreases with increased heart rates due to a failure to augment filling (ie, poor atrial transport).[15,16] Moreover, a single right coronary artery is an inefficient circulation for a systemic ventricle, particularly one that is chronically pressure overloaded and hypertrophic. Abnormal coronary artery branching patterns are common and perfusion defects are prevalent in patients with D-TGA and atrial switch surgery.[17,18] The perfusion

Figure 1. Pre-excited atrial fibrillation via a rapidly conducting right posteroseptal accessory pathway.

defects most commonly involve the inferior or anterior walls of the systemic right ventricle.[19]

It has been postulated that rapidly conducting atrial arrhythmias result in a reduction in stroke volume that leads to subendocardial ischemia in the context of an inefficient coronary circulation, with a mismatch between myocardial oxygen supply and demand.[14] Indeed, autopsies in patients who died suddenly revealed acute massive myocardial infarction of the systemic right ventricle in the setting of chronic subendocardial ischemic lesions

despite the absence of coronary atherosclerosis.[11] As such, patients with D-TGA and Mustard or Senning baffles with sustained atrial arrhythmias should be referred urgently for consideration of catheter ablation because they could provoke ischemia-related malignant ventricular arrhythmias.

Single ventricle with Fontan palliation

"Single ventricle" refers to a category of rare and complex forms of CHD whereby pulmonary and systemic venous
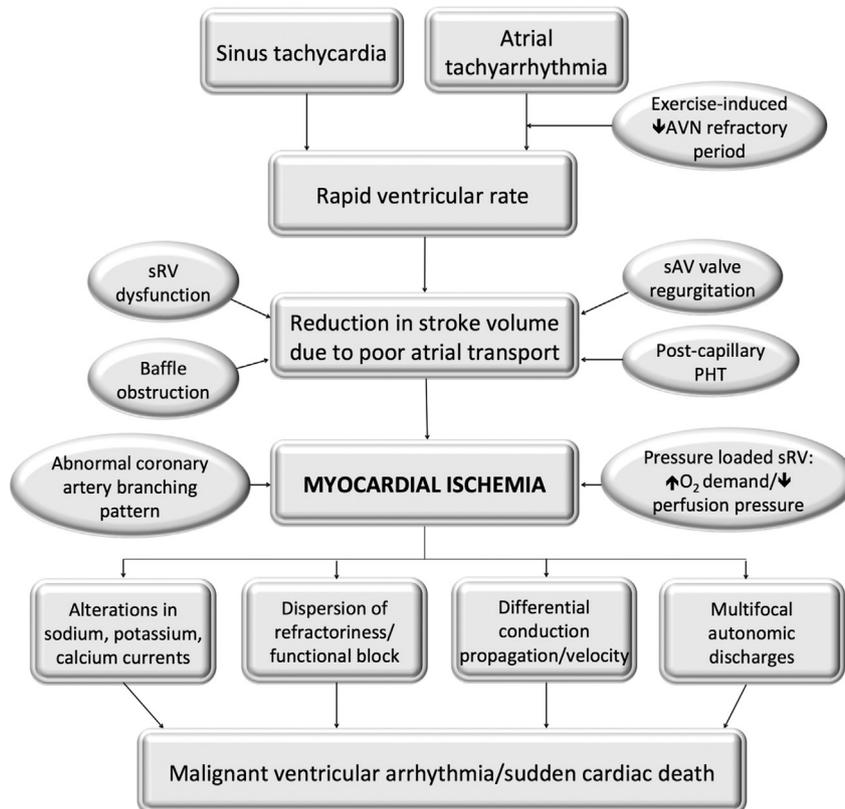

Figure 2. Proposed myocardial ischemia hypothesis as a cause for sudden cardiac death in dextro-transposition of the great arteries with Mustard or Senning baffles. Rectangles represent the hypothesized pathophysiological process and ovals potential contributing or aggravating factors. AVN, atrioventricular node; O_2, oxygen; PHT, pulmonary hypertension; sAV, systemic atrioventricular (tricuspid) valve; sRV, systemic right ventricle. Reproduced from Khairy[14] with permission from Wolters-Kluwer Health.

