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REVIEW

Risk of thromboembolic complications in adult congenital heart disease: A literature review

Risque thromboembolique des adultes ayant une cardiopathie congénitale : revue de la littérature

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Summary Adult congenital heart disease (ACHD) is a constantly expanding population with challenging issues. Initial medical and surgical treatments are seldom curative, and the majority of patients still experience late sequelae and complications, especially thromboembolic events. These common and potentially life-threating adverse events are probably dramatically underdiagnosed. Better identification and understanding of thromboembolic risk factors are essential to prevent long-term related morbidities. In addition to specific situations associated with a high risk of thromboembolic events (Fontan circulation, cyanotic congenital heart disease), atrial arrhythmia has been recognized as an important risk factor for thromboembolic events in ACHD. Unlike in patients without ACHD, thromboembolic risk stratification scores, such as the CHA_2DS_2-VASc score, may not be applicable in ACHD. Overall,

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

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after a review of the scientific data published so far, it is clear that the complexity of the underlying congenital heart disease represents a major risk factor for thromboembolic events. As a consequence, prophylactic anticoagulation is indicated in patients with complex congenital heart disease and atrial arrhythmia, regardless of the other risk factors, as opposed to simple heart defects. The landscape of ACHD is an ongoing evolving process, and specific thromboembolic risk scores are needed, especially in the setting of simple heart defects; these should be coupled with specific trials or long-term follow-up of multicentre cohorts.

MOTS CLÉS
Traitement anticoagulant ;
Thromboembolie ;
Arythmie ;
Cardiopathie congénitale

Résumé Les adulte ayant une cardiopathie congénitale (ACC) est une population sans cesse croissante soulevant des problématiques complexes. Le traitement médical et chirurgical initial est rarement curatif, et la grande majorité des patients devront faire face à des séquelles et des complications, en particulier des événements thromboemboliques. Cette complication potentiellement létale reste considérablement sous-diagnostiquée. Une meilleure identification et compréhension des facteurs de risque thromboembolique sont décisives pour prévenir la morbidité à long terme. À l'exception des situations spécifiques connues pour être associés à un risque élevé d'événements thromboemboliques (circulation de Fontan, cardiopathie cyanogène), l'arythmie supraventriculaire a été reconnue comme un important facteur de risque d'événements thromboemboliques chez les ACC. Les scores classiques de stratification du risque thromboembolique, tel que le CHA2DS2-VASc, ne peuvent pas s'appliquer aux ACC. Dans l'ensemble, après étude des données scientifiques publiées à ce jour, la complexité de la cardiopathie congénitale représente un important facteur de risque d'événements thromboemboliques. Par conséquent, l'anticoagulation prophylactique est indiquée chez les patients ayant une cardiopathie congénitale complexe et de l'arythmie supraventriculaire, quelles que soient les autres facteurs de risque, contrairement aux patients ayant une cardiopathie congénitale simple. La population d'adulte congénitaux est en pleine évolution et des scores de risque thromboembolique spécifiques sont nécessaires, en particulier dans le cadre de cardiopathie congénitale simple et doivent être intégrés dans des essais spécifiques ou des suivis à long terme de cohorte multicentrique.

Background

As a result of technical improvements in cardiac surgery and the medical management of congenital heart disease (CHD), more than 85% of patients now reach adulthood [1,2]. However, most adults with CHD experience cardiovascular complications over the long-term, especially thromboembolic events. Cerebral infarction is the most common manifestation of thromboembolism in adult congenital heart disease (ACHD) [3,4]. Stroke rates in ACHD are significantly higher than in matched controls, reaching 0.5—1% per year of follow-up (i.e. 10-fold higher than in populations without ACHD) [3—5]. Stroke incidence (including transient ischaemic attacks) was also estimated to be 4% over a 5-year follow-up in the Euro Heart Survey, which included 4000 patients with ACHD [5].

Thromboembolic events significantly affect outcome in terms of morbidity and mortality. Stroke episodes usually lead to a high proportion of permanent neurological damage in the ACHD population (almost 25% in a study by Hoffmann et al. [3]). Moreover, recent data from two large ACHD registries showed that thromboembolisms accounted for up to 14% of mortalities [6—8]. Consequently, thromboembolic risk stratification and anticoagulation management are crucial in ACHD.

