



Review

Atrial fibrillation in adults with congenital heart disease

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ABSTRACT

A convergence of epidemiological and clinical features has prompted a precipitous rise in the prevalence of atrial fibrillation (AF) in the expanding population of adults with congenital heart disease. Herein, we synthesize the current state of knowledge on epidemiological features, associated morbidities, and pathophysiological insights regarding AF in adults with congenital heart disease. Management issues are examined including surgical, pharmacological, and catheter-based therapies. Throughout, knowledge gaps and avenues for future research are identified. Although AF has been coined the next arrhythmic epidemic to strike adults with congenital heart disease, it has already usurped atrial macroreentrant tachycardia as the most common presenting arrhythmia over the age of 50 years. Much remains to be discovered about the mitigating role of types of congenital defects, residual hemodynamic lesions, surgical sequelae, and ramifications of shunts and cyanosis on mechanisms and determinants of AF. Thromboprophylaxis is the cornerstone of pharmacological management, with anticoagulation recommended in patients with moderate or complex congenital heart disease and those with significant valve disease or risk factors for stroke. Considering the limited success with antiarrhythmic drugs, catheter ablation is increasingly performed. Non-pulmonary vein sources, focal and reentrant arrhythmias, appear to be important triggers for AF in this population. As such, they should be identified and addressed during catheter ablation interventions. The nascent literature on electrical isolation of pulmonary veins suggests that it is feasible and safe, although initial success rates appear to be modest. A more thorough understanding of underlying mechanisms and substrates carries the potential to further improve outcomes.

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1. Introduction

As life expectancy increases in the population with congenital heart disease (CHD) [1], a confluence of factors is driving an upsurge in the prevalence of atrial fibrillation (AF). Older age is associated with atrial electrophysiological changes that predispose to AF, including alterations in ion channel function, action potential properties, and calcium homeostasis, which enable afterdepolarizations and ectopic atrial activity [2]. Atrial fibrosis increases with age and contributes to structural remodeling that plays a key role in promoting and maintaining AF. In addition, as patients with CHD age, they risk acquiring comorbidities such as hypertension, diabetes, and obesity that further contribute to atrial dilation, fibrosis, and electrical remodeling that enhances vulnerability to AF

[2]. Although much remains to be learned about AF in adults with CHD, this review synthesizes the literature and current thinking, addresses management issues, and highlights knowledge gaps and areas for future research.

2. Epidemiological features

2.1. Prevalence

It has been estimated that, in 2010, some 1.4 million adults with CHD lived in the United States alone, with a prevalence that continues to rise [3]. Approximately 15% suffer from atrial arrhythmias [4]. A single center study that included 3311 patients with simple (49%), moderate (39%), or complex (12%) forms of CHD reported a 4.7% prevalence of AF [5]. Projections indicate that 50% of 20 year-olds with CHD will have an atrial tachyarrhythmia during their lifespan [4]. The risk of developing intra-atrial reentrant tachycardia (IART) or AF is 22-fold higher in patients with CHD than matched controls, with a prevalence of 8.3% in 42 year-olds, and up to 20% in those with conotruncal malformations [6].

Abbreviations: AF, atrial fibrillation; AT, atrial tachycardia; ASD, atrial septal defect; CHD, congenital heart disease; DOAC, direct oral anticoagulant; IART, intra-atrial reentrant tachycardia; PVI, pulmonary vein isolation.

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2.2. Age at presentation and pattern of AF

In a series of 199 patients with heterogeneous forms of CHD, the mean age at first documented episode of AF was 49 years [7]. However, age of onset varied according to type of CHD, with an earlier inception in those with complex CHD. Moreover, within a 3-year follow-up, the pattern of AF progressed in 25% of patients from paroxysmal (i.e., resolution without intervention in <7 days) to persistent (i.e., >7 days or requiring an intervention for termination) or permanent (i.e., no further attempt at termination) [7]. Rapid progression in the pattern of AF was also reported in 38% of patients with tetralogy of Fallot within 5 years of onset [8].