Table 1. Classification of congenital heart disease complexity

Complexity	Type of congenital heart disease
Simple	Native disease
	Isolated congenital aortic valve disease
	Isolated congenital mitral valve disease (except parachute valve, cleft leaflet)
	Small atrial septal defect
	Isolated small ventricular septal defect (no associated lesions)
	Mild pulmonary stenosis
	Small patent ductus arteriosus
	Repaired conditions
	Previously ligated or occluded ductus arteriosus
	Repaired secundum or sinus venosus atrial septal defect without residua
	Repaired ventricular septal defect without residua
Moderate	Aorto-left ventricular fistulas
	Anomalous pulmonary venous drainage, partial or total
	Atrioventricular septal defects, partial or complete
	Coarctation of the aorta
	Ebstein anomaly
	Infundibular right ventricular outflow obstruction of significance
	Ostium primum atrial septal defect
	Patent ductus arteriosus, not closed
	Pulmonary valve regurgitation, moderate-to-severe
	Pulmonary valve stenosis, moderate-to-severe
	Sinus of valsalva fistula/aneurysm
	Sinus venosus atrial septal defect
	Subvalvular or supravalvular aortic stenosis
	Tetralogy of Fallot
	Ventricular septal defect with:
	Absent valve or valves
	Aortic regurgitation
	Coarctation of the aorta
	Mitral disease
	Right ventricular outflow tract obstruction
	Straddling tricuspid or mitral valve
	Subaortic stenosis
Severe	Conduits, valved, or nonvalved
	Cyanotic congenital heart disease, all forms
	Double-outlet ventricle
	Eisenmenger syndrome
	Fontan procedure
	Mitral atresia
	Single ventricle (also called double inlet or outlet, common, or primitive)
	Pulmonary atresia, all forms
	Pulmonary vascular obstructive disease
	Transposition of the great arteries
	Tricuspid atresia
	Truncus arteriosus/hemitruncus
	Other abnormalities of atrioventricular or ventriculoarterial connection not included above (eg, crisscross heart, isomerism, heterotaxy syndromes, ventricular inversion)

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return predominantly egress into a single functional ventricular chamber, such that biventricular repair is not feasible.[20] The overall prevalence is approximately 2 per 10,000 live births. Fontan procedures consist of directing systemic venous return to the pulmonary artery, typically without an interposed right ventricle. The resultant tenuous balance between systemic venous hypertension and pulmonary arterial hypotension predisposes to a host of multisystemic complications.[21]

Atrial arrhythmias are common and associated with considerable morbidity. More than 50% of patients with an older atriopulmonary connection Fontan experience atrial tachyarrhythmias 20 years after surgical palliation.[22] Although atrial arrhythmias occur less frequently with more modern total cavopulmonary connection Fontan surgery, they nevertheless afflict 10% to 15% of patients by 15 years of follow-up.[23]

Importantly, persistent atrial tachyarrhythmias can be poorly tolerated in patients with Fontan physiology, even when they conduct 2:1. Rapid rates can result in worsening systemic AV valve regurgitation, thrombus formation within the Fontan pathway, heart failure, syncope, and rarely, sudden death. Unlike patients with D-TGA and Mustard or Senning baffles in whom atrial arrhythmias are susceptible to degenerating into fatal ventricular arrhythmias, there are reports of cardiac arrests in Fontan patients while in atrial tachycardia.[24] Moreover, atrial arrhythmias in patients with Fontan physiology are often resistant to antiarrhythmic drugs. In light of the fragile Fontan physiology, patients with sustained atrial arrhythmias should, therefore, be referred for early consideration of catheter ablation after ruling out underlying contributory hemodynamic conditions, including thrombosis.

