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Comparison of Congenital Cardiac Surgery Techniques through the Development of National and International Cohorts

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Comparison of Congenital Cardiac Surgery Techniques through the Development of National and International Cohorts

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Résumé

Plusieurs avancées exceptionnelles ont permis à un nombre grandissant d'enfants avec pathologies cardiaques complexes d'atteindre l'âge adulte. Ainsi, plus de patients développent maintenant des complications en lien avec leur maladie ou leurs antécédents chirurgicaux. Malheureusement, en raison de nombreux obstacles limitant la recherche en cardiopathie congénitale adulte, un écart de savoir perdure et freine l'optimisation des soins. En attendant le couplage de grands registres pédiatriques et adultes facilitant l'accès aux données existantes, les projets multicentriques indépendants demeurent essentiels. Cette thèse présente deux études multicentriques de cohorte comparant des techniques opératoires couramment utilisées dans le traitement de pathologies congénitales cardiaques complexes dans le but de promouvoir la santé des patients à long terme.

La première étude visait à évaluer l'impact chronique du type de procédure de Fontan sur le risque thromboembolique. Pour ce projet nord-américain, 522 patients avec connexion atriopulmonaire (21.4%), tunnel latéral (41.8%) ou conduit extracardiaque (36.8%) ont été recrutés. À l'aide d'analyses multivariées contrôlant pour la décennie opératoire et les effets variables dans le temps de l'arythmie et de la thromboprophylaxie, l'étude a conclu à un plus faible risque de complications thromboemboliques systémiques (rapport des risques instantanés [RRI] : 0.20 ; intervalle de confiance [IC] à 95% : 0.04-0.97) et combinées (RRI : 0.34 ; IC à 95% : 0.13-0.91) avec le conduit extracardiaque. Ces résultats remettent en question la croyance populaire selon laquelle cette technique serait plus thrombogène en raison d'un grand contact avec du matériel synthétique et d'un débit limité par le calibre fixe du greffon.

La deuxième étude avait pour but d'investiguer, auprès de patients avec tétralogie de Fallot ou sténose pulmonaire corrigée nécessitant une implantation de valve pulmonaire, l'efficacité immédiate et l'innocuité d'une intervention concomitante sur la valve tricuspide. Pour ce projet pancanadien, 542 patients ayant subi un remplacement isolé de la valve pulmonaire (66.8%) ou une chirurgie combinée des valves pulmonaire et tricuspide (33.2%) ont été enrôlés. À l'aide d'analyses multivariées, cette étude a révélé que la chirurgie combinée était

associée à une plus grande réduction du grade de régurgitation tricuspidienne qu'un remplacement isolé de la valve pulmonaire (rapport de cotes [RC] : 0.44 ; IC à 95% : 0.25-0.77) sans une augmentation des complications périopératoires (RC : 0.85 ; IC à 95% : 0.46-1.57) ou du temps d'hospitalisation (ratio du taux d'incidence : 1.17 ; IC à 95% : 0.93-1.46). Ces résultats questionnent la pertinence d'une gestion conservatrice de l'insuffisance tricuspide sévère. De plus, ils confirment qu'une procédure ciblée peut améliorer de façon sécuritaire la fuite modérée au-delà de l'effet produit par la décharge du ventricule – une stratégie potentiellement avantageuse auprès de jeunes patients déjà à haut risque de défaillance cardiaque droite.

En conclusion, avec une puissance statistique plus élevée que les études précédemment publiées, ces travaux ont permis une comparaison valide et pertinente de techniques opératoires couramment utilisées en chirurgie cardiaque congénitale, ce qui influencera possiblement la pratique. Ultimement, cette thèse souligne l'importance de promouvoir la collaboration afin de répondre aux besoins émergents des patients avec pathologies congénitales cardiaques complexes.

Nombre de mots : 498 mots.

Mots-clés : chirurgie cardiaque congénitale, cœur univentriculaire, procédure de Fontan, maladie thromboembolique, arythmie atriale, thromboprophylaxie, tétralogie de Fallot, régurgitation tricuspidienne, plastie de la valve tricuspide, remplacement de la valve tricuspide.

Abstract

Outstanding technical advances have made possible for a growing number of infants with complex heart disease to survive into adulthood. Consequently, more patients are now living long enough to experience late complications related to their underlying pathology or sequelae from past interventions. However, due to the inherent challenges of carrying research in adult congenital heart disease, important knowledge gaps prevent further optimization of care. Waiting on broad linkage of pediatric and adult databases to facilitate access to data, stand-alone multicenter research initiatives remain essential. The current body of work presents two multicenter cohort studies which were designed to help improving the long-term health of patients with complex heart disease through a comparison of common operative techniques.

The first study sought to evaluate the chronic impact of Fontan surgery type on the thromboembolic risk. This North American cohort enrolled 522 patients with univentricular palliation consisting of an atriopulmonary connection (21.4%), lateral tunnel (41.8%) or extracardiac conduit (36.8%). In multivariable analyses stratified by surgical decade and controlling for the time-varying effects of atrial arrhythmias and thromboprophylaxis, extracardiac conduits were independently associated with a lower risk of systemic (hazard ratio [HR]: 0.20 vs. lateral tunnel; 95% confidence interval [CI]: 0.04-0.97) and combined (HR: 0.34 vs. lateral tunnel; 95% CI: 0.13-0.91) thromboembolic events. These results cast doubt on the widely held notion that extracardiac conduits are potentially more thrombogenic than lateral tunnels by virtue of greater exposure to synthetic material and relative flow restriction through a fixed pathway.

The second study investigated, in patients with repaired tetralogy of Fallot or equivalent disease undergoing a first pulmonary valve implant, the early effectiveness and safety of concomitant tricuspid valve intervention. This pan-Canadian cohort included 542 patients who underwent isolated pulmonary valve replacement (66.8%) or combined pulmonary and tricuspid valve surgery (33.2%). In multivariable analyses, combined surgery was associated with a greater reduction in tricuspid regurgitation grade than isolated pulmonary valve replacement (odds ratio [OR]: 0.44; 95% CI: 0.25-0.77) without an increase in early adverse events (OR:

0.85; 95% CI: 0.46-1.57) or hospitalization time (incidence rate ratio: 1.17; 95% CI: 0.93-1.46). These results strongly question the appropriateness of conservative management of severe tricuspid regurgitation at the time of pulmonary reintervention. Furthermore, they confirm that concomitant tricuspid valve intervention can safely improve moderate insufficiency beyond the effect of right ventricular offloading – a strategy likely worthwhile to adopt in a population of young adults already at high risk of right heart failure.

In conclusion, with higher statistical power than previously published studies, the presented body of work allowed for a valid comparison of common surgical techniques used in congenital cardiac care, which will likely impact current practices. Ultimately, this thesis underlines the importance of fostering collaboration in order to meet the emerging health needs of patients with complex heart disease.

Word count: 461 words

Keywords: congenital cardiac surgery, univentricular heart, Fontan procedure, thromboembolism, atrial arrhythmia, thromboprophylaxis, tetralogy of Fallot, tricuspid regurgitation, tricuspid valve repair, tricuspid valve replacement.

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List of Abbreviations and Acronyms

4C	Canadian Congenital Cardiac Collaborative
AARCC	Alliance for Adult Research in Congenital Cardiology
ACC	American College of Cardiology
AHA	American Heart Association
Ao	Aorta
APC	Atriopulmonary connection
ASA	Aspirin
CI	Confidence interval
CIHR	Canadian Institutes of Health Research
CPB	Cardiopulmonary bypass
EC	Extracardiac conduit
ECG	Electrocardiography
FRQ-S	Fonds de recherche du Québec en santé
HR	Hazard ratio
IQR	Interquartile range
IRR	Incidence rate ratio
IVC	Inferior vena cava
LPA	Left pulmonary artery
LT	Lateral tunnel
LV	Left ventricle/ventricular
MHICC	Montreal Health Innovations Coordinating Center
MPA	Main pulmonary artery
N/A	Not applicable
N/S	Not significant
NYHA	New York Heart Association
OR	Odds ratio
P-y	Person-years

PR	Pulmonary regurgitation
PS	Pulmonary stenosis
PV	Pulmonary valve
PVR	Pulmonary valve replacement
PVR+TVI	Pulmonary valve replacement with concomitant tricuspid valve intervention
RA	Right atrium
RCT	Randomized controlled trial
RPA	Right pulmonary artery
RR	Relative risk
RV	Right ventricle/ventricular
SCOTIA-PVR	Surgical Correction Of Tricuspid Insufficiency in Adult congenital patients requiring Pulmonary Valve Replacement
SD	Standard deviation
SVC	Superior vena cava
TACTIC	The Anti-Coagulation Therapy Initiative in Congenital heart disease
TEE	Thromboembolic event
TTE	Transthoracic echocardiography
TOF	Tetralogy of Fallot
TR	Tricuspid regurgitation
TV	Tricuspid valve
TVI	Tricuspid valve intervention
VSD	Ventricular septal defect

À mes parents,

*qui n'attendront certainement pas de comprendre
l'anglais avant d'encenser ce travail.*

Je vous aime.

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Introduction

"[Patients with congenital heart disease] need [ongoing] expert care to optimize the quality of their lives and to help them to avoid premature death. […] The promises offered to them as children must also be honoured in their adult years." [1; p.833] --- Dr. Gary D. Webb

Changing Prevalence of Congenital Heart Disease

Cardiac anomalies represent, in high-income countries, the most common, deadly and costly type of major congenital malformations [2-4]. In Canada and the United States, we estimate their occurrence between 7 and 9 cases per 1,000 live births [5-7], resulting in approximately 40,000 new diagnoses a year [8,9]. Of that number, a third of affected newborns display a complex lesion such as tetralogy of Fallot, a univentricular heart, transposition of the great arteries, truncus arteriosus, or an endocardial cushion defect [5].

Until the 1950s, a diagnosis of complex heart disease was universally fatal. Fortunately, due to remarkable advances in prenatal screening and pediatric surgical care, early deaths are becoming infrequent. Between 1987 and 2005, a population-based study from Quebec [10] concluded in a 67% reduction in the mortality risk of infants born with severe heart disease. During the same period, this gain translated into an increase in their median age of death from 2 to 23 years. Nowadays, we expect that over 80% of infants operated for a complex defect will reach adulthood [11,12].

These extremely encouraging results are causing a major demographic shift (Figure 1). Once seen as a problem of the young, congenital heart disease is becoming increasingly prevalent in adults. This trend is particularly obvious among those living with a severe lesion. For instance, between 1985 and 2010, there was a 3-fold increase in the prevalence of complex defects reported among patients over the age of 18 [13,14]. In 1985, 60% of those with a severe lesion were minors. In contrast, by 2010, adults surpassed children by a ratio of 2:1. We currently estimate that over 1.7 million adults are living in North America with a congenital heart disease, 10% of whom (≈ 170,000) are dealing with a complex defect surgically corrected during infancy [14,15].

Figure 1. Demographic shift in the population living with congenital heart disease

Histogram bars depict the proportion of Quebecers with congenital heart disease who died in 1987-1988 (left x-axis) and 2004-2005 (right x-axis) according to age at death (y-axis). Bold black curves represent the same distributions in the full population of Quebec. This figure shows a significant increase in the proportion of patients with congenital heart disease surviving to adulthood and a life expectancy approaching that of the general population. Reproduced from Khairy et al. with permission from Elsevier [10; p.1153].

Late Complications in Repaired Congenital Heart Disease

In recent years, follow-up of this growing population revealed that surgery, no matter how successful, does not imply cure. Patients surviving long enough invariably experience complications related to their underlying pathology or sequelae of therapeutic interventions. Leading causes of morbidity and mortality among adults with congenital heart disease include arrhythmia, heart failure, thromboembolic events, endocarditis and repeated surgeries.

Atrial arrhythmia is present in about 15% of patients [16] and accounts for the majority of unscheduled hospitalizations [17]. Its burden is especially high among those with complex disease. For instance, we estimate the 20-year cumulative incidence of atrial arrhythmia in a 65-year-old from the general population around 18% [18]. Among those with congenital heart disease, this risk equals that of a of 40-year-old with a simple lesion, and that of a 20-year-old with a complex repair [16]. Sinus node dysfunction and atrioventricular block can also result from a malformation of the conduction system or surgery [19]. These conditions may require pacemaker insertion at a young age, which, in turn, correlates with excess lead failure and revision [20-22]. Sudden death secondary to sustained ventricular arrhythmia is rather uncommon. However, its incidence also increases with disease severity [23]. Adults with corrected tetralogy of Fallot, for example, display more than 50 times the risk of age-matched controls [23-25]. Such data can be extremely daunting for patients and their family.

Heart failure is the primary mode of death among those with complex disease [26-28]. While residual lesions causing hemodynamic stress often precede its onset, we now recognize that several cell-signalling pathways responsible for gross malformations may also trigger the abnormal development of coronaries, myocytes and conduction tissue fibers [29,30]. These microscopic changes can further compromise ventricular function. The complex interactions between genetic and acquired factors may explain why, in many cases, heart failure fails to respond to conventional therapies [31].

Thromboembolic events, such as strokes, are diagnosed at least 10 times more frequently in those with congenital heart disease than in the general population [32,33]. A low flow state is particularly conducive to the formation of blot clots. After Fontan palliation, for example, thromboembolic complications are reported in up to 20% of young adults [34] and account for

1 in 4 late deaths [35]. The incidence of endocarditis is also high [36]. In patients with a corrected defect, infections often occur in the presence of prosthetic material [37,38] or persistent shunts [39]. Reoperation is the third leading cause of death among adults with complex disease [28]. While many redo procedures performed electively seem to yield excellent results [40], surgeries such as Fontan conversions and transplantations remain high-risk and continue to disproportionally contribute to the death toll [28,40].