In a recent multicenter study conducted across 12 North American centers, AF accounted for 29% of presenting arrhythmias in patients with CHD, whereas IART and focal atrial tachycardia (AT) were responsible for 62% and 9.5%, respectively [9]. A clear link between AF and age was identified, with AF surpassing IART as the most common presenting arrhythmia in patients ≥ 50 years of age (51.2%, Fig. 1A). The predominant pattern of AF was paroxysmal (62%), but permanent atrial arrhythmias increased with age from 3% in those <20 years to 23% in patients ≥ 50 years. Furthermore, the coexistence of AF with regular atrial tachyarrhythmias was observed. Twelve percent of patients who initially presented with IART or focal AT developed AF over an average follow-up of 11 years. It is, therefore, common for adults with CHD to initially present with organized atrial arrhythmias that progress towards AF and for the pattern to transform from paroxysmal to persistent or permanent forms [7,9].

2.3. Complexity of heart disease

Certain types of CHD have been associated with a higher prevalence of AF, including secundum atrial septal defect (ASD), atrioventricular

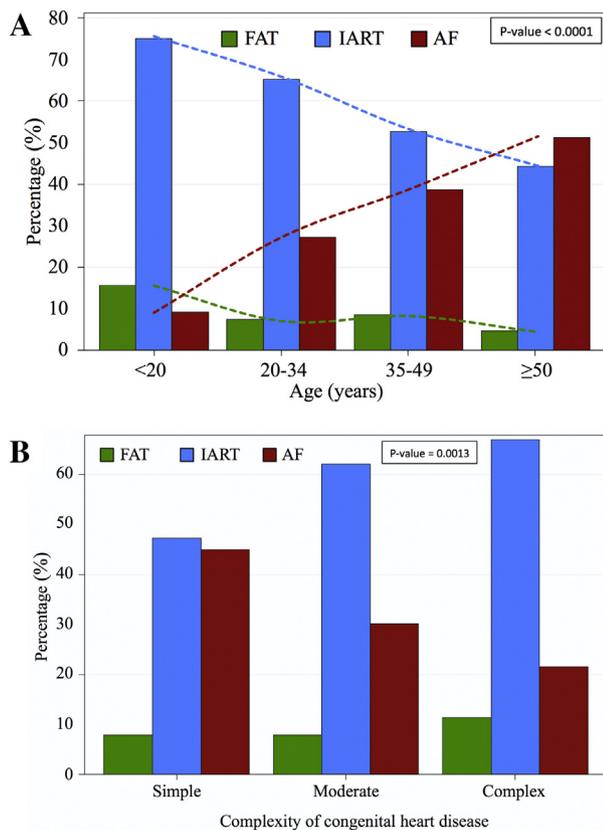


Fig. 1. Distribution of the type of atrial arrhythmia according to age (Panel A) and to congenital heart disease complexity (Panel B). AF denotes atrial fibrillation; FAT, focal atrial tachycardia; IART, intraatrial reentrant tachycardia. Reproduced with permission from Labombarda F et al [9].

septal defect, tetralogy of Fallot, transposition of the great arteries with atrial baffle surgery, heterotaxy syndrome, and single ventricle physiology with Fontan palliation [10]. The prevalence of AF is generally higher in patients with more complex CHD. However, among those with atrial arrhythmias, the proportion with AF as the presenting arrhythmia decreases with CHD complexity [9]. Indeed, AF was the presenting arrhythmia in 45% of patients with simple, 30% with moderate, and 22% with complex CHD, respectively (Fig. 1B). These seemingly paradoxical observations likely reflect the fact that patients with complex CHD are more likely to initially present with IART or focal AT and that patients with simpler forms of CHD are older on average than those with more complex disease.

3. Atrial arrhythmias and adverse events

Atrial arrhythmias are the leading cause of morbidity and hospitalizations in adults with CHD, with nearly 150,000 admissions for arrhythmias reported in the United States between 1998 and 2005 [11]. Moreover, they have been associated with heart failure, sudden death, and stroke [4,12,13]. The risk of all-cause death is 5-times higher in patients with CHD and AT or AF compared to those without atrial arrhythmias [6]. Although a causal relationship cannot be established by retrospective observational studies [4,14,15], atrial arrhythmias have been noted to trigger malignant ventricular arrhythmias and sudden death in susceptible individuals. In a multicenter case-control study of adults with CHD, atrial arrhythmias were associated with 3.5-fold increased odds of sudden death of presumed arrhythmic etiology [16].