In this review, we aim to describe the factors associated with thromboembolism in ACHD, to identify patients at risk who require active management. We discuss the potential benefit of anticoagulation prophylaxis, and the risk stratification in this setting, according to the available literature.

Factors associated with thromboembolic events

The risk of thromboembolism has been studied in different cohorts. Results varied according to the study, depending on population size and study methods [3,4,9,10]. Importantly, the risk differed according to CHD type and complexity, with a high risk in patients with transposition of the great arteries, univentricular heart and cyanotic CHD (Table 1) [3,4]. Erythrocytosis consecutive to chronic cyanosis in cyanotic CHD induces blood hyperviscosity, which is associated with a higher risk of bleeding and thromboembolic events—both

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Table 1 Lifetime cumulative risk of thromboembolic events, according to main congenital heart defect [3,4].

Congenital heart defect	Risk of thromboembolic events[a]
Shunt[b]	+
Coarctation	+
Ebstein's anomaly	—
Tetralogy of Fallot	+
Transposition of the great arteries	++
Univentricular heart	++
Cyanotic	+++

[a] Thromboembolic event risk ≤ 1.5%; + 1.5% < thromboembolic event risk ≤ 3%; ++3 < thromboembolic event risk ≤ 5%: +++ thromboembolic event risk > 5%.
[b] Patent ductus arteriosus, atrial septal defect, ventricular septal defect or atrioventricular septal defect.

potentially life-threatening complications [11]. Indeed, thrombocytopoenia, platelet function abnormalities, disseminated intravascular coagulation, decreased production of coagulation factors, because of impaired liver function and vitamin K deficiency, and primary fibrinolysis have all been described in erythrocytosis [12—15]. Interventional sites (stents or grafts), frequent catheterization and residual lesions also increase the risk of thrombosis in ACHD [16—19]. Finally, persistent shunts, regardless of direction, and paradoxical emboli are related to an increased risk of stroke in this population [20].

In addition to the type of underlying heart defect, the occurrence of atrial arrhythmia is an important risk factor for thromboembolic events, whatever the CHD complexity [4] (Table 2). The prevalence of atrial arrhythmia in the ACHD population is increasing, currently reaching 15%, which is three times higher than that observed in the general population [21]. Among patients with complex CHD, up to 50% will experience atrial arrhythmia before the age of 65 years [21]. Intra-atrial re-entry tachycardia is the most common atrial arrhythmia in ACHD [22]. However, the prevalence of intracardiac thrombi in adults with CHD undergoing cardioversion for non-fibrillation atrial tachycardia has been reported as being up to 42% [23]. Furthermore, intra-atrial re-entry tachycardia is frequently associated with atrial fibrillation [24], and the predominant pattern of atrial arrhythmia is paroxysmal [22]. Consequently, atrial arrhythmia is associated with a twofold higher risk of stroke than in ACHD without atrial arrhythmia, with an incidence of 1—2% per patient-year [21]. However, this does not reflect the ''natural history'' of atrial arrhythmia in ACHD, as current thromboprophylactic management was practised in these studies, which may have led to an underestimation of the incidence of thromboembolism [9,25,26].

Other risk factors for thromboembolic complications are more common, and include recent myocardial infarction, diabetes mellitus, hypertension, cardiac surgery and heart failure (Table 2). As in the non-ACHD population, heart failure is highly predictive of stroke, especially among the youngest patients (odds ratio for the group aged 18—49 years 5.94, 95% confidence interval 3.49—10.14, in the study by Lanz et al.) [3,4,10], and is a severe complication associated with high morbidity and mortality in ACHD [6,27]. Thrombus formation, because of blood stasis, has been proposed as a

Table 2 Factors predictive of thromboembolic events studied in large series including > 1000 patient-years.

	Lanz et al. [4]	Heidendael et al. [9]	Mandalenakis et al. [10]	Hoffmann et al. [3]
Endocarditis	NS	NA	NA	NA
Atrial arrhythmia	NS	7.6 (0.90—55.60)	2.93 (1.78—4.83)	2.2
Recent myocardial infarction	8.38 (1.77—39.58)	NA	NA	25.1
Diabetes	2.33 (1.66—3.28)	NA	NS	NA
Heart failure	5.94 (3.49—10.14)	NS	6.94 (4.96—10.34)	NA
Hypertension	NS	NS	3.89 (2.44—6.22)	NA
Cardiac surgery (high risk)	NS	NA	NA	NA
Catheter intervention	NS	NA	NA	11.1
Pacemaker	NS	NS	NA	2.2
Vascular disease	NS	NS	NA	7.2
Pulmonary hypertension	NS	NS	NA	NA
Age > 55 years	NS	7.8	NA	NA
Chronic kidney disease	NS	NA	NA	NA

Data are expressed as odds ratio (95% confidence interval) or proportion. NA: not applicable (data could not be extracted from the study); NS: not significant.