Overall, late complications generate high healthcare resource utilization and costs. We report, in adults with congenital heart disease, a risk of hospitalization 2 to 3 times that of the general population [41,42]. In North America, this translates annually into an extra 20,000 admissions and 500 million dollars in health spending [41,43,44].

Challenges in Optimizing Care

The emerging burden of late complications in adults with congenital heart disease provides a huge incentive to optimize care. Since the late 1990s, Canada has been at the vanguard of the management of these patients. The Canadian Adult Congenital Heart Network, supported by the Canadian Cardiovascular Society, was among the first associations to promote governmental awareness, advocate for optimal resource allocation and publish clinical guidelines on the matter [45-52]. More specific recommendations were then issued by American Heart Association/ American College of Cardiology (AHA/ACC) [53-59] and the European Society of Cardiology [60,61].

While guidelines have greatly contributed to standardizing the provision of care for adults, they, unfortunately, continue to rely on weak scientific evidence. The 2008 AHA/ACC guidelines, for instance, included 513 recommendations, from which more than 65% were based on expert opinion, small unadjusted studies or extrapolation from data on acquired disease (level C evidence) [59]. In 2018, the same working group released an update. In this heavily simplified version containing only 179 recommendations, more than 50% of the contents remained of level C evidence [58]. Furthermore, from the perspective of a surgeon, current guidelines incorporate very little data pertaining to intraoperative decision-making.

This paucity of high-quality evidence poses a real threat to the health of patients. There are, however, numerous challenges in closing this knowledge gap [62]. Cardiac malformations represent rare and very heterogeneous conditions. It is, therefore, inherently difficult to gather large enough samples to generate powered analyses. Many complex lesions were also historically described using various nomenclature and classification systems. This confusing language now limits our ability to effectively retrieve and combine data [63]. Another important challenge is that outcomes of interest in adults often occur long after treatment exposure. In many cases, prolonged latency precludes the use of high-quality prospective designs such as randomized controlled trials [64].

Over the last decade, several North American registries and databases were created with the hope to overcome some of these barriers [65]. A common observation is, however, that large datasets often miss the granularity required to produce comparative, as opposed to descriptive, research [65-67]. For example, more adults undergoing congenital cardiac procedures are entered in the Society of Thoracic Surgeons' Adult Cardiac Surgery Database than in its congenital equivalent [68]. This unfortunately results in most of the patients' pediatric history being lost. While broad linkage between datasets is certainly possible and desirable [69,70], many regulatory and contracting issues prevent comprehensive integration of data [67]. Waiting for this important issue to be solved, stand-alone multicenter observational projects remain the main driving force behind comparative research in adult congenital care [64].

Purpose and Relevance of the Thesis

In this context, the general aim of the thesis was to compare operative techniques used in congenital cardiac surgery through the development of large multicenter retrospective cohort studies. More specifically, the goal was to identify, among studied procedures, the ones most likely to minimize the risk of late complications in teenagers and young adults with complex disease.

In greater details, the first specific aim of the thesis was to evaluate the association between Fontan surgery type and the long-term risk of thromboembolic events (objective 1). As previously stated, thromboembolic complications represent one of the leading cause of death after univentricular palliation [35]. A common belief is that certain operative techniques may prevent, while other may aggravate, thrombosis by virtue of their design [71,72]. However, given a paucity of evidence, the topic remains extremely controversial. An international cohort study was proposed as a way to bridge this important knowledge gap.

The second specific aim was to evaluate, in adults with previously corrected tetralogy of Fallot or pulmonary stenosis, the early safety (objective 2) and effectiveness (objective 3) of combined pulmonary and tricuspid valve surgery. Pulmonary valve disruption, severe regurgitation and chronic right ventricular volume overload often occur following pediatric repair and, unfortunately, trigger late reoperation in a majority of adults [73]. Tricuspid annular dilatation and functional insufficiency are commonly associated lesions [74,75]. While some surgeons have taken a rather aggressive stand towards concomitant correction of tricuspid insufficiency, others remain reluctant to address the issue by fear that an additional procedure may increase operative risk and lengthen the recovery of patients, without necessarily improving valvular competence beyond the effect of right ventricular offloading. A national cohort study was, therefore, designed and conducted to explore each of these concerns.

Outline of the Thesis

The following body of work includes four chapters. Chapter 1 summarizes the state of knowledge surrounding each of the previously listed research objectives. Chapter 2 describes the methodology of the national and international cohort studies conducted to meet these objectives. Chapter 3 presents obtained results in the form of 2 scientific articles.

The first article entitled "Thromboembolic Risk After Atriopulmonary, Lateral Tunnel, and Extracardiac Conduit Fontan Surgery", was published in the *Journal of the American College of Cardiology* on August 27, 2019 (objective 1) [76].

The second article entitled "Tricuspid Intervention Following Pulmonary Valve Replacement in Adults With Congenital Heart Disease" was published in the same journal on March 10, 2020 (objectives 2 and 3) [77].

Finally, chapter 4 discusses the strengths and limitations, as well as the anticipated clinical and scientific impacts of the presented findings.

Chapter 1. Comprehensive Literature Review

This chapter introduces some of the key clinical concepts required to fully understand the scope of the two presented projects. The section also summarizes and appraises evidence already published on each of the previous stated research objectives.

1.1. Thromboembolic Risk After Fontan Surgery in Patients with Univentricular Heart

1.1.1. Univentricular Heart and Fontan Palliation

The term "univentricular heart" refers to a wide range of severe congenital cardiac defects characterized by hypoplasia or absence of one of the two ventricles, which results in a single functional pumping chamber driving both pulmonary and systemic flow, and in obligatory mixing of venous and arterial blood (Figure 2) [78-81]. Common malformations producing univentricular hearts include tricuspid atresia, hypoplastic left heart syndrome, mitral atresia, double-inlet ventricle, and unbalanced atrioventricular canal. Together, these defects account for approximately 1 in 2,500 live births [5,82,83].

Although every condition resulting in a univentricular heart is rather unique and requires individualized treatment, most infants born with such severe disease ultimately undergo what is called "Fontan palliation". In simple terms, the aim of Fontan surgery is to separate venous and arterial circuits and to translocate the single ventricle in a systemic position [84,85]. Venous return is disconnected from the heart and directly reconnected to the lungs, through which blood flows then passively (Figure 2). This physiology is far from ideal as it increases central venous pressure and limits cardiac output [86,87]. However, given the inherent challenges of mechanically supporting or transplanting neonates, it remains standard of care [88-90].

Figure 2. Normal and univentricular circulations

Normal circulation	**Univentricular circulation at birth**	**Univentricular circulation after Fontan palliation**

This graph depicts the flow and oxygen saturation of blood delivered to the lungs and systemic organs in a normal, and a native and palliated univentricular circulation. Red arrows represent oxygen-rich blood, blue arrows, oxygen-poor blood, and purple arrows, venous and arterial blood mixing. The circled "P" denotes pulsatile flow.

Historically, Fontan palliation consisted in an atriopulmonary connection (APC), a direct anastomosis between the right atrium and the pulmonary arteries (Figure 3) [91-94]. It was initially thought that using the right atrium, a pulsatile chamber, would improve flow. However, within a few years, it became obvious that high venous pressure caused the chamber to dilate and lose contractility, which often resulted in poor hemodynamics [95-97]. Thus, starting in the late 1980s, this method was largely abandoned in favor of others excluding the right atrium, termed total cavopulmonary connections (Figure 3) [95,98]. These modifications, which are still in use today, include the lateral tunnel (LT) and the extracardiac conduit (EC). In both methods, a hemi-Fontan or bidirectional Glenn is first created between the superior vena cava and the right pulmonary artery. In the lateral tunnel, the inferior vena cava is then connected to the lungs using a small portion of the right atrial wall enclosed by a synthetic patch. The atrium is, therefore, only partially excluded from the Fontan pathway. In contrast, in the extracardiac conduit, a tube graft is used to complete the connection and the atrial chamber is fully bypassed.

Figure 3. Fontan surgery types

| Atriopulmonary connection | Lateral tunnel | Extracardiac conduit |

IVC = inferior vena cava; RA = right atrium; RPA = right pulmonary artery; SVC = superior vena cava. Adapted from D'Udekem et al. with permission from Wolters Kluwer Health [99; p.I-158].
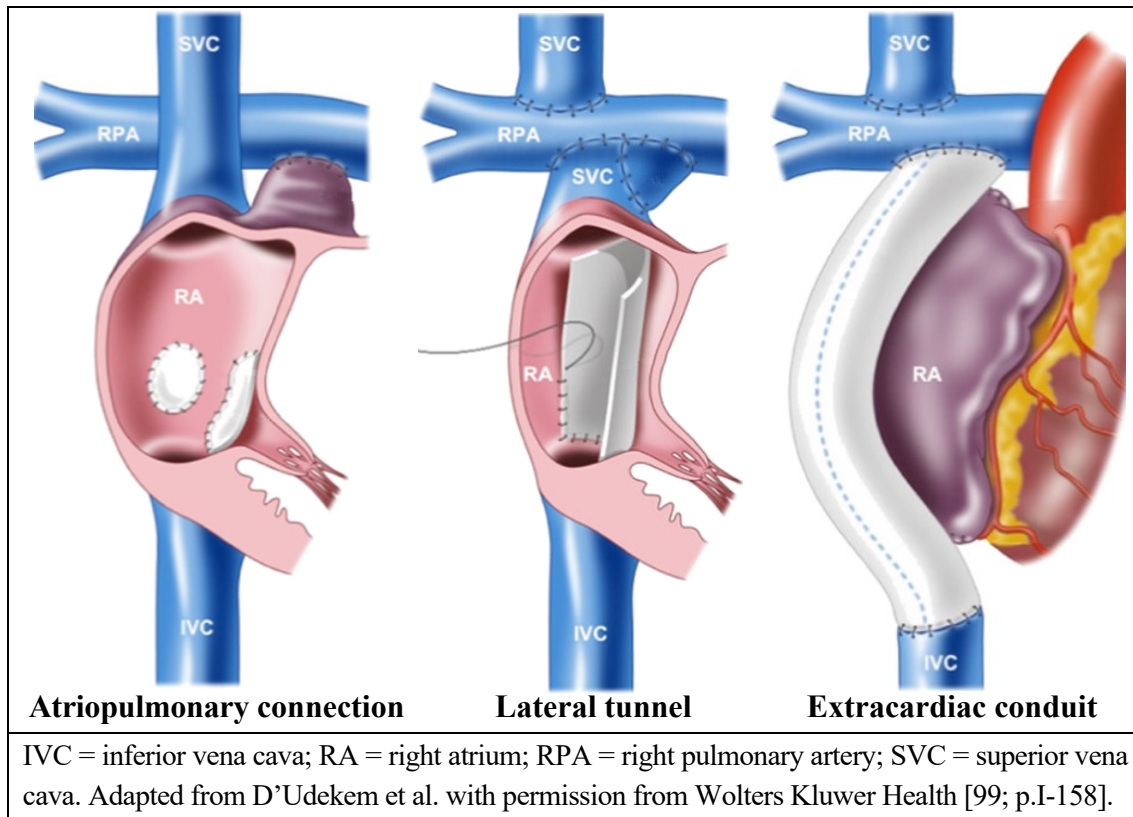
Nowadays, most Fontan surgeries are performed in planned stages [88]. First, neonates are treated with procedures aimed at balancing pulmonary and systemic blood flow. Then, between 4 and 8 months of age, they undergo superior cavopulmonary anastomosis. Finally, between 2 and 4 years of age, palliation is completed with the lateral tunnel or the extracardiac conduit. A small fenestration is also often punched in the Fontan pathway and closed at a later date [100]. Together, staging and fenestration lead to a more progressive increase in central venous pressure and reduce perioperative risks [101-103]. Under these conditions and with improving patient selection, we now estimate that 60% of infants with univentricular heart survives full palliation [83,104], and that more than 85% of Fontan survivors reaches adulthood [34,35,105,106].

1.1.2. Incidence and Pathophysiology of Thromboembolism after Fontan Palliation

Although Fontan surgery can be lifesaving, its abnormal hemodynamics invariably increase the risk of long-term complications [97,105,107]. In the average young adult, blood clots are quite unusual. In contrast, in those with a single ventricle, they occur at rate between 0.74 and 5.2 events per 100 person-years [108-112], for a cumulative incidence of about 20% at 25 years [34]. While many detected thrombi remain asymptomatic [113-115], arterial clots can result in strokes, myocardial infarctions, the loss of a limb, or mesenteric ischemia. Venous events, such as pulmonary emboli and intracardiac thrombi, may cause Fontan failure, or in the presence of a fenestration, trigger paradoxical events. Thus, in this population, thromboembolism gives rise to significant morbidity and mortality. Supporting this statement, we estimate that more than 50% of symptomatic events diagnosed in patients with univentricular palliation leads to permanent disability or death [108,109,116]. Overall, despite intense monitoring and prevention, thromboembolic complications continue to account for approximately 1 in 4 late deaths [35].