While AF, as opposed to atrial arrhythmias in general, has not specifically been linked to sudden death in adults with CHD, there is some evidence in the general population that this may be the case [17]. Moreover, atrial arrhythmias can conduct rapidly to the ventricles in young adults with intact atrioventricular nodes and may be poorly tolerated in some forms of CHD. In a population with transposition of the great arteries, atrial baffle surgery, and implantable cardioverter-defibrillators, atrial tachyarrhythmias often preceded or coexisted with ventricular arrhythmias leading to appropriate shocks [18]. Consistently, a multicenter case-control study in a similar patient population found that atrial arrhythmias were associated with a nearly 5-fold increased risk of sudden death [19].

Atrial arrhythmias have also been associated with a 2- to 3-fold increased risk of other adverse events, including stroke, heart failure, hospital admissions, and cardiac interventions [4,15]. In a multicenter study, the thromboembolic risk associated with AF did not differ significantly from IART [12]. Most other studies have lacked the granularity to distinguish between types of atrial arrhythmias in assessing associations with adverse events. For example, in a recent study based on administrative data that purported to assess the burden of AF in patients with CHD, “AF” was liberally defined as either atrial flutter or AF on the basis of *International Statistical Classification of Diseases* codes [6]. Atrial arrhythmias were associated with heart failure (hazard ratio 11.4), ischemic stroke (hazard ratio 2.5), and all-cause mortality (hazard ratio 5.5). Finally, small retrospective studies have suggested that atrial arrhythmias negatively impact quality of life in adults with CHD [20,21]. Ongoing larger studies should provide valuable insights regarding patient-reported outcomes associated with AF in adults with CHD [22].

4. Pathophysiological considerations

A comprehensive appraisal of molecular mechanisms underlying AF is beyond the scope of this review. In general, AF is conceptualized as involving triggers that induce the arrhythmia and a substrate that sustains it [23]. While most triggers for paroxysmal AF in structurally normal hearts arise from pulmonary veins, caution is warranted in extrapolating mechanistic studies to the CHD population considering the unique anatomical and physiological features. Duration of atrial volume

overload has been identified as a key factor promoting atrial fibrosis linked to atrial arrhythmias in patients with CHD [24]. Considering the extent of myocardial and electrical remodeling of atrial tissue in patients with CHD associated with conditions such as chronic cyanosis and hemodynamic stress, extra-pulmonary vein triggers could potentially play a more decisive role [25]. In addition, in some patients, venous anomalies such as a persistent left superior vena cava, can be the source of non-pulmonary vein triggers for AF [26].

Few studies have described electrophysiological features in patients with CHD and AF. Patients with atrial septal defects (ASD) have a longer right atrial effective refractory period and a greater conduction delay when compared to matched controls [27]. Left atrial remodeling is also commonly associated with ASDs in the form of left atrial enlargement, fibrosis, and increased conduction times [28]. Intraoperative epicardial mapping studies demonstrated that atrial activation patterns differed in patients with ASDs and paroxysmal versus long-standing persistent AF [29]. Whereas reentrant or focal activation driving AF was confined to the right atrium in patients with paroxysmal forms, multiple sources arising from pulmonary veins or the posterior left atrium were observed in those with long-standing AF.

Another study that involved detailed mapping in two individuals provided provocative observations regarding the presence of focal drivers for AF in some patients with CHD [30]. Circumscribed areas exhibiting continuous electrical activity coexisted with parts of the atrium activated in a regular manner (Fig. 2). Radiofrequency ablation at this site terminated AF demonstrating that, at least in some patients, AF recorded on the surface electrogram may result from focal activity giving rise to fibrillatory conduction. It is also possible for IART circuits that involve scars or patches to degenerate into AF. Moreover, some adults with CHD have irregularly irregular electrocardiographic patterns consistent with AF. Yet, detailed intracardiac electroanatomic mapping studies reveal stable single- or multiple-loop circuits in the context of extensive atrial scarring that results in electrical dissociation of portions of the dilated atrial chambers. The importance of focal and reentrant non-pulmonary vein triggers in adults with CHD and AF is a topic that remains ripe for research and merits formal assessment on a large scale.