Eisenmenger syndrome and other fragile physiologies

Eisenmenger syndrome represents the most advanced form of pulmonary arterial hypertension related to CHD. Chronic exposure of the pulmonary vascular bed to increased flow and pressure from a left-to-right shunt leads to an increase in pulmonary vascular resistance and remodelling. If the rise in pulmonary vascular resistance is severe enough, it results in shunt reversal with cyanosis. Although the incidence of Eisenmenger syndrome is declining due to enhanced recognition and earlier surgical or percutaneous interventions, it remains a classic example of the tenuous hemodynamic conditions encountered in adults with CHD.

The right ventricle cannot accommodate to marked changes in preload that may result from atrial arrhythmias. Systemic hypotension induced by rapid heart rates can lead to increased right-to-left shunting, with a profound drop in oxygen saturation. Indeed, recent studies suggest that of all forms of CHD, Eisenmenger syndrome is associated with the highest incidence of sudden death at a rate of 4.7 per 1000 patient-years, and at a median age of 38 years.[25] Pulmonary hypertension leads to right atrial dilation and remodelling, which predisposes to the development of atrial arrhythmias. In patients with Eisenmenger syndrome, atrial arrhythmias are strongly associated with mortality in multivariable analyses, with reported hazard ratios ranging from 3.4 to 9.0.[26,27] In light of the potential for atrial arrhythmias to lead to hemodynamic instability and given their strong association mortality, they should be managed promptly in a centre with appropriate expertise. This includes cardiac anaesthesiologists adept at managing the precarious balance between systemic and pulmonary vascular resistance and volume status.

Who to Anticoagulate for Atrial Arrhythmias?

It could be argued that the single most important issue in managing atrial arrhythmias in adults with CHD is risk assessment and prevention of thromboembolic complications. It has been known for decades that atrial arrhythmia, be it atrial fibrillation or flutter, is the most powerful predictor of

stroke, conferring a 4- to 7-fold higher risk in the general population.[28] A high stroke risk is observed regardless of the arrhythmia pattern, whether paroxysmal or sustained, and is independent of a rate vs rhythm control treatment strategy.[29,30] Moreover, morbidity and mortality resulting from ischemic strokes secondary to atrial arrhythmias are far greater than from strokes of other causes. Approximately 60% of such strokes are disabling and 20% are fatal.[31,32]

Although the association between atrial arrhythmia and thromboembolism is less well studied in patients with CHD, the data appear consistent. In a retrospective cohort of >23,000 adults with CHD, the absence of sinus rhythm was the single factor associated with the highest prevalence of cerebrovascular accidents.[33] Moreover, in the Quebec administrative database of more than 38,000 patients with CHD, a strong and significant association between atrial arrhythmias and stroke was observed.[34] Considering the high prevalence of atrial arrhythmias in adults with CHD, common management questions include who to anticoagulate and which agent to prescribe. Herein, we will address the former. Please refer to the article by Mongeon et al.[35] in this issue of *Canadian Journal of Cardiology* for a detailed review of circumstances in which it is reasonable to favour a non–vitamin K antagonist oral anticoagulant over a vitamin K antagonist and situations in which a non–vitamin K antagonist oral anticoagulant is not currently recommended (eg, Fontan circulation or cyanotic CHD) or contraindicated (eg, mechanical valve, mitral or tricuspid valve stenosis with enlarged and diseased atria, or cardiac surgery in the preceding 3 months).

Long-term anticoagulation

The **A**nticoagulation **T**herapy in **C**ongenital Heart Disease (TACTIC) study was specifically designed to quantify the incidence of thromboembolic events and bleeding rates in patients with CHD and atrial arrhythmias, and identify associated factors.[36] A total of 482 patients, aged 32.0 ± 18.0 years, were enrolled from 12 North American centres and followed for an average of 11 years. Patients with CHD were classified as having simple, moderate, or complex forms of CHD on the basis of a previously proposed classification scheme (Table 1).[37] Although the study was observational in nature, it was conducted according to clinical trial data management standards including multiple levels of data quality control and blinded adjudication of qualifying arrhythmias and all outcomes. Survival free from a thromboembolic event was 89% at 10 years and 85% at 15 years.