With regards to the pathophysiology of thromboembolism, univentricular palliation represents, by virtue of its design, an ideal substrate for clot formation. In the absence of a functional ventricle, blood stasis is thought to increase cellular interactions and chronically activate platelets and the coagulation cascade [117]. High central venous pressure is also thought to dysregulate the hepatic production of clotting factors [118-120]. Furthermore, inherent endothelial dysfunction and coagulation abnormalities are frequently reported among infants with severe congenital heart disease [121-126]. Other factors suspected to contribute to the high burden of thromboembolic events seen after Fontan palliation are summarized in Table 1 [72]. Although most of these factors are associated with a low level of evidence, they remain at the core of available prevention and treatment guidelines [71]. Based on this data, most patients currently undergoing univentricular palliation receive long-term thromboprophylaxis. In low-risk individuals, a growing body of evidence supports the use of aspirin, an antiplatelet [111,113,127,128]. In contrast, in those displaying high-risk features, such as a blind-ended pulmonary artery stump, atrial arrhythmia, ventricular dysfunction or protein-losing enteropathy, an anticoagulant, like warfarin, is typically prescribed [71].

Table 1. Elements of the Virchow's triad contributing to thromboembolism after Fontan surgery

Arm of the Virchow's triad	Thrombogenic contributors
Endothelial dysfunction: - Injury to vessel wall - Exposure of blood to large artificial surfaces - Activation of the coagulation system	Central venous line use Cardiopulmonary bypass Thrombogenic foreign material (e.g., extracardiac conduit) Surgical sites Inherent endothelial dysfunction
Abnormal blood flow: - Abnormal flow rates and shear stress - Turbulent blood flow - Activation of the coagulation system	Cardiopulmonary bypass Surgery type (e.g., atriopulmonary connection) Ventricular dysfunction Arrhythmias Flow dead ends (e.g., pulmonary artery stump) Lower cardiac output Higher venous pressures Nonpulsatile systemic venous flow Chamber dilatation Conduit stenosis Right-to-left intracardiac shunt (e.g., fenestration)
Hypercoagulability: - Hypercoagulable state	Cardiopulmonary bypass Thrombophilia factors Liver dysfunction Pre- and post-Fontan coagulation factors abnormalities Protein losing enteropathy Increased platelet reactivity
Adapted from Attard et al. with permission from Elsevier [72; p.206].	

1.1.3. Impact of Fontan Surgery Type on the Thromboembolic Risk

It remains unclear whether any type of Fontan surgery should be considered, in and of itself, more thrombogenic and prompt anticoagulation [71]. The atriopulmonary connection, for instance, is often regarded as very thrombogenic as there is a high prevalence of atrial chamber dilatation, arrhythmia and partial thrombosis reported among survivors [97,107,129,130]. However, this technique also yields the longest follow-up and was performed at a time of low prevention. Nowadays, central venous access and bicaval cannulation are often avoided [131,132]. No pulmonary artery stump is left behind without oversewing the pulmonary valve [131,133-135]. Immobilized patients are anticoagulated, and those who are ambulatory receive,

at a minimum, antiplatelet therapy [71]. Thus, an evaluation of the thromboembolic risk associated with the procedure must take into account these important changes in practice. In the early 1990s, a large proportion of patients with extracardiac conduits was also systematically anticoagulated [136]. This clinical decision was based on the belief that exposing venous blood to a long synthetic conduit without any growth potential would likely trigger clot formation, and was initially fueled by reports of acute graft thrombosis causing death [137-139]. However, as similar events were later described in patients with lateral tunnels [140-142], this practice was progressively abandoned.

In the current literature, there are relatively few studies reporting thromboembolic complications after Fontan surgery as a primary outcome and providing measures of incidence as opposed to prevalence. Thus, at the present time, only six retrospective cohorts can be acknowledged as objectively comparing thromboembolic risk across surgical techniques [108-110,112,128,143]. Their findings are summarized in Table 2. Between 1995 and 2013, 5 out of 6 studies concluded in a similar risk of thromboembolic events with the atriopulmonary connection, lateral tunnel or extracardiac conduit [108-110,128,143]. Factors such as fenestration, thromboprophylaxis, prior clots and atrial arrhythmia were commonly identified as potential confounders. Unfortunately, due to small or unbalanced sample sizes, powered multivariable analyses could not be performed. A last study published in 2017 reported higher risks of systemic (hazard ratio [HR]: 1.98; 95% confidence interval [CI]: 1.21-3.12) and venous (HR: 2.28; 95% CI: 1.86-3.63) thromboembolic events with the atriopulmonary connection as compared to other methods. It remained, however, underpowered to independently evaluate lateral tunnels (n=78) and extracardiac conduits (n=23). Furthermore, as it only included adults followed in clinic for more than 12 months, the presence of a major selection bias caused by a differential in mortality between treatment groups could not be excluded. In conclusion, while surgical technique is routinely factored in the decision to anticoagulate or not patients with a single ventricle, there is currently no strong evidence informing on the inherent thrombogenicity of operative methods. This knowledge gap must certainly be addressed.

Table 2. Studies published on the association between Fontan surgery type and thromboembolic risk

Author and year	Design and inclusion criteria	n	Surgery type	Follow-up interval	Death and reintervention	Atrial tachyarrhythmia	Prophylaxis	Thromboembolic risk
Rosenthal 1995 [108]	Single-center retrospective cohort Fontan surgeries performed between 1978-1994	70	APC = 20 (29%) LT = 23 (34%) EC = 25 (37%) (Kawashima = 2) Mean age at Fontan: 7.8±7.6y	Mean: 5.2±4.7y Total: 357p-y APC = 5.5±4.9y LT = 1.9±1.5y EC = 8.3±4.7y	3% mortality at 30d and 26% at 5y.	Present in 71% of patients with vs. 43% of those without TEE (p=0.08).	Not routinely administered.	14 first TEE/intracardiac thrombi, of which 43% were asymptomatic, 20% resulted in death, 14% in permanent disability and 66% in full recovery. Incidence of TEE = 3.9 events/100p-y: 6.9 for LT, 3.6 for APC, and 3.0 for EC; Fontan type was not significantly associated with TEE (p=N/S).
Coon 2001 [143]	Single-center retrospective cohort Fontan surgeries performed between 1978-1999 with echocardiographic follow-up	592	APC = 80 (14%) LT = 480 (81%) EC = 32 (5%) Median age at Fontan: 1.9y (range 0.8-35.1y)	Median: 22m (range 1d-20y)	---	Present in 19% of patients with TEE and a valid ECG.	ASA for fenestration; anticoagulation for arrhythmia.	52 first intracardiac thrombi, of which 85% were asymptomatic. Freedom from event at 1, 3 and 8y: 91, 89 and 81% for APC, and 92, 90 and 83% for LT; Fontan type was not significantly associated with TEE (p=N/S).
Seipelt 2002 [109]	Single-center retrospective cohort Fontan surgeries performed between 1986-1998	101	APC = 40 (40%) LT = 61 (60%) Mean age at Fontan: 7.3±8.1y	Mean: 5.7±3.5y APC = 6.5±4.6y LT = 3.5±2.1y	14% mortality at 30d and 18% at 5y. 2 Fontan conversions without censoring.	Present in 21% of patients.	No therapy or ASA prior to 1995, then anticoagulation.	13 first TEE/intracardiac thrombi, of which 38% were asymptomatic; 8% resulted in death, 15% in permanent disability and 77% in full recovery. Incidence of TEE = 3.3 events/100 p-y; Freedom from event at 3 and 5y: 91 and 85% for APC, and 94 and 94% for LT; Fontan type was not significantly associated with TEE (p=0.201).

Table 2. Studies published on the association between thromboembolic risk and Fontan surgery type (…)

Author and year	Design and inclusion criteria	n	Surgery type	Follow-up interval	Death and reintervention	Atrial tachyarrhythmia	Prophylaxis	Thromboembolic risk
Cheung 2005 [110]	Single-center retrospective cohort Fontan surgeries performed between 1980-2002	102	APC = 64 (63%) LT = 21 (20%) EC = 17 (17%) Mean age at Fontan: 6.2±4.8y	Mean: 6.6±3.8y Total: 542p-y	11% mortality at 30d and 6 additional late deaths.	---	No therapy, ASA or anticoagulation for APC or LT. Anticoagulation for EC.	4 first TEE/intracardiac thrombi, of which 25% were asymptomatic. Incidence of TEE = 0.74/100 p-y; 3 events reported after an APC and 1 after an EC. Fontan type does not seem associated with the risk of TEE (no statistical test performed).
McCrindle 2013 [128]	Secondary analysis of multicenter (6) RCT Fontan surgeries performed between 1998-2003 without contraindication to randomization	111	LT = 16 (14%) EC = 95 (86%) Mean age at Fontan: 4.8±2.8y	Follow-up at 3, 6, 12, 18, 24 and 30m.	0.9% mortality at 30d, 1.8% at 2.5y. 2 study withdrawals.	---	Randomized to ASA or anticoagulation.	25 first TEE/intracardiac thrombi, of which 28% were asymptomatic and 4% resulted in death. Freedom from event at 2.5y = 69%. **Fontan type was not significantly associated with TEE in univariable (p=0.20) and multivariable (p=N/S) analyses.**
Egbe 2017 [112]	Single-center retrospective cohort Adult Fontan patients with at least 1y of clinic follow-up between 1994-2014	387	APC = 286 (74%) LT = 78 (20%) EC = 23 (6%) Mean age at Fontan: 14±8y Mean age at study onset: 28±7y	Mean: 8±2y Total: 2317p-y	52 deaths. 8 Fontan conversions and 3 transplants without censoring.	Present in 72% of patients. Freedom from TEE at 20y 43% with and 71% without arrhythmia (p=0.002)	ASA routinely administered; anticoagulation for arrhythmia or prior TEE.	98 first TEE/intracardiac thrombi. Incidence of TEE = 5.2 events/100 p-y; Freedom from event at 20y: 39% for APC, and 74% for LT/EC. APC Fontan was significantly associated with increased TEE (p=0.001). **APC was associated with increased systemic (HR: 1.98; p=0.02) and venous (HR: 2.28; p=0.01) TEE in multivariable analyses.**

APC = atriopulmonary connection; ASA = aspirin; EC = extracardiac conduit; ECG = electrocardiography; HR = hazard ratio; LT = lateral tunnel; N/S = not significant; p-y = person-years; RCT = randomized controlled trial; TEE = thromboembolic event. Bold findings result from multivariable analyses.

1.2. Early Safety and Effectiveness of Combined Pulmonary and Tricuspid Valve Surgery in Patients with Repaired Tetralogy of Fallot

1.2.1. Surgical Management of Tetralogy of Fallot in the Infant

Tetralogy of Fallot, which affects approximately 1 in 3,000 live births, is the commonest form of cyanotic congenital heart disease [5-7]. It is caused by an anterocephalad deviation of the infundibular septum resulting in 4 distinct features: 1) a non-restrictive ventricular septal defect, 2) pulmonary stenosis, 3) aortic overriding, and 4) right ventricular hypertrophy (Figure 4) [144-146]. The malformation triggers pressure overload of the right ventricle and shunting of deoxygenated blood towards vital organs. Thus, infants require prompt surgical intervention to avoid heart failure, hypoxic injuries and death [147].

Definitive repair of tetralogy of Fallot entails closure of the ventricular septal defect and relief of the right ventricular outflow tract obstruction. Depending on its severity and nature, treatment of the stenosis may involve resection of infundibular muscle, incision or excision of the pulmonary valve, and patch augmentation of the outflow tract, the main pulmonary artery, or both [148]. Historically, symptomatic infants were palliated using an aortopulmonary shunt before undergoing definitive repair at an older age [149-153]. However, since the late 1980s, a single procedure is usually carried between 3 and 12 months of age [154-156]. This strategy yields excellent results and allows almost all infants to safely reach adulthood [157,158]. In the very young, surgical correction often commands a ventriculotomy and transannular patch (Figure 5) [156]. In contrast, in older infants, current evidence favors, whenever possible, the use of a transatrial-transpulmonary approach with preservation of the pulmonary annulus and valve [159].