5. Associated factors

Considering that IART is the most common arrhythmia in adults with CHD, the literature has primarily focused on factors associated with these circuits. These include older age, prior cardiac surgeries, greater complexity of CHD, later repair, coexisting sinus node

dysfunction, and right atrial enlargement [6,31]. Few investigations have specifically addressed factors associated with AF [32–34]. In a multicenter study on adults with tetralogy of Fallot, factors independently associated with AF included a lower left ventricular ejection fraction and left atrial dilation [31]. Left atrial dimension has also been associated with AF in a single-center series of adults with CHD and 24-hour Holter monitors [35]. Consistently, a retrospective review of patients with CHD who underwent cardioversion for AF or IART found that patients with AF had a higher prevalence of residual left-sided obstructive lesions [36].

It is also worth noting that factors associated with AF in the general population, such as obesity, hypertension, obstructive sleep apnea, and male gender, also appear to be related to AF in patients with CHD [37]. In a multicenter study of patients with heterogeneous forms of CHD and atrial arrhythmias, factors independently associated with AF as the presenting arrhythmia were older age, hypertension, and number of cardiac surgeries (Fig. 3) [9]. Variables associated with new-onset AF during follow-up included older age and cardiovascular risk factors. The importance of considering associated conditions in patients with CHD is increasingly recognized [38]. While screening for and aggressively managing cardiovascular risk factors and coexisting comorbidities that promote AF favorably impacts the AF burden in non-CHD populations [39,40], comparable data specific to adults with CHD are lacking.

The association between ASD and AF has long been known. The main cause of morbidity in adults with ASDs is atrial arrhythmias. Approximately 10% of untreated patients with ASDs develop atrial arrhythmias, predominantly AF, by 40 years of age [41]. The incidence continues to rise with age, with AF reported in >50% of patients after the age of 60 [42]. Several studies have assessed the impact of ASD closure on AF burden, including a meta-analysis of 26 reports that incorporated 1841 patients with surgical closure and 945 with percutaneous closure [43]. Both approaches resulted in a significant reduction in the prevalence of atrial arrhythmias. Older age at the time of closure appears to be the factor most consistently associated with atrial arrhythmias during follow-up, with no difference between percutaneous or surgical approaches [43,44]. Nevertheless, a 4.1% annual incidence of new-onset AF has been reported following ASD closure [45], with a lower risk among those treated during childhood or early adulthood [46].

6. Management

6.1. Surgical considerations

Hemodynamic and arrhythmic complications are so intimately linked that it is strongly recommended for adults with CHD and new-onset or worsening arrhythmias to rule-out potential contributory conditions such as regurgitant or obstructive lesions, shunts, ischemia, and ventricular dysfunction [10]. Occasionally, the work-up reveals conditions that should be addressed by transcatheter or surgical interventions. The type and timing of surgical interventions can have a profound impact on long-term arrhythmia outcomes. AF can be addressed surgically by means of the Cox-Maze III procedure that includes pulmonary vein isolation (PVI), strategically placed incisions designed to interrupt macroreentrant circuits, and left atrial appendage ligation or removal. Surgical incisions are placed with the intention of allowing the electrical impulse to propagate from the sinus node to both atria. Activating most of the atrial myocardium is thought to result in preservation of atrial transport function.

Surgical ablation at the time of attendant open heart surgery is most often reserved for patients with pre-existing AF [10]. However, concomitant preventive atrial arrhythmia surgery could also be considered in patients without pre-existing arrhythmias deemed to be at high risk for new post-operative arrhythmias. A modified right atrial Maze in addition to a left atrial Cox-Maze III procedure should be considered in patients with univentricular hearts and AF undergoing Fontan conversion or revision, since it has been associated with favorable outcomes