In multivariable analyses, the only factor independently associated with thromboembolic events was complexity of CHD. As shown in Figure 3, thromboembolic event rates in patients with simple, moderate, and complex forms of CHD were 0.00%, 0.93%, and 1.95% per year, respectively (P < 0.001). Rates were not significantly different among patients with IART vs atrial fibrillation. The overall rate of major bleeding on anticoagulation was low (< 1%/year) and independently associated with a higher **H**ypertension (systolic blood pressure > 160 mm Hg), **A**bnormal liver or renal function, **S**troke, **B**leeding tendency or predisposition, **L**abile INR in patients taking a vitamin K antagonist, **E**lderly (aged > 65 years), **D**rugs (antiplatelet agents or alcohol use) (HAS-BLED) score. Importantly, 93% of the population had
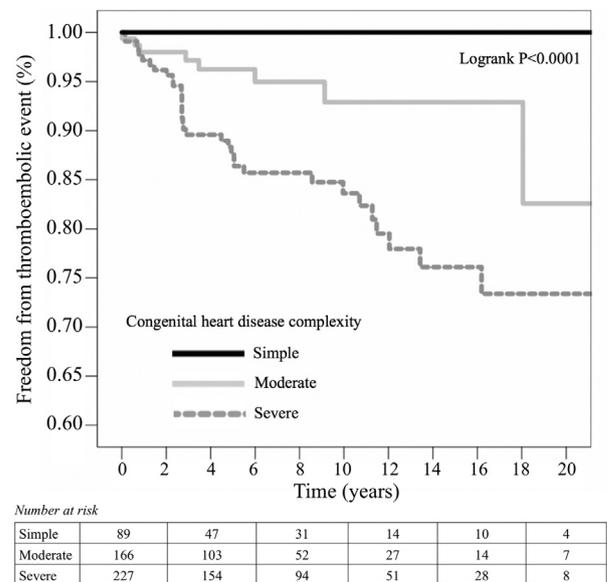

Figure 3. Freedom from thromboembolic events according to congenital heart disease complexity. Reproduced from Khairy et al.[36] with permission from Elsevier.

a HAS-BLED score of 0 or 1, reflecting a relatively young, low-risk population.

The TACTIC study provided evidence to support the inclusion of CHD complexity as an important factor to consider in thromboprophylaxis management decisions, a notion initially proposed by the Pediatric and Congenital Electrophysiology Society (PACES)/Heart Rhythm Society (HRS) expert consensus statement.[1] Despite anticoagulation in 53% of patients with complex CHD, the thromboembolic event rate (1.95%/year) exceeded the major bleeding rate (0.66%/year), suggesting that anticoagulation should generally be recommended in patients with complex CHD and IART or atrial fibrillation. The thromboembolic event rate in patients with CHD of moderate complexity (0.93%/year) likewise exceeded the major bleeding rate, suggesting that long-term anticoagulation is reasonable in this setting.