Figure 4. Tetralogy of Fallot

| **Normal heart** | **Tetralogy of Fallot** |

1. ventricular septal defect; 2. pulmonary stenosis; 3. aortic overriding; 4. right ventricular hypertrophy.   Ao = aorta; MPA = main pulmonary artery; PV = pulmonary valve; RA/V = right atrium/ventricle; TV = tricuspid valve. Adapted free of copyrights from the webpage of the Centers for Disease Control and Prevention's National Center on Birth Defects and Developmental Disabilities. [160]

Figure 5. Tetralogy of Fallot repair

| **Transventricular approach** | **Transatrial-transpulmonary approach** |

Reproduced from Gaca et al. with permission from the Radiological Society of North America [161; p.54].
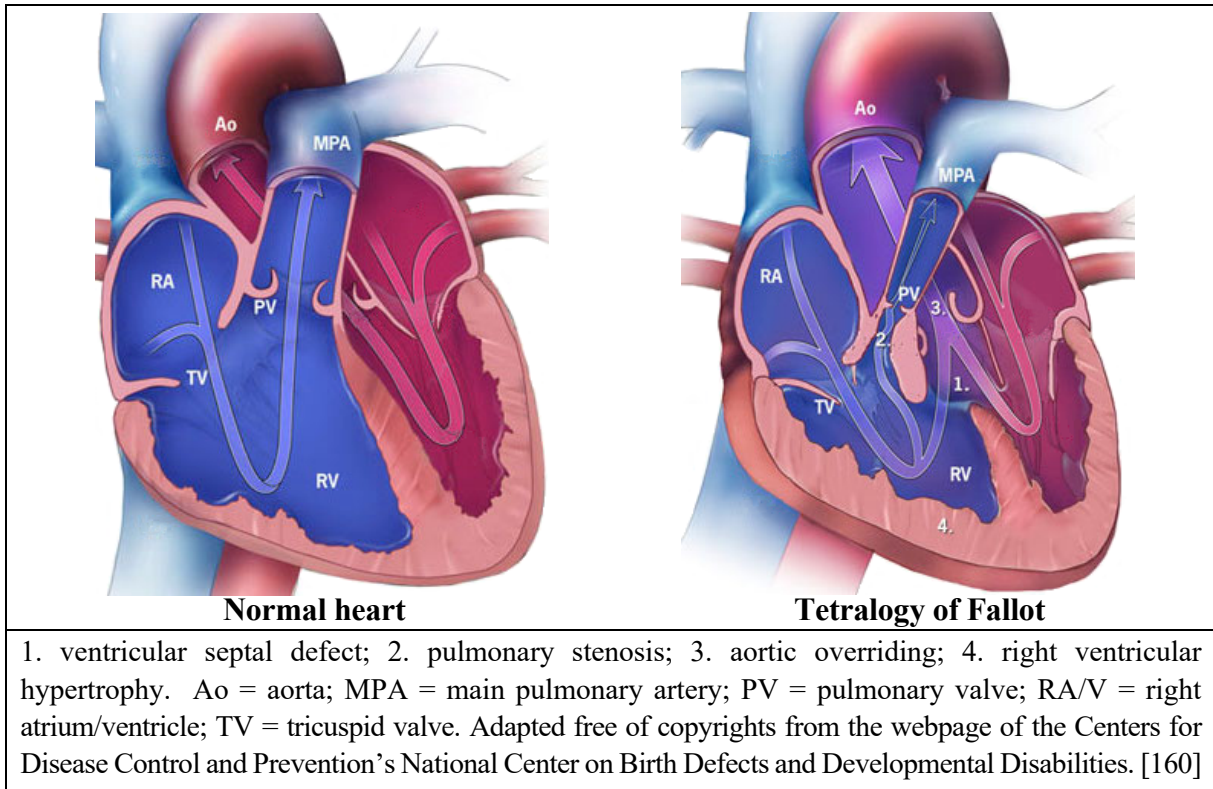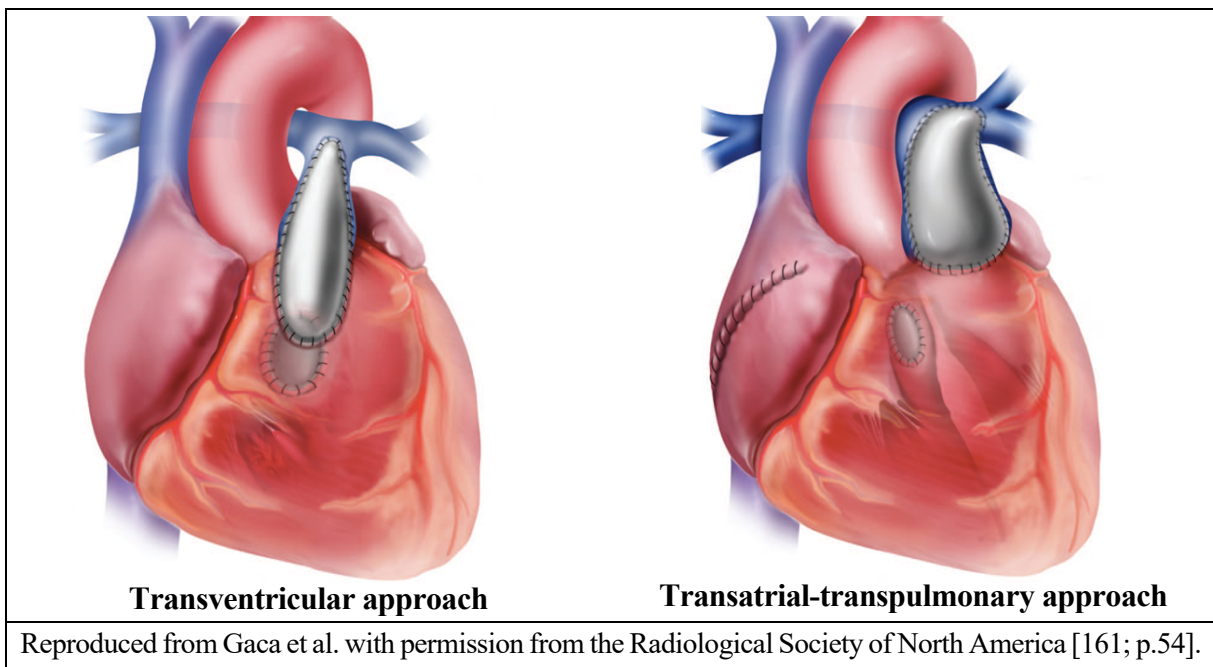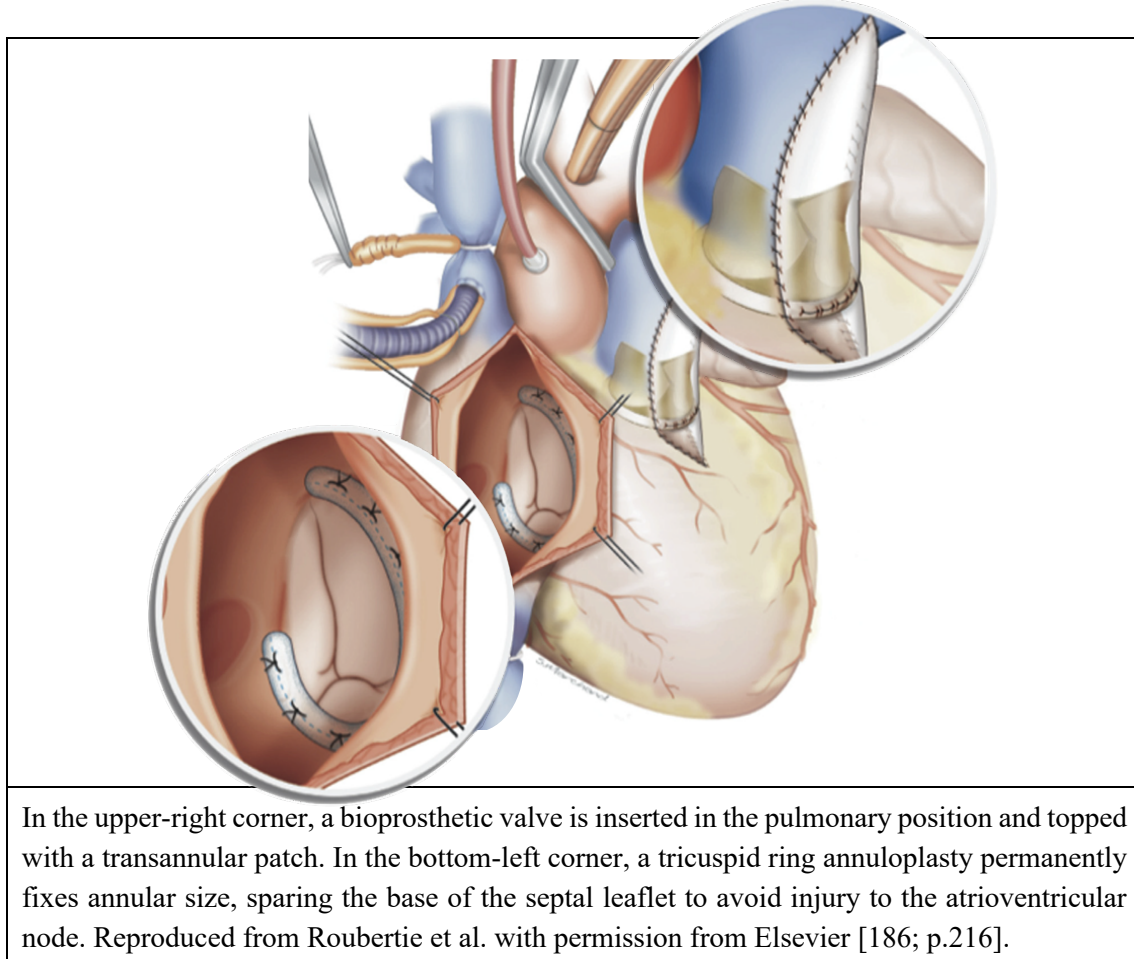
1.2.2. Pulmonary Valve Replacement in the Adult

While operative techniques are constantly evolving, relief of right ventricular outflow tract obstruction in children remains often obtained at the expense of a competent pulmonary valve. Pulmonary regurgitation, although better tolerated than stenosis, leads to progressive right heart dilatation, fibrosis and dysfunction [73,162]. This sequence of events is now recognized as an important determinant of ventricular arrhythmia [24,163], biventricular failure [164,165] and premature death [165-171] 30 to 40 years after repair. As a result, most young adults diagnosed with significant pulmonary insufficiency eventually undergo valve replacement.

As a general rule, a competent pulmonary valve should be inserted before irreversible myocardial damage occurs [172-175]. However, the decision to operate must also factor in procedural risks and the limited lifespan of commercially available bioprostheses [176,177]. While there is still no strict consensus on optimal timing of a first pulmonary valve implant after tetralogy of Fallot repair, current AHA/ACC guidelines recommend the procedure in patients with moderate-to-severe pulmonary regurgitation and symptoms or 2 of the following criteria: 1) mild-to-moderate right or left ventricular dysfunction, 2) severe right ventricular dilatation (end-diastolic volume index ≥160mL/m^2, end-systolic volume index ≥80mL/m^2, or end-diastolic volume ≥2 times that of the left ventricle), 3) right ventricular systolic pressure $\geq2/3$ systemic pressure, or 4) a decline in objective exercise tolerance [58].

In addition to pulmonary insufficiency, other problems such as aneurysmal dilatation of the right ventricular outflow tract [163,178], pulmonary stenosis [179], intracardiac shunts [180], sustained atrial arrhythmia [181,182], inducible ventricular tachycardia [183] and tricuspid regurgitation [75,184] may also contribute to late morbidity and mortality. Pulmonary valve replacement (PVR) is, therefore, often performed in combination with a reconstruction of the outflow tract, repair of stenotic pulmonary arteries, closure of residual atrial and ventricular septal defects, and cryoablation [185]. Surgical management of concomitant tricuspid regurgitation remains, however, extremely controversial (Figure 6).

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Figure 6. Pulmonary valve replacement with concomitant tricuspid valve repair

In the upper-right corner, a bioprosthetic valve is inserted in the pulmonary position and topped with a transannular patch. In the bottom-left corner, a tricuspid ring annuloplasty permanently fixes annular size, sparing the base of the septal leaflet to avoid injury to the atrioventricular node. Reproduced from Roubertie et al. with permission from Elsevier [186; p.216].

1.2.3. Mechanisms and Implications of Tricuspid Regurgitation in Repaired Tetralogy of Fallot

Tricuspid regurgitation is, after pulmonary insufficiency, the second commonest lesion diagnosed following tetralogy of Fallot repair [74,75,184]. It is generally described as a multifactorial issue arising from both functional changes and iatrogenic injuries [187]. Functional regurgitation occurs in response to chronic pulmonary insufficiency and volume overload. As the right ventricle distends, the tricuspid valve annulus dilates, and its elliptical saddle shape becomes more planar and circular [74,188]. The subvalvular apparatus also stretches [189]. These alterations ultimately translate into tethering and failure of coaptation of the leaflets [190]. Iatrogenic injuries may result from both open-heart surgeries and transcatheter

interventions. Perimembranous ventricular septal defect closure, for instance, routinely involves patch anchoring to the tricuspid annulus to protect the atrioventricular node. This technique may cause leaflet entrapment [75,191]. In small infants operated via a transatrial-transpulmonary approach, difficult exposure of the defect may require vigorous retraction of the valve or temporary leaflet detachment. This, again, may induce damage [192-194]. Extensive myomectomy can also disrupt the subvalvular apparatus and cause a flailed segment [75,191]. Finally, transvenous insertion of pacemaker and defibrillator leads may perforate leaflets, severe chordal attachments or trigger fibrosis [195].

Despite its high prevalence and chronicity, there is, unfortunately, limited evidence on the clinical impacts of tricuspid insufficiency in the specific setting of repaired tetralogy of Fallot [75,184]. Thus, patient management remains heavily based on data extrapolated from acquired disease. In the general adult cardiac population, the lesion was long perceived as a marker of disease severity rather than an independent risk factor for negative outcomes. There is, however, a growing body of evidence now supporting that it is unlikely an innocent bystander, but an important condition worth detecting and potentially treating [196-202]. A recent study by Chorin et al., for example, investigated the prognostic relevance of tricuspid insufficiency in over 20,000 hospitalized patients monitored for up to 4 years after discharge. Using carefully adjusted multivariable analyses, they concluded in higher risks of readmission for heart failure and mortality with both moderate and severe regurgitation [201]. Another highly relevant study was published by Benfari et al. in 2019. In this cohort of over 11,000 patients with left heart failure and functional insufficiency at baseline, any grade of tricuspid regurgitation greater than trivial was independently associated with worse dyspnea, peripheral edema, cardiac output, renal function and survival on follow-up [202]. Based on these findings, tricuspid regurgitation is now thought to promote right heart failure through perpetuation of volume overload, irrespective of its underlying cause. In patients with repaired tetralogy of Fallot, already at high risk of right heart failure, this rationale explains the growing interest in actively treating tricuspid regurgitation at the time of pulmonary valve replacement.