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mechanism of stroke in patients with heart failure [28]; neuroendocrine and haemorheological abnormalities have also been suggested [29]. Nevertheless, atrial arrhythmia is frequently associated with heart failure, and is underdiagnosed because of the asymptomatic hallmark [30]. This overlap between atrial arrhythmia, heart failure and stroke has also been observed in ACHD [4,31], underlying the importance of atrial arrhythmia in the natural history of ACHD.

Thromboembolic event risk assessment in ACHD with atrial arrhythmia

How underlying structural CHD, in addition to the associated factors discussed above, should be considered together to allow the best estimate of thromboembolic risk remains unclear. Making a decision about thromboprophylaxis in ACHD with atrial arrhythmia is challenging. The risk of thromboembolic events and bleeding must be evaluated in atrial arrhythmia management, and must be individually weighed [32].

The CHA_2DS_2-VASc composite score (Congestive heart failure, Hypertension, Age $\geq$ 75 years [Doubled], Diabetes, Stroke/transient ischaemic attack/thromboembolism [Doubled]—Vascular disease, Age 65—74 years and Sex category [Female]) is used to estimate an annual thromboembolic risk; it is the most commonly used and recommended thromboembolic risk stratification tool in atrial fibrillation [33]. Oral anticoagulant therapy is recommended when the CHA_2DS_2-VASc score is $\geq$ 2. Although scores are simple and easy to use, they have limited predictive accuracy [34]. Nevertheless, the extent to which such a score may be applicable to the specific ACHD population is unclear.

As an illustration, among others, in a retrospective study including 229 patients with ACHD with atrial arrhythmia from the nationwide CONCOR registry, a CHA_2DS_2-VASc score $\geq$ 2 was associated with a near fourfold increased thromboembolic risk [9]. However, the cut-off value for age was most predictive at $\geq$ 55 years in the ACHD population (hazard ratio 7.8), rather than the usual cut-off at 65 years in the CHA_2DS_2-VASc score. A study in Japan showed that thromboembolic events occurred even in patients with a low or intermediate risk, as indicated by the $CHADS_2$ score (Congestive heart failure, Hypertension, Age $\geq$ 75 years, Diabetes, Stroke/transient ischaemic attack/thromboembolism [Doubled]) or the CHA_2DS_2-VASc score [26]. Recently, a retrospective cohort study from 12 North American centres, which enrolled 482 patients with ACHD with documented sustained atrial arrhythmia, showed that freedom from thromboembolic events was 84.7 $\pm$ 2.7% at 15 years [25]. Again, the $CHADS_2$ and CHA_2DS_2-VASc scores were not predictive of thromboembolic event risk, and CHD complexity was the only factor independently associated with thromboembolic events. The authors proposed the inclusion of CHD complexity in the CHA_2DS_2-VASc score. However, this did not adequately predict residual thromboembolic event risk in the study model. As discussed above, CHD complexity may be an important risk factor for thromboembolic events. In 2015, Jensen et al. recommended anticoagulation therapy in patients with previous intracardiac repair, cyanosis, Fontan palliation or systemic right ventricle, despite a CHA_2DS_2-VASc score of 0 [35].

Alternative strategies to prevent thromboembolism in ACHD

In historical trials, involving non-ACHD populations, the use of vitamin K antagonists (VKA), such as warfarin, was significantly associated with a reduction in thromboembolic events of about 64% [36]. Warfarin has many limitations, including a narrow therapeutic range, delayed onset and offset of action, numerous drug and food interactions, significant pharmacogenetic variations, and the need for intensive monitoring to ensure effective and safe anticoagulation.