In contrast, there were no thromboembolic events in patients with simple forms of CHD despite 44% not receiving anticoagulation. As such, there is likely a subgroup of patients with simple CHD and atrial arrhythmias in whom the risk-to-benefit ratio does not favour routine anticoagulation. Otherwise stated, having simple CHD does not appear to be a sufficient indication to justify routine anticoagulation in the setting of atrial arrhythmias. In the absence of more granular thromboembolic risk scores specific to patients with CHD, it would appear reasonable to further stratify patients with simple forms of CHD according to established risk scores such as **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75 years, **D**iabetes Mellitus, **S**troke, Transient Ischemic Attack or Thromboembolism (2 points) (CHADS$_2$) or **C**ongestive Heart Failure, **H**ypertension, **A**ge (65-74 years 1 point, ≥ 75 years 2 points), **D**iabetes Mellitus, **S**troke, Transient Ischemic Attack or Thromboembolism (2 points), **Va**scular Disease (history of myocardial infarction, peripheral arterial disease or aortic atherosclerosis), Female **S**ex **C**ategory (CHA$_2$DS$_2$-VASc). Conceptually, it would be interesting to have an
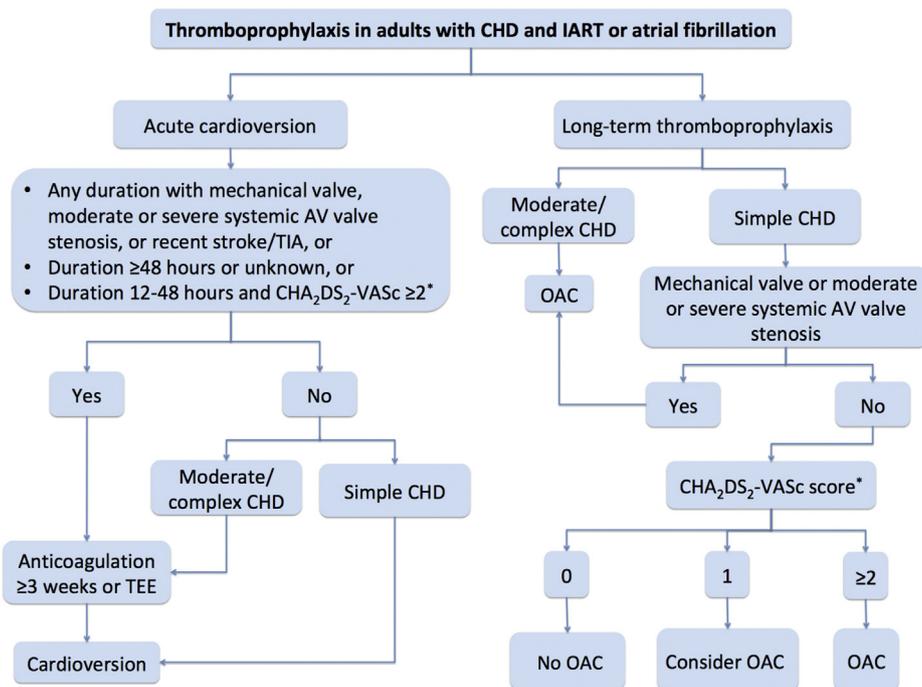
Figure 4. Pericardioversion and long-term anticoagulation for intra-atrial reentrant tachycardia (IART) or atrial fibrillation in adults with congenital heart disease (CHD). AV, atrioventricular; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ($\geq$ 75 years, 2 points; 65-74 years, 1 point), Diabetes, Stroke, transient ischemic attack, or thromboembolism (2 points), VAscular disease, Sex category (female); OAC, oral anticoagulation; TEE, transesophageal echocardiography; TIA, transient ischemic attack. *Excluding female sex from the CHA_2DS_2-VASc score.

integrated score that includes CHD complexity. For example, a Con_2-$CHADS_2$ or Con_2-CHA_2DS_2-VASc score could be proposed that assigns 1 and 2 points to moderate and complex CHD (Con_2), respectively. Such speculative scores remain to be validated.

Anticoagulation pericardioversion

There is less data to guide decisions regarding anticoagulation in the acute pericardioversion period for atrial arrhythmias in adults with CHD. In 19 patients with CHD and transesophageal echocardiography before cardioversion, atrial thrombus was identified in 37%.[38] In another series of 63 patients who underwent 80 electrical cardioversions, 59 were guided by transesophageal echocardiography.[39] No thromboembolic complication occurred using the general strategy of anticoagulation for $\geq$ 4 weeks before cardioversion

targeting an international normalized ratio $\geq$ 2 or, alternatively, transesophageal echocardiography. The latter was performed in all high-risk patients (eg, complex CHD, mechanical valve, prior thromboemboli, systemic hypertension, heart failure, or ventricular dysfunction).[39]