1.2.4. Impact of Concomitant Tricuspid Valve Surgery on the Risks of Perioperative Complications and Residual Insufficiency

Evidence from the management of patients with acquired disease

For many years, surgeons avoided combining tricuspid valve interventions (TVI) to left-sided heart surgeries as operative risks were thought to be prohibitive [203,204]. However, we now understand that, although they are often performed in advanced disease stages and high-risk settings, tricuspid procedures are rather safe [205-207]. In 2014, a scoping review of 12 studies including more than 4,000 cases concluded in similar risks of perioperative death and complications such as bleeding, wound infection, respiratory failure, and renal dysfunction following cardiac surgery with or without tricuspid valve repair [206]. Three years later, an impactful cohort study including over 88,000 patients also reported that adding a tricuspid intervention to a mitral or coronary procedure was not associated with increased mortality [207]. While some surgeons still leverage concerns of prolonged ventilation and hospitalization times and of a higher incidence of atrioventricular block with combined procedures [207], many have come to accept these potential risks given mounting evidence of clinical benefits.

Functional tricuspid insufficiency was long thought to spontaneously regress after correction of its underlying cause (e.g., mitral regurgitation) and to remain essentially unaffected by targeted procedures [208-212]. However, 4 recent meta-analyses reported that concomitant tricuspid interventions, performed at any grade of regurgitation greater than trivial, resulted in a lower risk of recurrent or worsening insufficiency (odds ratio [OR] from 0.03 to 0.30) [213-216]. Two of them also concluded, at a median follow-up of 5 years, in a survival benefit with the procedure (HR from 0.38 to 0.68) [214,215]. In view of these findings and with 3 randomized controlled trials currently investigating lower thresholds for intervention (NCT02675244, NCT02996552, NCT03129737), momentum for more aggressive treatment of tricuspid regurgitation at the time of left-sided heart surgery is building [217,218].

Evidence from the management of patients with repaired tetralogy of Fallot

Data from the management of acquired disease certainly influenced congenital practices. We now estimate that between 20 and 30% of adults with repaired tetralogy of Fallot requiring pulmonary valve replacement also receive a tricuspid valve intervention (PVR+TVI) [186,219-222]. Six retrospective cohort studies (N=346) published between 2010 and 2019 directly attempted to compare outcomes of congenital patients undergoing isolated pulmonary valve replacement (n=209) to those undergoing combined surgery (n=127) [186,219-224]. Unfortunately, as most of them were too small to support multivariable analyses, they mainly generated descriptive data. This data is summarized in Table 3.

Overall, studies reported similar unadjusted postoperative tricuspid regurgitation grades with or without combined surgery. However, patients exposed to an additional procedure usually displayed worse preoperative tricuspid insufficiency, and right ventricular dilatation and dysfunction. They were also older, more symptomatic, and had a greater number of comorbidities. Thus, it is virtually impossible to say if tricuspid surgery is truly ineffective [223,224] or if this perceived lack of effectiveness simply results from confounding by indication [186,220]. In one of those studies, an exploratory analysis adjusting for baseline tricuspid regurgitation revealed lower residual insufficiency with combined surgery (relative risk [RR]: 0.67; p=0.005) [220]. One could, therefore, suspect the presence of confounding. With regards to perioperative complications, none of the listed studies attempted to objectively compare clinical, or safety, outcomes between groups. Death and reintervention frequencies were generally reported. However, the small number of patients limits statistical power and precludes further analyses. In conclusion, the paucity of high-quality evidence and ongoing controversy surrounding combined pulmonary and tricuspid valve surgery in adults with repaired tetralogy of Fallot clearly highlights the need for larger research initiatives in the field allowing for better confounding control.

Table 3. Studies published on the safety and effectiveness of combined pulmonary and tricuspid valve surgery

Author and year	Design and inclusion criteria	n	Procedure and baseline TR	Follow-up interval	Death and reoperation	Echocardiographic findings
Kogon 2010 and 2015 [223,224]	Single-center retrospective cohort First PVR between 2002-2008 TOF and PS patients of any age	35	PVR = 19 Moderate TR = 18 Severe TR = 1 PVR+TVI = 16 Moderate TR = 8 Severe TR = 8	1 month, 1-3 years	2 perioperative deaths in the PVR group No reoperation	At baseline, patients who underwent PVR+TVI had higher mean TR, RV dilatation and dysfunction grades than those who underwent isolated PVR. At 1 month, echocardiographic parameters were improved. Patients with PVR+TVI still displayed higher mean RV dilatation and dysfunction grades, but similar TR (1.31 vs. 1.29; p=0.81). At the latest follow-up, parameters remained improved, but the PVR+TVI group displayed again worse TR (1.87 vs. 1.12; p=0.005). **At 1 month, in a log-transformed linear model adjusted for diagnosis and preoperative TR and RV dilatation, there was no association between TVI and residual TR (RR omitted; p=0.54).**
Cramer 2015 [219]	Single-center retrospective cohort First PVR between 1999-2012 TOF patients ≥ 16 years old	36	PVR = 18 Moderate TR = 14 Severe TR = 4 PVR+TVI = 18 Moderate TR = 6 Severe TR = 12	6 months	No death	At baseline, patients who underwent PVR+TVI had higher mean TR grade and RV volumes than those who underwent isolated PVR. At 6 months, echocardiographic parameters were improved and there was no longer a difference in TR grade (0.94 vs. 0.71; p=0.47) or RV volumes between groups.
Roubertie 2015 [186]	Single-center retrospective cohort First PVR between 2002-2014 TOF patients ≥ 16 years old	41	PVR = 25 Moderate TR = 16 Severe TR = 9 PVR+TVI = 16 Moderate TR = 8 Severe TR = 8	1 year	1 perioperative death in the PVR group 2 redo-TVI in the PVR group	Patients with moderate TR: At baseline, patients who underwent PVR+TVI had higher NYHA class and RV volumes than those who underwent isolated PVR. At 1 year, echocardiographic parameters were improved, but RV volumes remained higher after TVI. No patient in either group had more than mild TR (p=N/A). Patients with severe TR: At baseline, patients who underwent PVR+TVI had lower NYHA class and RV volumes than those who underwent isolated PVR. At 1 year, echocardiographic parameters were improved, but NYHA class and RV volumes remained lower after TVI. More than mild TR was reported in 0 and 7 of the patients with and without TVI, respectively (p=0.002).

Table 3. Studies published on the safety and effectiveness of combined pulmonary and tricuspid valve surgery (…)

Author and year	Design and inclusion criteria	n	Procedure and baseline TR	Follow-up interval	Death and reoperation	Echocardiographic findings
Bokma 2015 [220]	Multicenter (3) retrospective cohort First PVR between 2000-2007 TOF and PS patients ≥ 12 years old	129	PVR = 100 Mild TR = 81 Moderate TR = 18 Severe TR = 1 PVR+TVI = 29 Mild TR = 7 Moderate TR = 10 Severe TR = 12	Discharge, 5 years	5 late deaths in unspecified groups	**In a linear model adjusted for preoperative TR (RR=0.58; p<0.001), TVI was associated with a significant reduction in early postoperative TR (RR=0.67; p=0.005)** At 5 years, the proportion of patients with increased TR since surgery was similar between groups (p=0.30). In patients with PVR+TVI, late TR remained, however, lower than seen preoperatively (p<0.001).
Taejung Kim 2019 [221]	Single-center retrospective cohort First PVR between 2000-2016 TOF patients ≥ 18 years old	67	PVR = 29 Mild TR = 17 Moderate TR = 11 Severe TR = 1 PVR+TVI = 38 Mild TR = 4 Moderate TR = 10 Severe TR = 24	6 months	---	Patients who underwent PVR+TVI had higher preoperative TR grades and indexed RV volumes than those who underwent isolated PVR. At 6 months, there was no significant difference in TR grades between groups (no statistical test). The proportion of patients with mild TR increased from 11 to 66% following PVR+TVI, and from 59 to 72% following isolated PVR.
Lueck 2019 [222]	Single-center retrospective cohort First PVR between 2009-2017 TOF patients ≥ 18 years old	28	PVR = 18 No TR = 4 Mild TR = 11 Moderate TR = 3 PVR+TVI = 10 No TR = 3 Mild TR = 4 Moderate TR = 3	Discharge	2 perioperative deaths, 1 per group	Patients who underwent PVR+TVI had higher baseline TR, RV dilatation and dysfunction grades than those who underwent isolated PVR. At discharge, RV and RA dilatation grades remained higher after TVI, but TR grades were similar between groups (p=1.00).
N/A = not applicable; NYHA = New York Heart Association; PVR = pulmonary valve replacement; PS = pulmonary stenosis; RA/V = right atrial/ventricular; RR = relative risk; TOF = tetralogy of Fallot; TR = tricuspid regurgitation; TVI = tricuspid valve intervention. Bold findings result from multivariable analyses.						

Chapter 2. Methodology

This chapter provides an overview of the methodology of the national and international cohort studies constituting the building blocks of the thesis. For each of the two projects, this section describes study design; the processes of patient recruitment, data acquisition, and quality control; as well as the statistical methods used to analyze research objectives.

2.1. The Fontan TACTIC Cohort (Article 1)

2.1.1. Study Design

The Anti-Coagulation Therapy Initiative in Congenital heart disease (TACTIC) was launched in 2012 by Drs. Paul Khairy and Robert Hamilton. This retrospective cohort study was supported by the Alliance for Adult Research in Congenital Cardiology (AARCC) and involved the following 12 North American centers:

- Montreal Heart Institute, Montreal, Quebec, Canada

- Sainte-Justine University Hospital Center, Montreal, Quebec, Canada

- The Hospital for Sick Children, Toronto, Ontario, Canada

- Ahmanson/University of California Los Angeles Adult Congenital Heart Disease Center, Los Angeles, California, United States

- Oregon Health and Science University, Portland, Oregon, United States

- The Wisconsin Adult Congenital Heart Program, Milwaukee, Wisconsin, United States

- Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, United States

- Stanford University Departments of Pediatrics and Medicine, Palo Alto, California, United States

- University of Colorado Denver, Aurora, Colorado, United States

- Boston Children's Hospital and Brigham and Women's Hospital, Boston, Massachusetts, United States

- Milton S. Hershey Medical Center, Hershey, Pennsylvania, United States

- Nationwide Children's Hospital, Columbus, Ohio, United States

The goals of TACTIC were to characterize thromboprophylaxis prescription patterns and to explore the risk factors associated with thromboembolic and bleeding events in two overlapping cohorts. The first one included patients with a wide spectrum of congenital heart diseases also suffering from atrial arrhythmia, and the second, those with Fontan palliation with or without a diagnosis of arrhythmia. The study was managed by a dedicated team based at the Montreal Health Innovations Coordinating Center (MHICC). This team included a project manager, secretary, data manager and biostatistician. The candidate joined the project once data collection was completed. Using the second patient group, also termed the Fontan TACTIC cohort, she formulated a new research objective: comparing thrombogenicity across surgical techniques. She then worked in collaboration with the biostatistician to validate part of the dataset and produce statistical analyses. Finally, she wrote the first article presented in the following chapter.

2.1.2. Patient Recruitment and Definition of Exposure

The Fontan TACTIC cohort included all patients 1) born before July 1, 2011, 2) who underwent Fontan palliation, 3) survived their index surgery, and 4) remained followed at the institution where the procedure was performed.

Eligible cases were identified using local surgical databases. Patients were then divided into three groups based on the initial type of Fontan palliation they had received: an atriopulmonary connection, a lateral tunnel, or an extracardiac conduit. Classic Fontan operations as well as Kreutzer and Bjork modifications were all considered atriopulmonary connection variants even if some technically included the hypoplastic ventricle.

2.1.3. Data Acquisition

Data collection consisted in a detailed chart review. It was performed at each site by local study personnel using paper case report forms ([Appendix 1](#)). Once completed, documents were scanned, encrypted and electronically transmitted to the MHICC. Data entry was then performed in Montreal by two study team members blinded to the work of one another and saved on a protected network.

2.1.4. Quality Control

Adjudication of critical events and four additional layers of quality control were integrated to the TACTIC study. The process of adjudication consisted in a review of any death, diagnosis of arrhythmia, bleeding event or thromboembolic complication by a blinded group of four physicians. Other layers of control included 1) a procedure for flagging illegible data, invalid formats, and invalid codes during data entry; 2) double entry followed by a masked comparison of datasets; 3) the use of systematic range and consistency checks; and 4) a review of the electronic entries and case report forms of a randomly selected sample of $\sqrt{(n+1)}$ subjects by an independent staff. Identified discrepancies automatically generated a trackable form used by members of the MHICC and collaborating sites to provide adequate corrections. Quality control procedures were also regularly audited. An error rate >0.5% was scheduled to trigger re-training of the personnel and an in-depth review of processes.

2.1.5. Analysis Plan by Research Objective

Objective 1: Evaluate the association between Fontan surgery type and the risk of a first thromboembolic event.

Exposure

APC and EC (vs. LT) Fontan surgery

Outcome

The adjudicated diagnosis of a first systemic or venous thromboembolic complication. Systemic events were categorized as cardiac, neurologic, peripheral arterial, renal, or mesenteric; and venous events, as cardiac, peripheral venous or pulmonary.

Analysis

Associations between surgical exposure and arterial, venous, and combined outcomes were estimated using three separate multivariable cause-specific Cox proportional hazard ratio models. Patients were followed until a first thromboembolic event (failure), or until their last recorded visit, Fontan conversion, transplantation or death (censoring/competing event).