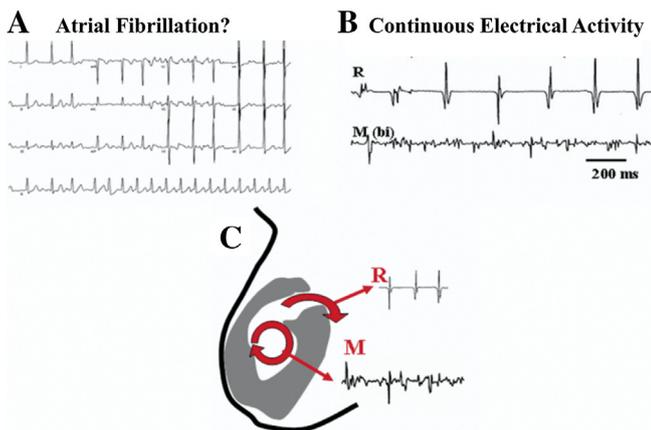


Fig. 2. Focal continuous electrical activity giving rise to fibrillatory conduction. Mapping during atrial fibrillation (Panel A) revealed an area of continuous electrical activity at the right atrial free wall (Panel B and C) while other parts of the atrium were activated in a regular manner.

Reproduced with permission from de Groot NM et al [30].

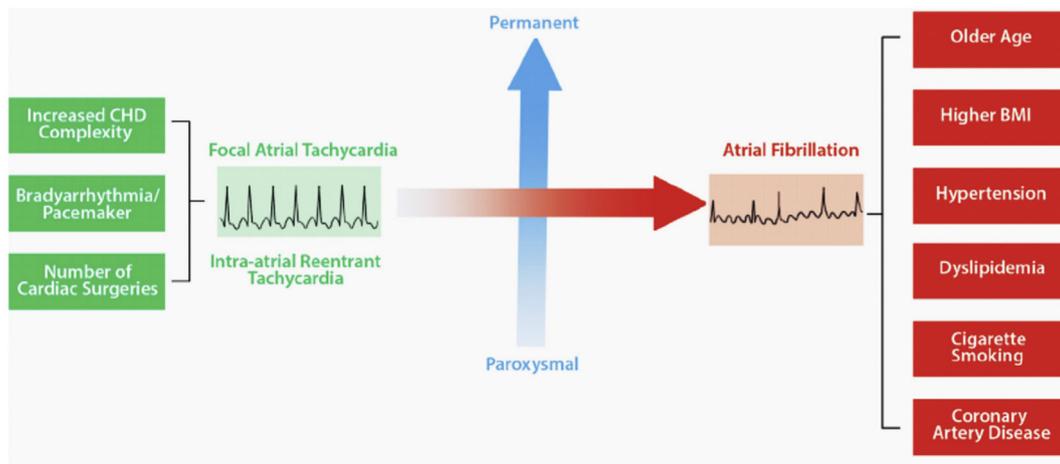


Fig. 3. Atrial arrhythmias in the aging population with congenital heart disease: changing types and patterns. Factors associated with focal atrial tachycardia and intra-atrial re-entrant tachycardia (IART) in patients with congenital heart disease include younger age, more complex disease, a greater number of cardiac surgeries, and bradyarrhythmias/pacemakers. By contrast, factors associated with atrial fibrillation include older age, higher body mass index, cardiovascular risk factors, and coronary artery disease. As age increases, atrial fibrillation surpasses IART to become the most prevalent atrial arrhythmia, and the pattern transitions from predominantly paroxysmal to permanent forms. CHD denotes congenital heart disease. Reproduced with permission from Labombarda F et al [9].

[10,47]. Concomitant atrial arrhythmia surgery may also be considered in patients with Ebstein anomaly undergoing cardiac surgery [10]. Other prophylactic indications for a left atrial Cox-Maze III procedure, such as during surgical correction of a structural defect associated with left atrial dilation (e.g., left-sided valvular heart disease), are less well established. Naturally, prophylactic arrhythmia surgery is not recommended if it substantially increases surgical morbidity or mortality risks.

6.2. Pharmacological therapy

6.2.1. Acute cardioversion

In hemodynamically stable patients, intracardiac thrombus should be ruled-out and cardiac function assessed prior to cardioversion. In patients with cardiac malpositions (i.e., mesocardia or dextrocardia) or marked atrial enlargement, changes in pad configuration may be required to ensure that the electrical shock vector traverses the heart. Conversion rates with ibutilide and sotalol have ranged from 50 to 80%, but bradycardia, hypotension and torsades de pointes are reported complications [48–50]. Successful pharmacological cardioversion has also been reported in 41% of CHD patients with dofetilide [51]. To our knowledge, there is no efficacy or safety data regarding acute cardioversion of AF with class IA, IC, or other class III drugs in patients with CHD.

