

Thrombotic and Thromboembolic Complications in Patients With Adult Congenital Heart Disease

Behnood Bikdeli ^{1,2,*}, Phillip Green ¹, Matthew J. Lewis ¹, Marlon S. Rosenbaum ¹

¹ Division of Cardiology, Department of Medicine, Columbia University Medical Center, New York-Presbyterian Hospital, New York, USA

² Center for Outcomes Research and Evaluation, Yale University School of Medicine, New Haven, USA

* Corresponding author: Behnood Bikdeli, Church Street, Suite 200, New Haven, USA. Tel: +203-7645653, E-mail: bb2813@cumc.columbia.edu; behnood.bikdeli@yale.edu

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Abstract

Improved medical and surgical interventions have increased the longevity of patients with congenital heart defects and most such patients live into adulthood. Thrombotic and thromboembolic complications constitute a major cause of mortality and morbidity in patients with adult congenital heart disease (ACHD). Such events include acute coronary syndromes, ischemic stroke (cardioembolic due to thrombus formation in the systemic ventricle, secondary to atrial arrhythmias, or due to paradoxical embolism), and venous thromboembolism. Some thrombotic phenomena are also specific to patients with ACHD, such as those related to Fontan circulation. We provide a succinct overview of thrombotic and thromboembolic complications in patients with ACHD, focusing on stroke and venous thromboembolic events.

INTRODUCTION

Thrombosis and thromboembolism are the most common etiology for acute coronary syndromes, stroke, and venous thromboembolism (VTE) and thereby considered as the leading cause of death worldwide [1, 2]. With remarkable improvements in medical and surgical care to patients with congenital heart disease, many of them now survive into adulthood [3]. In fact, the number of patients with adult congenital heart disease (ACHD) now exceeds that of the pediatric population. Increased longevity and several biological factors (including increased thrombogenicity) [4, 5], pathophysiological factors (such as increased risk of atrial arrhythmias) [6] and iatrogenic factors (such as Fontan physiology) puts this growing population at increased risk of thrombotic and thromboembolic complications including VTE, stroke, and acute coronary syndromes [7] (Fig 1). Despite commonness of these phenomena, and the growing burden of ACHD, however, there remains a paucity of data on epidemiology, prognostication and management approach for these patients.

The significance of such thrombotic complications also led to release of a scientific statement by the American heart association (AHA) on thrombosis prevention and treatment in patients with congenital heart disease [8]. Although patent foramen ovale (PFO) with or without precedent stroke is an important clinical scenario, we opted to exclude that population from the current review. Further, acute coronary syndrome in patients with ACHD is an emerging topic with

potential distinct association with certain syndromes [9]. In the current mini-review, we chose to focus on broad aspects of thrombosis and thromboembolic risk related to VTE and stroke in patients with ACHD. We highlight the areas that require urgent research attention.

ISCHEMIC STROKE

Acute ischemic stroke, most often of embolic nature, may occur in several patient subsets with ACHD [12]. Embolic stroke in such patients may have various etiologies including thrombus formation and embolization from a dysfunctional systemic ventricle, left atrial appendage thrombus formation in the setting of atrial fibrillation (AF)/ flutter, or paradoxical embolism via a right-to-left shunt.

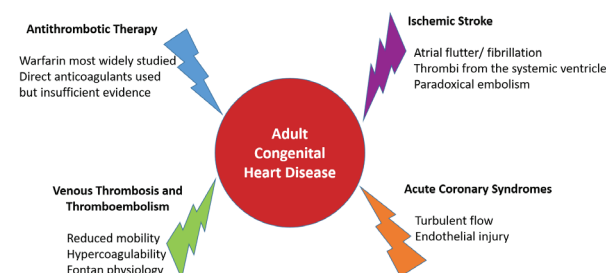


Figure 1: Major Thrombotic and Thromboembolic Presentations in Patients with Adult Congenital Heart Disease

Table 1: Select Set of Recommendations From the AHA Scientific Statement on Prevention and Treatment of Thrombosis in Patients With Congenital Heart Disease^a