Potential confounders were pre-selected based on available literature and suspected pathophysiological relevance, and they were represented in a directed acyclic graph (Figure 7; Appendix 3). They were then tested in a bivariable Cox model with forced retention of Fontan surgery type and progressively added to the analysis using the change-in-estimate method with a 10% cut-off. Thromboprophylaxis and the development of atrial tachyarrhythmia were treated as time-varying variables. Initial thromboprophylaxis was defined as the oral or injectable regimen (antiplatelet, anticoagulant, or none) prescribed at the time of discharge from the hospital following surgery. Diagnosis of atrial tachyarrhythmia was evaluated just prior to Fontan completion. For both variables, any change from baseline were then recorded along the duration of treatment (thromboprophylaxis) or time to diagnosis (arrhythmia).

As some of the potential confounders displayed a small percentage of missing values (<2%), listwise deletion was applied when necessary. Nevertheless, final models only contained complete variables.

Two regression approaches were then considered to account for the potential confounding effect of surgical era: a first stratifying by decades (<1970, 1970-1979, 1980-1989, 1990-2000 and >2000) and a second free of further stratification. Stratified models triggered a >10% change in hazard ratio estimates and improved fit based on the Akaike information criterion. They were, therefore, preferred over unstratified models.

Figure 7. Conceptual framework underlying objective 1

APC = atriopulmonary connection; EC = extracardiac conduit; LT = lateral tunnel.
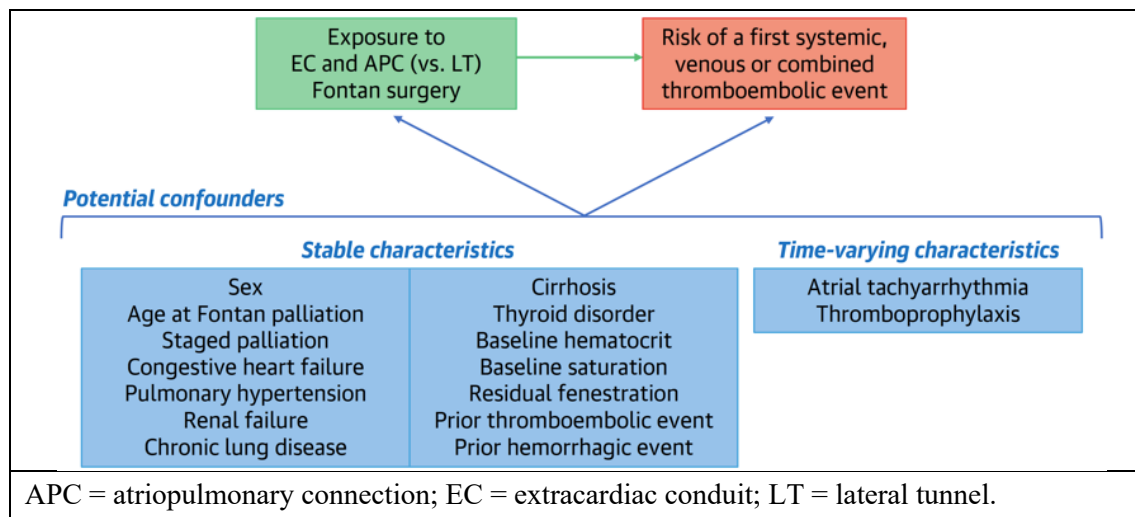
2.2. The SCOTIA-PVR Cohort (Article 2)

2.2.1. Study Design

The Surgical Correction Of Tricuspid Insufficiency in Adult congenital patients requiring Pulmonary Valve Replacement (SCOTIA-PVR) initiative was launched in 2016 by the candidate to address objectives 2 and 3 of her thesis. With the support of the Canadian Congenital Cardiac Collaborative (4C), this retrospective cohort became the first study to involve surgeons from all 8 university hospital centers across the country offering congenital cardiac surgery:

- Queen Elizabeth II Halifax Infirmary/Izaak Walton Killiam Health Center, Dalhousie University, Halifax, Nova Scotia

- Montreal Heart Institute/Sainte-Justine University Hospital Center, Université de Montréal, Montreal, Quebec

- Institut universitaire de cardiologie et de pneumologie de Québec/Centre hospitalier universitaire de Québec, Université Laval, Quebec City, Quebec

- Royal Victoria Hospital/Montreal Children's Hospital, McGill University, Montreal, Quebec

- University of Ottawa Heart Institute/Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Ontario

- Toronto General Hospital/The Hospital for Sick Children, University of Toronto, Toronto, Ontario

- Mazankowski Alberta Heart Institute/Stollery Children's Hospital, University of Alberta, Edmonton, Alberta

- St. Paul's Hospital/British Columbia Children's Hospital, University of British Columbia, Vancouver, British Columbia

The candidate designed and conducted this pan-Canadian project under the supervision of her co-directors. She developed the protocol and study objectives. She coordinated research ethics approvals and the signature of data transfer agreements between sites. She elaborated a budget, obtained internal funding and travelled to each of the collaborating centers to collect data. Finally, she responsibly managed all databases, performed the statistical analyses and wrote the second article presented in the following chapter.

2.2.2. Patient Recruitment and Definition of Exposure

The SCOTIA-PVR cohort included all patients 1) 18 years of age or older, 2) with previously corrected tetralogy of Fallot or pulmonary stenosis, 3) who underwent a first surgical pulmonary valve implant 4) between January 1, 2000 and December 31, 2016, and 5) had more than trace tricuspid regurgitation on preoperative transthoracic echocardiography. Patients with pulmonary atresia and a history of right-ventricle-to-pulmonary-artery conduit, and those with complex intracardiac repairs, such as complete atrioventricular septal defect and double-outlet right ventricle repairs, were excluded.

Eligible cases were identified using local surgical databases. Patients were then divided into two groups based on the type of reintervention they had received: an isolated pulmonary valve replacement, or a pulmonary valve replacement with concomitant tricuspid valve intervention. Tricuspid intervention was defined as any procedure purposefully performed on the valve to improve its competence and included both repairs and replacements.

2.2.3. Data Acquisition

Data collection entailed a comprehensive review of both pediatric and adult patient charts. This task was performed by the candidate after obtaining, at each site, hospital affiliations as a research student or volunteer supervised by a local investigator. Data entry was carried out following a coding manual (Appendix 2). It was performed on a set of three pre-formatted electronic spreadsheets designed to parallel the flow of information in medical records. Spreadsheet 1 contained preoperative and intraoperative variables, including surgical exposure. Spreadsheets 2 and 3 included clinical and echocardiographic outcome variables without any mention of treatment allocation. In an attempt to reduce observer bias, each spreadsheet was filled separately, usually starting with outcome data. Once the work was completed, datasets were encrypted, saved on a protected portable drive, transported to the Montreal Heart Institute, and transferred on its secure network.

2.2.4. Quality Control

Two layers of quality control were integrated to the SCOTIA-PVR study. First, electronic spreadsheets were carefully designed to automatically flag empty cells and aberrant values. This resulted in most errors being detected at the time of entry and immediately corrected. Second, upon merging of the databases, descriptive statistics were produced to identify outliers and logical inconsistencies. For continuous variables, values found within the first and last fifth percentiles were reviewed against patient records. For categorical variables, implausible values were identified through testing of conditional assumptions before being confirmed by local investigators.

2.2.5. Analysis Plan by Research Objective

Objective 2: Evaluate the early safety of performing pulmonary valve replacement with concomitant tricuspid valve intervention

First specific question

Is PVR+TVI associated with a risk of serious perioperative complications similar to that of isolated PVR?

Exposure

PVR+TVI (vs. isolated PVR)

Outcome

A composite of 7 early adverse events including 1) perioperative death, 2) reintervention for bleeding, 3) major infection, 4) thromboembolic event, 5) implantation of a new cardiac electronic device, 6) acute renal failure leading to new-onset hemodialysis, and 7) readmission.

Perioperative death was defined as any fatality occurring during the index admission or within 30 days of surgery. Readmissions were monitored for up to 30 days following hospital discharge. Other complications were reported within 30 days of surgery.

Analysis

The association between PVR+TVI and the risk of a positive composite endpoint was estimated in the entire cohort using multivariable logistic regression.

Potential confounders were pre-selected based on available literature and suspected pathophysiological relevance. Relationships between variables were represented in a directed acyclic graph (Appendix 3) and those likely to introduce a collider bias were excluded. The remaining confounding variables (Figure 8) were then tested along with surgical exposure and selected using the change-in-estimate method with a 5% cut-off. There was no missing value in the dataset used for the analysis.

The association between PVR+TVI and each of the 7 separate endpoints was then explored using a similar approach. Higher confounding adjustment thresholds were, however, used to avoid overfitting. More information on these secondary analyses is provided in the data analysis section of the related article. In response to reviewers' comments, propensity-based matching weight analyses were also performed for each study outcome and published as supplemental material with the manuscript.

Objective 2: Evaluate the early safety of performing pulmonary valve replacement with concomitant tricuspid valve intervention (…)

Second specific question

Is PVR+TVI associated with a hospitalization time similar to that of isolated PVR?
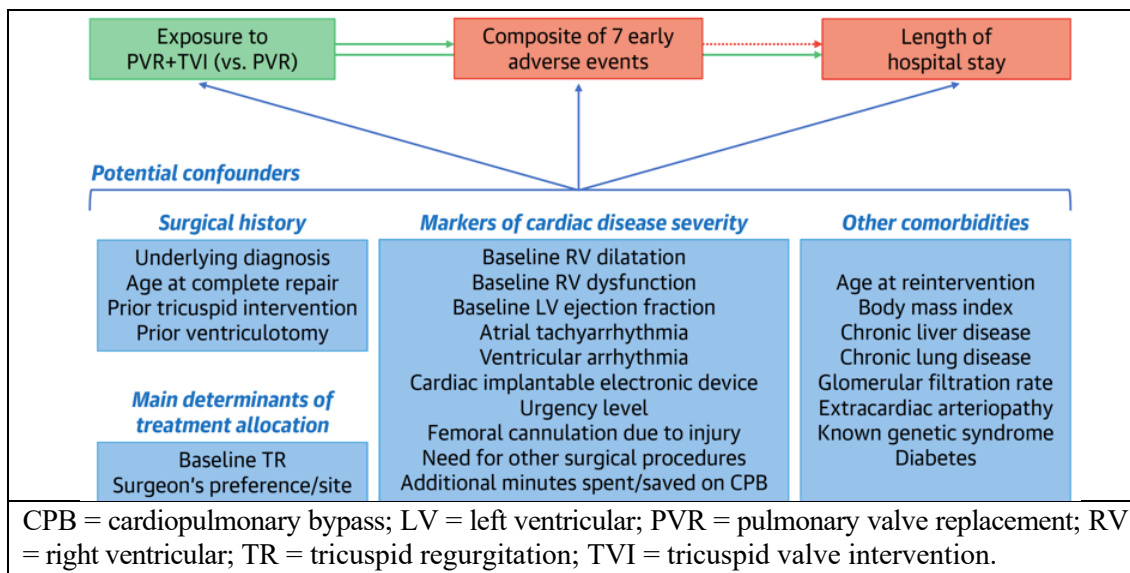
Exposure

PVR+TVI (vs. isolated PVR)

Outcome

Length of hospital stay calculated in days from the date of surgery until discharge home or to a rehabilitation facility.

Analysis

The association between PVR+TVI and length of hospital stay was estimated in both operative and admission survivors using truncated negative binomial regression. This approach was preferred over Poisson regression due to the obvious presence of overdispersion. A directed acyclic graph (Appendix 3) and a conceptual framework (Figure 8) were elaborated. Confounding control was, again, performed using the 5% change-in-estimate method. There was no missing data. The operative and admission survivor models yielded similar results. Thus, only the one estimated on patients who survived until discharge was presented. Finally, results were, again, validated using propensity-based matching weight analyses.

Figure 8. Conceptual framework underlying objective 2

CPB = cardiopulmonary bypass; LV = left ventricular; PVR = pulmonary valve replacement; RV = right ventricular; TR = tricuspid regurgitation; TVI = tricuspid valve intervention.

Objective 3: Evaluate the early effectiveness of performing pulmonary valve replacement with concomitant tricuspid valve intervention

Third specific question

Is PVR+TVI associated with better postoperative tricuspid valve competence than isolated PVR?
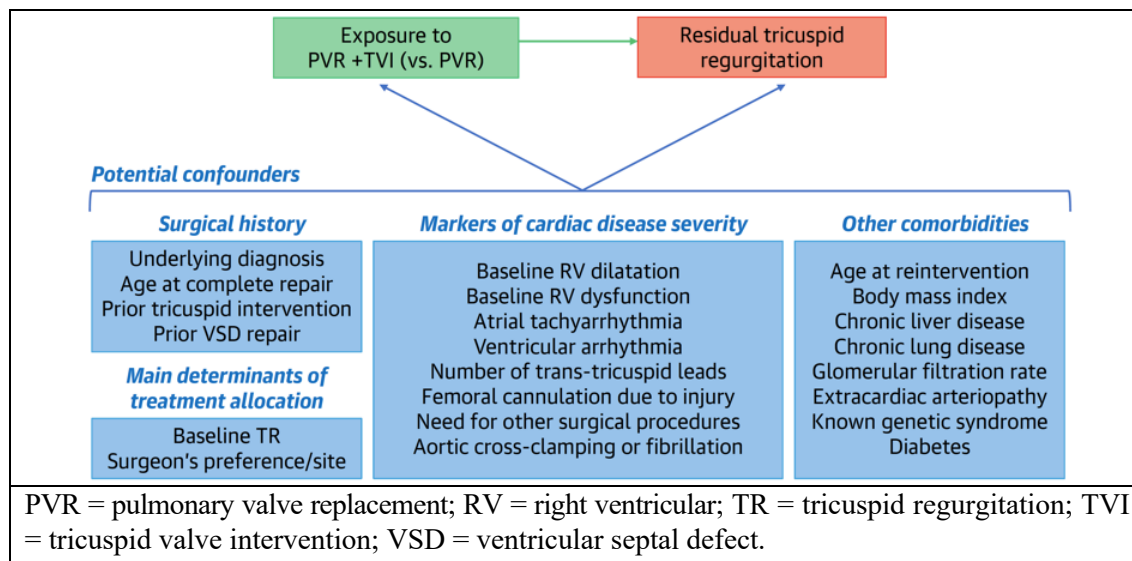
Exposure

PVR+TVI (vs. isolated PVR)

Outcome

Residual tricuspid regurgitation graded as absent/trivial, mild, moderate or severe on the first postoperative transthoracic echocardiographic study completed within 3 months of surgery.