Recently, the Canadian Cardiovascular Society amended recommendations for anticoagulation in the pericardioversion period in the atrial fibrillation management guidelines.[40] It was recognized that there is likely a subgroup of patients with nonvalvular atrial fibrillation of brief duration with a low 30-day risk of thromboembolic events after cardioversion despite no preceding anticoagulation. High-risk features that warrant anticoagulation for at least 3 weeks before cardioversion or, alternatively, a transesophageal echocardiogram to rule out thrombus, include a mechanical valve, moderate or severe systemic AV valve stenosis, and a recent stroke or transient ischemic attack (within 6 months). In patients

Table 2. Recommendations for primary prevention ICDs in adults with CHD

COR	LOE	Recommendation
I	B	ICD therapy is indicated in adults with CHD and a systemic LVEF $\leq$ 35%, biventricular physiology, and NYHA class II or III symptoms
IIa	B	ICD therapy is reasonable in selected adults with tetralogy of Fallot and multiple risk factors for sudden cardiac death such as LV systolic or diastolic dysfunction, nonsustained VT, QRS duration $\geq$ 180 ms, extensive RV scarring, or inducible sustained VT at the EP study
IIb	C	ICD therapy may be reasonable in adults with a single or systemic right ventricular ejection fraction < 35%, particularly in the presence of additional risk factors such as complex ventricular arrhythmias, unexplained syncope, NYHA functional class II or III symptoms, QRS duration $\geq$ 140 ms, or severe systemic AV valve regurgitation
IIb	B	ICD therapy may be considered in adults with CHD and syncope of unknown origin with hemodynamically significant sustained ventricular tachycardia or fibrillation inducible at the EP study

AV, atrioventricular; CHD, congenital heart disease; COR, class of recommendation; EP, electrophysiological; ICD, implantable cardioverter-defibrillator; LOE, level of evidence; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV; right ventricular; VT, ventricular tachycardia.

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Table 3. Risk score for appropriate ICD shocks in patients with tetralogy of Fallot

Variable	Exp(β)	Points attributed
Prior palliative shunt	3.2	2
Inducible sustained ventricular tachycardia	2.6	2
QRS ≥ 180 ms	1.4	1
Ventriculotomy incision	3.4	2
Nonsustained ventricular tachycardia	3.7	2
Left ventricular end-diastolic pressure ≥12 mm Hg	4.9	3
Total points		0-12

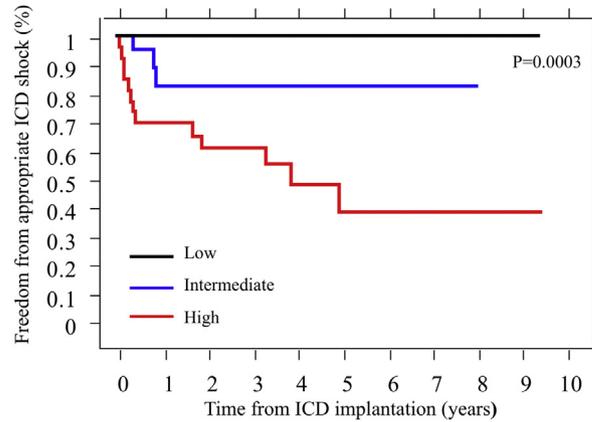Exp(β), exponential of the beta-coefficient; ICD, implantable cardioverter-defibrillator.

Adapted from Khairy et al.[59] with permission from the American Heart Association.