Non-VKA antagonist oral anticoagulants (NOACs) have emerged as therapeutic alternatives for stroke prevention in patients with non-valvular atrial fibrillation, and are more efficacious and safe than VKAs, with fewer intracranial bleedings [37—40]. The two prospective observational studies on the use of NOACs in patients with ACHD were published in 2016 and 2017 [41,42]. In the first registry [41], 75 patients with ACHD were included, and the main indication for anticoagulation was prevention of thromboembolic event in atrial arrhythmia (76%). These studies showed that NOACs were effective, with frequent mild side-effects, such as minor bleedings (47%), but few complications. Recent guidelines have promoted NOAC use in ACHD [43], whereas the Pediatric and Congenital Electrophysiology Society (PACES)/Heart Rhythm Society (HRS) expert consensus statement limited NOAC use to ACHD with simple complexity [44], and did not recommend it in other ACHD groups, particularly patients with Fontan circulation [45]. Indeed, one of the first cases of thrombosis in a patient with Fontan circulation on apixaban suggested that apixaban at usual doses is ineffective in preventing thrombus formation in this setting [46]. Furthermore, impaired renal function is common in ACHD [47], and particular attention should be paid before initiation of NOAC treatment.

More recently, left atrial appendage occlusion has been shown to be a viable alternative to anticoagulation, in case of significant contraindication. So far, no specific study has been performed in ACHD.

Evaluation of the bleeding risk

ACHD is a population of patients who are more likely to experience bleeding, making the decision process particularly challenging. Anticoagulation was independently associated with a fourfold higher risk of bleeding in ACHD, while antiplatelet drugs exhibited an annual major bleeding rate that was 10 times lower than the rates with VKAs [25]. These results are consistent with meta-analyses comparing VKAs with aspirin in the general population [48]. Before initiating anticoagulation therapy in atrial fibrillation, the individual risk of bleeding must be estimated using the HAS-BLED score [49], which assigns 1 point for the presence of each of the following bleeding risk factors: hypertension (H), abnormal renal and/or liver function (A), previous stroke (S), bleeding history (B), labile international normalized ratio (L), elderly (E) and concomitant drugs and/or alcohol excess

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(D). A score ≥ 3 indicates a high risk of bleeding, especially intracranial haemorrhage. The HAS-BLED score is the most widely applied tool for predicting bleeding complications [50].

From the CONCOR registry, a major bleeding rate of 10.8% per year was found in patients treated with VKAs with a HAS-BLED score ≥ 2, compared with 3.5% in patients with a score < 2 (hazard ratio 2.6, 95% confidence interval 1.1—6.6; $P = 0.017$) [9]. Similarly, Khairy et al. found an association between major bleedings and the HAS-BLED score in a retrospective multicentre ACHD cohort [25]; there was no association between CHD complexity and major bleedings. Therefore, the HAS-BLED score could reasonably be extended to the ACHD population.

Two specific ACHD conditions

Cyanotic CHD

The occurrence of thromboembolic complications is particularly common in cyanotic CHD [3]. In a recent study, the prevalence of stroke reached 47%, with a high prevalence of silent thrombotic events, and a pulmonary thrombosis prevalence of 31% [51]. These rates are twice as high as those reported previously [52—54], because of the use of advanced diagnostic imaging techniques (magnetic resonance imaging, multidetector computed tomography and/or pulmonary scintigraphy).

Prophylactic phlebotomies were once believed to diminish haematocrit values and, consequently, prevent cerebrovascular events. However, this link has not been proven, whereas microcytosis secondary to repeated phlebotomies is a known independent risk factor for thromboembolic stroke [52,54]. Indeed, iron-deficient red blood cells are less deformable and increase blood viscosity, promoting thrombus formation [55].

Pulmonary thrombi are also frequent in cyanotic CHD, and may arise from multiple factors, such as local vascular injury in pulmonary hypertension, hypercoagulability and sluggish flow in the pulmonary arteries, and aneurysmal arteries can contribute to stasis and mural thrombus formation [56]. Among adults with Eisenmenger's syndrome, pulmonary thrombi have a high prevalence (20%, 95% confidence interval 10—33%), and relate to older age, biventricular dysfunction and slow pulmonary artery blood flow, rather than importance of right-to-left shunt (meaning lower oxygen saturation), degree of secondary polycythaemia or coagulation abnormalities [57].