Analysis

Residual tricuspid regurgitation grades were analyzed using multivariable ordered logistic regression. The same approach to confounding control (Appendix 3; Figure 9) was applied. There were, however, a few missing outcome measures (6.4%), which required the comparison of complete and incomplete cases. Despite no major differences between groups, next observation carried backward and multiple imputation methods were explored. The two techniques were compared to listwise deletion using sensitivity analyses. Given no obvious advantage in imputing data, the simplest approach, a complete-case analysis, was presented. Finally, results were, again, validated using propensity-based matching weight analyses.

Figure 9. Conceptual framework underlying objective 3

PVR = pulmonary valve replacement; RV = right ventricular; TR = tricuspid regurgitation; TVI = tricuspid valve intervention; VSD = ventricular septal defect.

Chapter 3. Research Findings

3.1. Article 1: Thromboembolic Risk After Atriopulmonary, Lateral Tunnel, and Extracardiac Conduit Fontan Surgery

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Contribution of the student: Dr. Deshaies performed the analyses in collaboration with Dr. Shohoudi and wrote the manuscript under the supervision of Drs. Khairy, Trottier and Poirier.

Contribution of co-authors: Drs. Khairy, Hamilton, Aboulhosn, Broberg, Cohen, Cook, Dore, Fernandes, Fournier, Kay, Mondésert, Mongeon, Opotowsky, Ting and Zaidi, and Mrs. Proietti participated to the design of the study and data acquisition. Drs. Khairy, Shohoudi, Trottier and Poirier contributed to the analyses and interpretation of the findings. All co-authors reviewed, critically appraised and approved this work.

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3.1.1. Abstract

Background: Thromboembolic events contribute greatly to morbidity and mortality following Fontan surgery for univentricular hearts.

Objectives: This study sought to evaluate the impact of type of Fontan surgery on thromboembolic risk.

Methods: A North American multicenter retrospective cohort study enrolled 522 patients with Fontan palliation consisting of an atriopulmonary connection (APC) (21.4%), lateral tunnel (LT) (41.8%) or extracardiac conduit (EC) (36.8%). Thromboembolic complications and new-onset atrial arrhythmia were reviewed and classified by a blinded adjudicating committee. Thromboembolic risk across surgical techniques was assessed by multivariable competing-risk survival regression.

Results: Over a median follow-up of 11.6 years, 10- and 20-year freedom from Fontan conversion, transplantation, or death was 94.7% and 78.9%, respectively. New-onset atrial arrhythmias occurred in 4.4, 1.2, and 1.0 case per 100 person-years with APC, LT, and EC, respectively. APC was associated with a 2.82-fold higher risk of developing atrial arrhythmias ($p<0.001$), with no difference between LT and EC ($p=0.95$). A total of 71 thromboembolic events, 32 systemic and 39 venous, occurred in 12.8% of subjects, for an overall incidence of 1.1%/year. In multivariable analyses, EC was independently associated with a lower risk of systemic (hazard ratio [HR]: 0.20 vs. LT; 95% confidence interval [CI]: 0.04-0.97) and combined (HR: 0.34 vs. LT; 95% CI: 0.13-0.91) thromboembolic events. A lower incidence of combined thromboembolic events was also observed with antiplatelet agents (HR: 0.54; 95% CI: 0.32-0.92) but not anticoagulation ($p=0.53$).

Conclusion: The EC Fontan was independently associated with a lower thromboembolic risk after controlling for time-varying effects of atrial arrhythmias and thromboprophylaxis.

3.1.2. Condensed Abstract

A North American multicenter cohort study with blinded adjudication of outcomes enrolled 522 patients to assess the impact of type of Fontan surgery on thromboembolic complications. Over a median follow-up of 11.6 years, atriopulmonary connection (APC) Fontan surgery was associated with a 2.8-fold higher risk of new-onset atrial arrhythmias, with no difference between lateral tunnel (LT) and extracardiac conduit (EC) cavopulmonary connections. The overall incidence of thromboembolic events was 1.1%/year. After controlling for time-varying effects of atrial arrhythmias and thromboprophylaxis, the EC Fontan was independently associated with a lower thromboembolic risk (hazard ratio: 0.34 vs. LT; 95% confidence interval: 0.13-0.91).

3.1.3. Introduction

The Fontan-Kreuzter palliative surgery for univentricular hearts has greatly evolved since its initial description in the early 1970s [1,2]. While progression towards more streamlined circuits responded to the need to improve the poor fluid dynamics associated with valves and rudimentary pumping chambers, the effect of later modifications remains incompletely characterized [3-5]. Factors that complicate the objective comparison of outcomes with different surgical techniques include disease rarity, heterogeneity in surgical practice, and the need for long-term follow-up to assess adverse events. As a result, the effects of surgical approach on arrhythmias [6,7] and thromboembolic complications [8-11] remain debated. We, therefore, conducted a multicenter North American study to assess the effect of the type of Fontan surgery on thromboembolic complications in patients with univentricular hearts.

3.1.4. Methods

Study design and patient population

The study was conducted as part of the TACTIC (The AntiCoagulation Therapy In Congenital heart disease) initiative. In brief, this multicenter retrospective cohort study involved three Canadian and nine American centers via the Alliance for Adult Research in Congenital Cardiology (AARCC), and it was designed to generate two overlapping patient cohorts through the application of a single research protocol. The first cohort, described previously, included patients with a wide spectrum of congenital cardiac pathologies and a unifying diagnosis of sustained atrial arrhythmia [12,13]. In contrast, the current study was based on a second cohort consisting solely of patients with Fontan palliation during childhood. Subjects were recruited irrespective of any diagnosis of tachyarrhythmia. Enrollment was, however, restricted to those born before July 2011 who had survived their index surgery and were followed at the same institution that performed the procedure. Such criteria were applied to maximize data completeness over long-term follow-up.

Eligible participants were identified retrospectively at each of the 12 participating institutions through the use of local surgical databases. Upon recruitment, subjects were divided into three groups based on their initial type of Fontan palliation: atriopulmonary connection (APC), lateral tunnel (LT) or extracardiac conduit (EC).

Data abstraction and outcomes of interest

Data collection proceeded at each site with a waiver of consent following local human research ethics board approval. It was performed in accordance with the International Council of Harmonization Tripartite Guidelines for Good Clinical Practice and lasted a total of 26 months, ending on March 1, 2015. The process involved a review of databases and individual patient charts. Baseline characteristics, recorded at the time of Fontan completion, included age; sex; number and type of previously performed surgical and catheter-based interventions; and presence of ongoing heart failure, pulmonary hypertension and respiratory, renal, hepatic, and endocrine comorbidities. Pre-operative heart failure was defined as chronic diuretic use or as New York Heart Association (NYHA) functional class III or IV symptoms, independent of medical therapy. Diagnosis of pulmonary arterial hypertension was made in accordance with clinical guidelines available at the time of enrollment [14].

Thromboprophylaxis and the onset of atrial tachyarrhythmias were carefully monitored throughout follow-up. New-onset atrial arrhythmia was defined as a documented high rate atrial event (>100 beats/min) persisting for >30 s and adjudicated as focal atrial tachycardia, intra-atrial re-entrant tachycardia, or atrial fibrillation [15-17]. Prescribed oral and injectable thromboprophylactic agents of all classes were recorded along with doses and dates of use before being classified into three categories: antiplatelet, anticoagulant, or dual therapy.

The primary outcome was thromboembolic complications, including both systemic and venous events. Systemic thromboemboli were classified as cardiac, neurologic, peripheral arterial, renal, or mesenteric [12,13,18,19]. Neurologic events included transient ischemic attacks and strokes. Transient ischemic attacks were defined as sudden focal deficits lasting <24 h without evidence of infarction on imaging. Strokes included deficits persisting for ≥24 h with or without confirmatory imaging, or for <24 h in the presence of positive images or in

association with invasive treatment strategies [20]. Peripheral arterial complications were diagnosed on the basis of the six cardinal signs of acute limb ischemia: pain, pallor, paralysis, pulse deficit, paresthesia, and poikilothermia [21]. Renal and mesenteric events required imaging confirmation. Venous thromboemboli were subdivided into cardiac, peripheral venous and pulmonary events [12,13]. Appropriate confirmatory imaging studies were mandated for diagnoses of deep venous thromboses and pulmonary emboli. Systemic cardiac thromboemboli included thrombus within native cardiac chambers and embolic myocardial infarction. Venous cardiac events consisted of thrombi within Fontan pathways. These complications were identified and characterized using echocardiography, magnetic resonance imaging or angiography, as deemed appropriate. Additional outcomes of interest, all perceived as competing risks, included Fontan conversions, transplantations and deaths.

Adjudication process, study coordination, and quality control

All thromboembolic events, deaths, and qualifying arrhythmias were adjudicated by a blinded committee consisting of four physicians. Discrepancies were reviewed against case report forms and all other supportive documents required as per protocol, and were subjected to discussion for final adjudication.

The Montreal Health Innovations Coordinating Center oversaw data collection, integration, and entry. The project management team also produced regular quality checks, participated in resolution of discrepancies, and generated statistical analyses. Data quality control consisted of a double data-entry process; procedures for flagging illegible data, invalid formats, and invalid codes; and systematic range and consistency checks. In addition, generated databases were thoroughly inspected by an independent internal quality-control group, who reviewed a randomly selected sample of $\sqrt{(n + 1)}$ subjects, where n represented the entire study group. The review process entailed a comparison of electronic entries to case report forms and the listing of any discrepancies and corrections on separate data clarification forms. The observed error rate of 0.02% before database lock was lower than the acceptable limit defined a priori at <0.5%.

Data analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) (25th-75th percentile), based on normality of distribution. Categorical variables were presented as frequencies and percentages. Continuous baseline characteristics of the three Fontan groups were compared using analyses of variance or Wilcoxon rank-sum tests. Comparisons of categorical variables were performed using chi-square or Fisher exact tests, as appropriate. Cumulative incidences and survival curves were generated using Kaplan-Meier estimates, in which censoring occurred as a result of Fontan conversion, transplantation, or death. Curves were compared using log-rank tests. Trends in thromboprophylaxis use by Fontan type were obtained by plotting the proportion of patients on the different therapies at 0, 5, 10, 15, 20, 25 and 30 years of follow-up. At each time interval, the denominator included all patients who were alive, free of competing events and in follow-up. Proportions were linked to display general tendencies.

First occurrences of systemic, venous, and combined thromboembolic events were evaluated separately using multivariable cause-specific proportional hazard models in which Fontan conversions, transplantations, and deaths were introduced as competing risks. All confounding variables defined above and listed in Table 1 were pre-selected according to their suspected pathophysiological and clinical relevance. Thromboprophylaxis use and the development of atrial arrhythmias were treated in a time-varying fashion. All characteristics were independently tested in a two-variable Cox model with forced retention of Fontan type. Following verification of proportionality assumptions when appropriate, the variables leading to a >10% change in surgical technique hazard ratio (HR) estimates were introduced in multivariable analyses. The final impact of confounding variables was re-evaluated using the same 10% cut off. Two survival regression approaches were then considered: the first, stratifying by surgical era (<1970, 1970-1979, 1980-1989, 1990-2000 and >2000) and, the second, without further stratification. The first approach was ultimately retained as it yielded a better fit on the basis of Akaike information criterion. All 2-tailed p-values <0.05 were considered statistically significant. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

TACTIC was designed as an exploratory study. It was estimated that a sample size of 500 patients would provide 80% power to detect HRs for combined thromboembolic events ranging from 1.71 to 1.95 for exposure variables (e.g., type of Fontan) prevalent in 20-50% of the study population.

3.1.5. Results

Baseline characteristics

A total of 522 eligible patients operated between 1974 and 2012 were enrolled, of whom 21.5% initially received an APC, 41.8% a LT, and 36.8% an EC. As depicted in Figure 1, the distribution of cases according to surgical method and year of Fontan completion revealed a rapid uptake of direct cavopulmonary connection methods starting in the early 1990s. Baseline characteristics of the 3 Fontan groups are summarized in Table 1. The APC was mostly carried out in older children and following systemic-to-pulmonary shunting. In contrast, LT and EC were undertaken in increasingly complex settings, with about one-quarter of cases performed as part of Norwood staging. LT and EC were also more frequently fenestrated. Still, the proportion of patients with a persistent fenestration at last follow-up was similar across surgical techniques. Pre-operative comorbidities were also comparable.