Setting	AHA Recommendation	Comment
Congenital Heart Disease and AF or Atrial Flutter	Warfarin therapy is recommended	NOACs have been empirically used but not formally tested in randomized trials. (We need additional studies to better identify the subgroups who are at highest risk of thromboembolic events.)
Fontan Circulation	Warfarin is recommended if patients have documented atrial thrombus, atrial arrhythmia, or a thromboembolic episode.	A study of 111 patients with Fontan surgery did not show a difference in the rate of thromboembolic events among patients randomized to warfarin compared with aspirin [10]. A subsequent analysis from the study, however, showed that patients achieving target INR, or those receiving aspirin, had lower thromboembolic events compared with those would had a subtherapeutic INR [11]. Better risk profiling of these patients and identification of optimal antithrombotic strategies are required.

^a Abbreviations: AF, atrial fibrillation; AHA, American heart association; INR, international normalized ratio; NOAC, non-vitamin K oral anticoagulant.

There are subsets of ACHD that are proposed to have an elevated risk of thrombosis, including those with cyanotic defects. For example, although a prior study of cyanotic patients had not revealed evidence of clinical stroke in 112 participants [13], another study of 162 patients with cyanotic congenital heart disease reported cerebrovascular events in 13.6% of patients [14]. More recently, a study of 98 patients with cyanotic congenital heart disease from Sweden reported imaging evidence of cerebral infarction in nearly half of participants. It is important to note that many of these neurologic events were diagnosed by imaging and were not associated with symptoms or clinical sequelae [15].

Despite the clinical rationale for increased thrombosis risk in many ACHD patients, in the absence of large studies specific to patients with ACHD, the evidence for antithrombotic therapy is extrapolated from data in broader cohort of patients. Generally, antiplatelets agents are employed for secondary prevention in acute cryptogenic stroke while anticoagulation is utilized for treatment of systemic ventricular thrombosis or paradoxical embolism from VTE. Of note, while anticoagulation is used in the setting of AF/Aflutter for patients with ACHD, the CHA₂DS₂-VASc score has not been specifically validated in this population. In one study, among patients with ACHD and atrial arrhythmias, congenital heart disease complexity, but not the CHA₂DS₂-VASc score, was predictive of subsequent thromboembolic events [16]. As such, multicenter research delineating thrombosis risk in the setting of AF/Aflutter in the ACHD population is warranted.

VENOUS THROMBOEMBOLISM (VTE)

Patients with ACHD may have specific factors that increase the risk of VTE [12]. In addition to thrombophilias that may be seen in some subsets of patients with ACHD, VTE risk may also be related to limited mobility, particularly in patients with class III or IV symptoms. Additionally, VTE in patients with ACHD could be due to specific hemodynamic and flow patterns, such as those with Fontan physiology. Patients with ACHD and Fontan physiology are a special subset, with increased risk of stroke, as well as embolic events from the right-sided structures, causing PE [17]. Studies have suggested an increased risk of thrombotic events and death in

patients who do not receive any antithrombotics [18]. Based on these, the consensus recommendation is to consider anticoagulation for patients with Fontan physiology, particularly if they have coexisting atrial arrhythmias, a history of prior embolic events, or evidence of poor venous flow [17]. However, choice of treatment varies across institutions with anticoagulation and aspirin both frequently used. While warfarin is the most frequently employed anticoagulant there is emerging data regarding the use of non-vitamin K oral anticoagulants in the adult Fontan patients [19, 20]. Randomized trials are necessary to determine both the choice of agent and the appropriate timing of anticoagulation.

CONCLUSIONS

In addition to hemodynamic, arrhythmic, and infectious complications, patients with ACHD are at significant risk for thrombotic and thromboembolic conditions. Clinicians should be mindful of thrombotic complication in patients with ACDH and consider appropriate diagnostic and therapeutic approaches. Further research is required to identify the highest-risk subgroups, and to test strategies that could safely mitigate the thrombotic/thromboembolic risk.

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