Risk score	Risk category	N	Annualized rate of appropriate shocks
0-2	Low	18	0%
3-5	Intermediate	24	3.8%
6-12	High	26	17.5%

Figure 5. Freedom from appropriate implantable cardioverter-defibrillator (ICD) shocks in primary prevention patients with tetralogy of Fallot according to their risk category. In patients with tetralogy of Fallot and primary prevention ICDs, Kaplan-Meier survival curves for freedom from first appropriate ICD shock are plotted and compared according to risk score classification. Risk score, corresponding risk category, number of patients, and annualized rate of appropriate shocks are summarized below. Adapted from Khairy et al.[59] with permission from the American Heart Association.

without such high-risk features, it was previously deemed acceptable to undergo electrical cardioversion without preceding anticoagulation if the duration of the acute episode was < 48 hours. However, a Finnish retrospective observational study of 7660 cardioversions in 3143 patients found that the risk of postcardioversion thromboembolic events was significantly higher in non-anticoagulated patients (1.1% vs 0.2%, $P = 0.001$) with a $CHA_2DS_2\text{-VASc}$ score ≥ 2.[41] Even within the 48-hour window, those with episodes of atrial fibrillation > 12 hours in duration were nearly 4-fold more likely to have a thromboembolic event after cardioversion.[42,43]

In addition, the PACES/HRS expert consensus statement recognized that adults with moderate or complex forms of CHD may be predisposed to thrombus formation even in the absence of atrial tachyarrhythmias. As such, a strategy of therapeutic anticoagulation for at least 3 weeks before cardioversion, or transesophageal echocardiography to rule out thrombus, appears reasonable for these high-risk patients regardless of arrhythmia duration.[24,44] In patients with Fontan surgery, the thromboembolic risk is particularly high[24,45-52] such that a low threshold for transesophageal echocardiography appears reasonable before cardioversion, even if an anticoagulant was received.[38,53] Importantly, cardioversion should not be delayed in the setting of hemodynamic instability. The proposed modified algorithms for pericardioversion and long-term anticoagulation are summarized in Figure 4.

Who to Refer for a Primary Prevention ICD?

The overall risk for sudden cardiac death in adults with CHD is low (<0.2%/year). Nevertheless, it is far higher than in age-matched controls and is among the top 2 causes of mortality, along with heart failure.[54] Reliably identifying adults with CHD at sufficiently high risk for sudden cardiac death to warrant primary prevention ICDs remains a major challenge. The population is remarkably heterogeneous. Risk factors identified in certain subtypes of patients may not be applicable to others. Moreover, interventions and surgical techniques are constantly evolving, such that risk stratification is a moving target. In the absence of randomized clinical trials specific to adults with CHD, the imperfect science of risk stratification largely relies on probability estimates informed by observational studies and extrapolations from evidence derived in non-CHD populations.

Selected recommendations for primary prevention ICDs are summarized in Table 2.[1] A primary prevention ICD is generally indicated in adults with CHD who meet standard criteria established by clinical trials in non-CHD populations, namely a left ventricular ejection fraction $\leq 35\%$ along with New York Heart Association class II or III symptoms.[55] In fact, this is the only class I recommendation for a primary prevention ICD in adults with CHD, with the rationale being that patients meeting these criteria have a $\geq 3.5\%$/year incidence of sudden death.[55] Importantly, the PACES/HRS expert consensus statement specifies that this criterion is only applicable to patients with a systemic left ventricle and biventricular physiology given the particularities of systemic right ventricles and univentricular hearts.[1] However, in a systematic review that included 412 adults with CHD and ICDs, only 10% met this class I indication. As such, it is believed that a substantial proportion of adults with CHD who stand to benefit from primary prevention ICDs do not meet this classic indication.