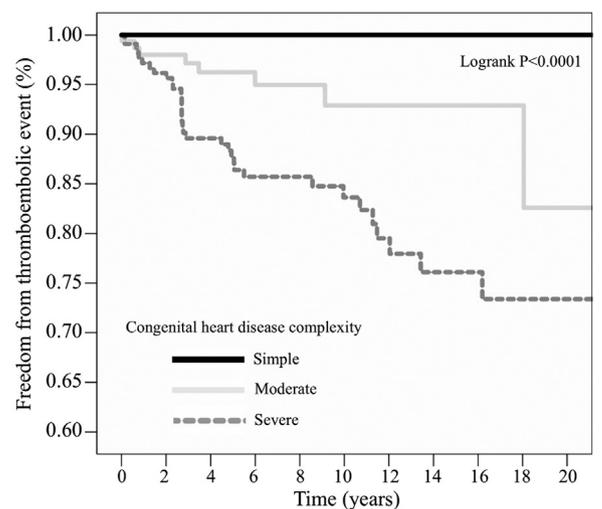
6.2.2. Maintenance of sinus rhythm

Rhythm control is generally preferred to rate control in patients with moderate or complex forms of CHD [10]. The choice of pharmacological therapies should take into consideration such factors as coexisting bradyarrhythmias, systemic or subpulmonary ventricular dysfunction, associated treatments, and childbearing potential in women. Current recommendations discourage class I antiarrhythmic drug use in patients with coronary artery disease or systolic dysfunction of a systemic or subpulmonary ventricle [10,47,52]. While sotalol is an alternative option, its use has been relegated to a class IIb indication as a first-line agent given concerns over proarrhythmia [53] and meta-analyses reporting increased all-cause mortality in the general population [54]. Class III antiarrhythmic agents have been associated with a lower risk of recurrent atrial arrhythmias when compared to other antiarrhythmic drugs in patients with CHD [55]. Amiodarone is considered a drug of choice in the setting of heart failure. However, long-term administration is limited by time- and dose-dependent side effects. The risk of amiodarone-induced thyrotoxicosis is 4- to 7-fold higher in patients with cyanotic CHD and Fontan palliation [56,57]. Dofetilide, another class III agent, is a reasonable alternative to amiodarone as a first-line

antiarrhythmic drug in adults with CHD and ventricular dysfunction [10,58]. In a multi-center study, atrial arrhythmias (mainly AF) resolved or improved on dofetilide in 49% of patients after a median follow-up of 3 years [51]. The most common reason for discontinuation was waning efficacy followed by side effects. Dofetilide requires a strict protocol of initiation and hospitalization owing to the risk of life-threatening torsade de pointes associated with excessive QT prolongation. Unfortunately, it is unavailable in many countries worldwide.

6.2.3. Prevention of thromboembolism

Prevention of thromboembolic complications is a critical issue in the pharmacological management of AF in adults with CHD. The prevalence of cerebrovascular accidents has been estimated to be 10- to 100-fold higher than in age-matched controls [59,60]. In the multicenter The AntiCoagulation Therapy In Congenital Heart Disease (TACTIC) study, the factor most strongly associated with thromboembolic events was complexity of CHD (Fig. 4) [12]. A hazard ratio of 3.5 was noted per



| Number at risk | | | | | | |
|----------------|-----|-----|----|----|----|----|
| | 0 | 2 | 4 | 6 | 8 | 10 |
| Simple | 89 | 47 | 31 | 14 | 10 | 4 |
| Moderate | 166 | 103 | 52 | 27 | 14 | 7 |
| Severe | 227 | 154 | 94 | 51 | 28 | 8 |

Fig. 4. Freedom from thromboembolic events according to congenital heart disease complexity. Reproduced with permission from Khairy P et al [12].

unit increase in category from simple to moderate to severe. No thromboembolic event occurred in patients with simple forms of CHD despite the absence of anticoagulation therapy in 44%. Although individual particularities must be taken into consideration, routine thromboprophylaxis is generally recommended in patients with AF and moderate or complex CHD [10,12]. In adults with non-valvular simple forms of CHD and AF, it appears reasonable to rely on established risks scores (i.e., CHADS₂ or CHA₂DS₂-VASc) to guide treatment decisions [10]. Importantly, a prohibitive risk of bleeding is uncommon in the young CHD population.