The potential role of anticoagulation treatment for primary prevention is controversial. In retrospective studies there is no difference in thrombosis incidence between patients with Eisenmenger's syndrome with and without anticoagulation [51,58]. Moreover, the risk of bleeding is also increased in these patients as a result of impaired liver function, reduced platelet count and platelet dysfunction. Some studies have also shown impairment in synthesis and function of clotting factors, which may contribute to both hypocoagulability and hypercoagulability [14]. Patients with cyanotic CHD and elevated haematocrit are hypocoagulable, as a result of impaired clot formation and strength, mainly because of impaired fibrinogen function despite a high level of plasma fibrinogen [59]. Haematocrit reduction seems to improve the haemostatic profile, and might stop bleeding [14].

Fontan circulation

Thromboembolic complications in patients with Fontan circulation are frequent, with a thromboembolism prevalence of 10—25% after a mean follow-up of 10 years [60—62]. However, thrombi are very often asymptomatic, leading to an underestimation of prevalence [63—66]; their locations are most commonly non-systemic, defined as Fontan conduit/right atrial thrombus or pulmonary embolism [61].

The cause of death of patients with Fontan circulation is usually multifactorial, and development of protein-losing enteropathy, ventricular failure, liver disease and arrhythmias are associated with an increased mortality rate [67,68]. However, all these factors promote thromboembolism formation which is a serious cause of late mortality (up to 25% in a study by Khairy et al.) [69].

In Fontan circulation, atrial arrhythmia is strongly associated with thromboembolic complications. This was observed in a retrospective study at the Mayo Clinic [63], which included 278 patients with atrial arrhythmia; the authors found an overall thromboembolic complication prevalence of 29%, and a thromboembolic event incidence of 6.5 per 100 patient-years. Most patients were asymptomatic at the time of thromboembolism diagnosis.

Another major risk factor for thromboembolic complications is the Fontan procedure with atriopulmonary connection [61]. A recent study exploring mechanisms of thrombus formation in the Fontan pathway using two-dimensional computer haemodynamic simulation demonstrated that the atriopulmonary connection model had the highest incidence of thrombus formation compared with total cavopulmonary models, because of slower blood flow at rest and significant blood flow stagnation in the atrium [70].

Moreover, haematological abnormalities may contribute to thrombus formation in Fontan circulation. A few studies have shown prothrombotic endothelial activation, including increased circulating levels of von Willebrand's factor, factor VIII and soluble thrombomodulin, as well as platelet activation, abnormal concentrations of procoagulant and anticoagulant factors (such as a decrease in protein C and protein S) in Fontan, creating a paradoxical increase in bleeding risk and clotting risk [71—74].

D-dimer is the most useful biomarker to screen and diagnose deep vein thrombosis and pulmonary embolism, with a high negative predictive value in the general population [75]. The detection of thrombus in patients with Fontan circulation is important for considering anticoagulation therapy. One recent study focused on 122 patients, and found 1800 μg/L to be the optimal cut-off for screening thrombus in Fontan circulation [73]. As expected, D-dimer concentration showed a better performance in ruling out thrombus than in detecting it (a negative predictive value of 95% versus a positive predictive value of 70%).

The question of anticoagulation in these patients has been a matter of debate for decades. A meta-analysis in 2015 showed a significantly lower incidence of thromboembolism after the Fontan procedure when aspirin or

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warfarin was used [76]. However, no significant difference was found in the incidence of early or late thromboembolism in patients receiving aspirin compared with warfarin. Importantly, the use of anticoagulant therapy was associated with a lower risk of thromboembolic complications compared with antiplatelet therapy alone for adults with atrial arrhythmia after a Fontan operation [63].

Conclusions

Thromboembolic complications are common in ACHD, and are associated with high morbidity and mortality rates in this population. Atrial arrhythmia is an important risk factor for thromboembolism. However, the underlying heart disease structural complexity principally drives this risk, and should probably be considered as the cornerstone for thromboembolic risk stratification. Accordingly, the traditional CHA_2DS_2-VASc score seems to be of limited value in the ACHD population. Prophylactic anticoagulation therapy is important to consider early, especially in patients with atrial arrhythmia and complex CHD. Because the bleeding risk is increased in ACHD, the individual risk of bleeding must also be estimated before initiating anticoagulation therapy; the HAS-BLED bleeding score seems suitable for estimating this risk in ACHD. Finally, new oral anticoagulation can be used in patients with mild-to-intermediate CHD complexity. However, further larger studies are required to confirm the safety and efficacy of this treatment in this population.

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Disclosure of interest

The authors declare that they have no competing interest.

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