By far, the most common subtype of CHD in ICD recipients is tetralogy of Fallot, which outnumbers all other forms of CHD combined.[56] In patients with tetralogy of Fallot, the incidence of sudden death appears to be nonlinear, with a marked increase 15 to 20 years after corrective surgery.[57] Over the past few decades, numerous observational studies have explored factors associated with ventricular arrhythmias and sudden death. Collectively, they paint a reasonably consistent portrait of the high-risk patient: surgical repair at an older age, impaired hemodynamics, ventricular fibrosis, and electrophysiological manifestations. Inducible sustained ventricular tachycardia carries prognostic

value above and beyond noninvasive markers and is most helpful in stratifying patients with a moderate pretest risk for sudden death.[58] The identification of factors independently associated with sudden death is highly dependent on the variables considered in predictive models, given the highly correlated nature of electromechanical factors. Table 3 summarizes a risk score derived in a population with primary prevention ICDs.[59] Freedom from ventricular arrhythmias treated by appropriate ICD shocks is plotted in Figure 5 according to the risk category.[59] Currently, a class IIA recommendation based on level B evidence states that ICD therapy is reasonable in selected adults with tetralogy of Fallot and multiple risk factors for sudden death identified by this and other studies.[1,60]

In contrast to the tetralogy of Fallot population in which primary prevention ICD recipients have a reasonably high rate of appropriate ICD therapies,[59] attempts to reliably identify high-risk patients with systemic right ventricles have been disappointing.[13] In patients with Mustard or Senning baffles, the factors most consistently associated with sudden cardiac death include atrial tachyarrhythmias (as discussed above), systemic ventricular dysfunction, severe tricuspid regurgitation, and a prolonged QRS duration.[1,12] In addition to difficulties in accurately quantifying systemic right ventricular systolic function, it should be noted that normal values for a subpulmonary right ventricular ejection fraction are roughly 20% lower than for a systemic left ventricle. It should not be assumed, therefore, that the cutoff value of 35% for a systemic left ventricular ejection fraction is applicable to a morphologic right ventricle.

The hope is that risk stratification for patients with systemic right ventricles will improve as a wider net is cast on potential associated factors, including variables implicated in the myocardial ischemia hypothesis pathway.[14] Currently, a weak class IIB indication based on level C evidence states that it may be reasonable to implant a primary prevention ICD in selected adults with a systemic right ventricular ejection fraction < 35% accompanied by additional factors such as complex ventricular arrhythmias, unexplained syncope, heart failure symptoms, QRS ≥ 140 ms, or severe tricuspid regurgitation.[1]

As class IIB recommendations, it may also be reasonable to consider primary prevention ICDs in patients with a single ventricular ejection fraction < 35%, or in those with syncope, a high clinical suspicion of ventricular arrhythmia, and no cause identified by thorough investigations.[1] Syncope in adults with CHD may have several potential etiologies, including bradyarrhythmias, atrial and ventricular tachyarrhythmias, and nonarrhythmic causes. Importantly, in the absence of a substrate for macroreentrant ventricular arrhythmias, such as in patients with tetralogy of Fallot, the value of programmed ventricular stimulation in adults with CHD is largely unknown. Inducible ventricular tachycardia did not predict future ventricular arrhythmias or sudden death in a small series of patients with transposition of the great arteries and intra-atrial baffles.[13]

Future progress in identifying appropriate candidates for primary prevention ICDs will require refining and validating risk stratification schemes on a large scale in patients with tetralogy of Fallot, and better defining high-risk features in other subgroups.

Conclusions

In summary, clinical scenarios that merit prompt referral for catheter ablation include Ebstein anomaly with ventricular pre-excitation, and atrial arrhythmias in patients susceptible to hemodynamic instability and sudden death, such as in the context of atrial switch surgery for transposition of the great arteries, Fontan physiology, and Eisenmenger syndrome. As a general guide, anticoagulation for atrial arrhythmias is indicated in those with valvular heart disease (ie, mechanical valves or at least moderate systemic AV valve stenosis), traditional risk factors for stroke, and moderate or complex CHD. Risk stratification for ventricular arrhythmias and sudden death involves numerous challenges. Primary prevention ICDs are generally indicated in patients with standard criteria and should be considered in selected high-risk patients with tetralogy of Fallot. Indications for ICDs remain more contentious in other subgroups of patients, such as those with systemic right ventricles and univentricular hearts, underscoring the critical need for future research.

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