There are no comparative studies in adults with CHD to guide the choice of anticoagulant. Direct oral anticoagulants (DOAC) may be a reasonable alternative to vitamin K antagonists in patients with simple forms of CHD and no prosthetic heart valve or hemodynamically significant valve disease [10]. In 2014, the expert consensus statement discouraged use of DOACs in patients with complex CHD, particularly those with Fontan palliation, in the absence of safety and efficacy data [10]. A few small case series have since provided reassuring safety data regarding bleeding complications [61–64]. The number of enrolled patients has thus far been insufficient to assess efficacy. Thromboembolic events have been observed in Fontan patients despite therapy with a DOAC (i.e., dabigatran [61] and apixaban [65]), but limited sample sizes preclude firm conclusions regarding risks. Larger comparative studies with careful monitoring are warranted.

6.3. Catheter ablation

Before opting for a rate control strategy or prior to committing a young adult with CHD and atrial arrhythmias to long-term amiodarone therapy, a percutaneous catheter ablation approach should be thoughtfully considered [10,47,66,67]. Outcomes for catheter ablation have improved considerably since the introduction of three-dimensional electroanatomic mapping systems and irrigated or large electrode-tip catheters capable of creating deeper lesions [68].

The largest series of PVI-based AF ablation in CHD consists of 57 patients, average age 51 years, 61% of whom had simple, 18% moderate, and 21% complex forms of CHD [69]. The AF pattern was paroxysmal in 37% and persistent in 63%. When PVI failed to achieve sinus rhythm, additional linear lesions were performed, rarely supplemented by ablation of complex fractionated atrial electrograms. Arrhythmia-free survival, which appears to have been reported on or off antiarrhythmic drugs, was 63% at 1 year and 22% at 5 years. Complexity of CHD was not a predictor of recurrence. Overall, 56% of patients had repeat interventions, with 3 procedures in 19% and 4 in 4%. At the second procedure, 65% had recovered pulmonary vein conduction. Another single center series included 36 patients with predominantly paroxysmal AF (72%) and CHD, most of whom had atrial (61%) or ventricular (17%) septal defects [70]. After a single procedure, AF free survival rates off antiarrhythmic drugs were 42% at 300 days and 27% at 4 years. Corresponding rates with or without antiarrhythmic drugs were 84% and 61%, respectively. Compared to a population without CHD, the success rate was not significantly different but a higher incidence of vascular site complications was noted (8%).

Other series have primarily focused on adults with ASDs. Successful transseptal access has ranged from 90 to 98%, with approximately 75% freedom from recurrence at one year [71,72]. Whereas most patients had transseptal access across a portion of the native septum, in others the closure device was directly punctured. For adults with newly diagnosed ASDs and AF, it is preferable to proceed with catheter ablation prior to ASD closure whenever feasible [73]. Descriptions of PVI in patients with complex CHD remain scarce [74,75]. In summary, AF ablation is feasible and appears to be safe in patients with various forms of CHD. However, the data is currently insufficient to claim equivalent outcomes to the non-CHD population.

7. Conclusion

The prevalence of AF is rapidly increasing in the aging population with CHD, and is associated with considerable morbidity. Regarded as the next epidemic in adults with CHD, AF is already the leading presenting arrhythmia over the age of 50. Much remains to be learned about the impact of congenital heart defects, shunts, cyanosis, surgical patches and sutures, and coexisting hemodynamic lesions on the pathophysiology and determinants of AF. Pharmacological management should include anticoagulation for those with moderate or complex forms of CHD. Limited data exist regarding efficacy of antiarrhythmic drugs. The growing literature on AF ablation supports feasibility and safety, albeit with modest results. A greater appreciation of underlying mechanisms and substrates may contribute substantially to further improving outcomes in adults with CHD and AF.

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Conflicts of interest disclosures

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