Competing events

The overall median follow-up duration was 11.6 (IQR: 7.75 to 19.0) years. During this period, 40 patients underwent Fontan conversion, 13 were transplanted, and 19 died (Table 2). The vast majority of conversions were performed in late APC survivors, with 25 resulting in EC and 12 in LT. Remaining patients had conversion of an intracardiac to an extracardiac circulation. Conversion and transplantation-free survival curves are presented in Figure 2. Overall event-free survival rates at 5, 10, 15 and 20 years were 98.3%, 94.7%, 90.1% and 78.9%, respectively, with a trend towards better outcomes associated with direct cavopulmonary connections (HR: 0.56; 95% confidence interval [CI]: 0.32-1.06; p=0.077).

Atrial arrhythmias

As shown in Figure 3, the unadjusted cumulative incidence of atrial arrhythmia steadily increased in all 3 Fontan groups following surgery. However, the incidence rate for new-onset atrial tachyarrhythmias was significantly higher in patients with APC compared to direct cavopulmonary connections (4.4, 1.2, and 1.0 case per 100 person-years with APC, LT, and EC, respectively; HR for APC vs. cavopulmonary connection: 2.82; 95% CI: 1.90-4.19; p<0.001). There was no difference in the incidence of atrial arrhythmias in patients with LT versus EC (HR: 1.02; 95% CI: 0.51-1.87; p=0.95).

Thromboprophylaxis

A gradual increase in the proportion of APC subjects on anticoagulants was observed over time (Figure 4). In contrast, patients with LT and EC more consistently received antiplatelet agents from the time of palliation until end of follow-up. At initiation of a first antiplatelet regimen, 94.6% of patients were exposed to aspirin at a dose >5 mg/kg/day, without exceeding 325 mg/day. At initiation of a first vitamin K antagonist, the targeted lower limit of the international normalized ratio was 2.0 in 93.9% of patients, with the most common targeted range being 2.0 to 3.0. Overall, the use of combined antiplatelet and anticoagulant therapy was marginal across Fontan types. Non-vitamin K antagonist oral anticoagulants were rarely prescribed.

Thromboembolic complications

Adjudicated thromboembolic complications are summarized in Table 2. There was a total of 71 events, 32 systemic and 39 venous, in 12.8% of subjects. First systemic and venous events occurred at median follow-up intervals of 11.8 (IQR: 3.0 to 18.3) and 6.4 (IQR: 0.8 to 18.0) years, respectively. As shown in Figure 5, cumulative thromboembolic event rates in the entire cohort 10, 15 and 20 years after Fontan surgery were 8.0%, 12.0% and 20.1%, respectively, corresponding to an overall incidence of 1.1%/year. Rates differed according to type of Fontan and were estimated at 1.5%, 1.0% and 0.6%/year for APC, LT and EC, respectively (p=0.024).

In bivariate analyses, sex, age at palliation, residual fenestration, and time-varying exposures to both thromboprophylaxis and atrial arrhythmias were identified as potential confounders. However, only the two time-varying exposures ultimately remained in the multivariable competing-risk Cox regression models evaluating the effect of Fontan type on systemic, venous and combined thromboembolic events. In the final models displayed in Table 3, EC was independently associated with a lower risk of systemic and combined thromboembolic complications (Figure 6). Corresponding HRs for EC versus LT were 0.20 (95% CI: 0.04-0.97) for systemic and 0.34 (95% CI: 0.13-0.91) for combined thromboembolic events. A lower risk of combined thromboembolic events was also observed with antiplatelet therapy (HR: 0.54; 95% CI: 0.32-0.92) versus no thromboprophylaxis or anticoagulation alone. Atrial arrhythmias were associated with a non-significantly higher rate of systemic thromboembolic events (HR 2.55; 95% CI: 0.91-7.10).

3.1.6. Discussion

The main findings of this multicenter TACTIC study, which enrolled 522 patients with univentricular hearts and Fontan palliation, include the following: 1) a high cumulative rate of thromboembolic events was noted, which exceeded 20% at 20 years of follow-up; 2) EC was associated with a lower thromboembolic risk than LT; 3) a lower risk of thromboembolic events was observed with antiplatelet therapy; and 4) the incidence of atrial arrhythmias was substantially lower with a total cavopulmonary connection Fontan compared to APC, and was similar between LT and EC.

The high thromboembolic burden associated with Fontan surgery is well established and has been linked to increased mortality [22]. The thromboembolic event rate observed in TACTIC is consistent with rates reported by other contemporary reports, which ranged from 0.74% to 5.2%/year [11,23-26]. To our knowledge, this study is the first to document an independent association between EC and lower rate of systemic and combined thromboembolic events when compared to LT. Several observational studies and 1 recent meta-analysis reported the absence of an association between type of cavopulmonary connection and clotting propensity [27]. However, methodological limitations preclude definitive conclusions. For

example, the first four negative studies published between 1990 and 2005 were cohorts with unadjusted analyses and intermediate follow-up [23-25,28]. A subsequent secondary analysis of a randomized trial comparing aspirin to warfarin likewise found no association, but was limited to 17 patients with a LT [9]. A larger retrospective study published in 2017 reported a higher thromboembolic event rate with an APC (n=286) compared to a total cavopulmonary connection (n=101), with a similar risk (HR: 2.12) to that observed in TACTIC [11]. However, it was underpowered to compare LT to EC, since only 23 patients had an EC in comparison to 192 in the current study.

In light of limited evidence, findings from this analysis raise provocative questions regarding the inherent thrombogenicity of various surgical approaches. The results cast doubt on the widely held notion that an EC is potentially more thrombogenic than a LT by virtue of greater exposure to synthetic material and relative flow restriction through a fixed pathway. Although the underlying pathophysiological mechanisms remain to be elucidated, it could be hypothesized that these pro-coagulant factors are counterbalanced by superior long-term hemodynamics, which positively influence thrombogenic risk. Indeed, laminar flow could potentially limit chronic local activation of the coagulation cascade and, when combined with a slight reduction in portal pressure, translate in improved synthesis and metabolism of blood components. These postulates remain to be validated. The interplay between these various factors merits careful research.

Optimal thromboprophylaxis in patients with Fontan surgery is a hotly debated topic. In this regard, TACTIC contributes to the growing literature, which suggests that antiplatelet agents afford protection and that anticoagulation therapy is not superior [29,30]. Underlying reasons as to why anticoagulation did not outperform antiplatelet agents remain speculative. Possibilities include the predominance of increased platelet activity in the pathogenesis of Fontan-related thrombosis [31], difficulties in achieving therapeutic anticoagulation levels with vitamin K antagonists, and residual confounding by indication. The results pave the way for future research to better identify high-risk candidates and to assess newer, potentially more effective, thromboprophylactic agents.

Finally, results of TACTIC are consistent with another international retrospective cohort study that reported no difference in the incidence of atrial tachyarrhythmias in patients with a LT (n=602) compared to an EC (n=669) [6]. Confirmation of these results is noteworthy, considering that the EC was proposed and heralded as an alternative to a LT in order to reduce the arrhythmia burden. Reasons as to why an EC is not less arrhythmogenic than a LT despite fewer atrial suture lines may include similar predisposing factors such as hypoxemic changes and dysregulation of the cardiac autonomic nervous system [32]. Moreover, the EC requires a cuff of atrial tissue for its inferior anastomosis, which results in damage to the crista terminalis and contains a high density of adrenergic nerve endings that have been implicated in arrhythmogenesis [33].

Limitations

The TACTIC study is observational and, therefore, subject to limitations related to unmeasured or unknown potential confounders. Attempts to limit such vulnerabilities included the involvement of several centers and the application of strict data handling and quality control standards classically applied to clinical trials. Selection bias was minimized by the use of a systematic approach to recruitment, relying on surgical databases rather than outpatient follow-up registries for patient identification. Furthermore, outcomes were blindly adjudicated using comprehensive definitions. Caution should be exercised in generalizing conclusions to all patients progressing along Fontan stages because the study was limited to those who survived full palliation and remained followed in tertiary centers.

3.1.7. Conclusions

High cumulative rates of adjudicated thromboembolic complications and atrial arrhythmias were observed in this North American multicenter cohort study that included over 500 patients with Fontan palliation. In competing-risk multivariable analyses that adjusted for time-varying confounding effects, an EC was associated with a lower risk of thromboembolic events than a LT, with a similar incidence of atrial tachyarrhythmias. Long-term antiplatelet therapy had a protective effect against combined events, unlike anticoagulation. In view of these

findings, future research should explore underlying mechanisms to explain differences in thrombogenicity observed across various surgical techniques and define optimal treatment strategies for thromboprophylaxis.

Perspectives

COMPETENCY IN MEDICAL KNOWLEDGE: Compared to lateral tunnel Fontan procedures, extracardiac conduits are associated with a similar incidence of atrial arrhythmias but a lower risk of systemic and combined thromboembolic complications.

TRANSLATIONAL OUTLOOK: Additional prospective studies are required to define optimal thromboprophylaxis strategies in patients undergoing Fontan palliation, identify high-risk clinical features, and clarify the role of target-specific oral anticoagulants.

3.1.8. Tables

Table 1.   Baseline characteristics

	All Types (N=522)	Fontan Type APC (N=112)	LT (N=218)	EC (N=192)	P-value
Clinical characteristics					
Female	231 (44.3)	62 (55.4)	84 (38.5)	85 (44.3)	0.014
Age at Fontan completion, yrs	3.8 (2.4-7.0)	6.9 (4.2-11.7)	2.9 (1.8-4.8)	4.0 (2.9-6.5)	<0.001
Oxygen saturation post-Fontan, %	89.8 ± 7.4	93.1 ± 8.2	88.2 ± 6.2	90.7 ± 8.1	<0.001
Surgical history					
Systemic-pulmonary shunts	244 (46.7)	65 (58.0)	111 (50.9)	68 (35.4)	<0.001
Blalock-Taussig	232 (44.4)	56 (50.0)	109 (50.0)	67 (34.9)	
Potts	4 (0.8)	4 (3.6)	0 (0.0)	0 (0.0)	
Waterston	14 (2.7)	8 (7.1)	5 (2.3)	1 (0.5)	
Norwood procedure	114 (21.8)	2 (1.8)	66 (30.3)	46 (24.0)	<0.001
Pulmonary artery banding	70 (13.4)	15 (13.4)	31 (14.2)	24 (12.5)	0.878
Superior cavopulmonary anastomosis	384 (73.6)	36 (32.1)	173 (79.4)	175 (91.2)	<0.001
Bidirectional Glenn	345 (66.1)	36 (32.1)	134 (61.5)	175 (91.2)	
Hemi-Fontan	39 (7.5)	0 (0.0)	39 (17.9)	0 (0.0)	
No prior staging procedure	45 (8.6)	20 (17.9)	14 (6.4)	11 (5.7)	<0.001
Creation of a fenestration	308 (59.0)	24 (21.4)	152 (69.7)	132 (68.8)	<0.001
Persistent fenestration	61 (11.7)	10 (8.9)	30 (13.8)	21 (10.9)	0.399
Preoperative comorbidities					
Congestive heart failure	27 (5.2)	9 (8.0)	7 (3.2)	11 (5.7)	0.157
Pulmonary arterial hypertension	4 (0.8)	2 (1.8)	0 (0.0)	2 (1.0)	0.118
Liver cirrhosis	3 (0.6)	2 (1.8)	1 (0.5)	0 (0.0)	0.167
Chronic lung disease	17 (3.3)	4 (3.6)	7 (3.2)	6 (3.1)	0.999
Thyroid disorder	8 (1.5)	3 (2.7)	4 (1.8)	1 (0.5)	0.272

Values are n (%), median (25th-75th percentile), or mean ± SD. APC = atriopulmonary connection; EC = extracardiac conduit; LT = lateral tunnel.

Table 2. Adjudicated thromboembolic and competing events according to Fontan type

	All Types (N=522)	Fontan Type			P-value
		APC (N=112)	LT (N=218)	EC (N=192)	
Age at last follow-up, yrs	15.6 (11.1-25.8)	32.1 (27.2-37.8)	14.6 (10.9-21.5)	12.6 (10.3-16.5)	<0.001
Duration of follow-up, yrs	11.6 (7.8-19.0)	24.8 (21.5-27.5)	11.8 (8.2-17.4)	8.5 (5.3-11.7)	<0.001
Thromboembolic events					
Patients with events	67 (12.8)	34 (30.4)	24 (11.0)	9 (4.7)	<0.001
Total number of events	71	37	25	9	<0.001
Systemic	32 (45.1)	18 (48.7)	12 (48.0)	2 (22.2)	0.101
Cardiac	8 (11.3)	7 (18.9)	1 (4.0)	0 (0.0)	
Neurologic	20 (28.2)	10 (27.0)	9 (36.0)	1 (11.1)	
Peripheral	2 (2.8)	0 (0.0)	1 (4.0)	1 (11.1)	
Renal	2 (2.8)	1 (2.7)	1 (4.0)	0 (0.0)	
Venous	39 (54.9)	19 (51.4)	13 (52.0)	7 (77.8)	0.506
Peripheral	5 (7.0)	1 (2.7)	2 (8.0)	2 (22.2)	
Cardiac	32 (45.1)	17 (46.0)	10 (40.0)	5 (55.6)	
Pulmonary	2 (2.8)	1 (2.7)	1 (4.0)	0 (0.0)	
Competing events					
Deaths	19 (3.6)	10 (8.9)	7 (3.2)	2 (1.0)	<0.001
Fontan conversions	40 (7.7)	37 (33.0)	3 (1.4)	0 (0.0)	<0.001
Transplantations	13 (2.5)	5 (4.5)	5 (2.3)	3 (1.6)	0.270

Values are median (25th-75th percentile) or n (%), unless otherwise indicated. Abbreviations as in Table 1.

Table 3. Factors associated with thromboembolic events in multivariable Cox regression analyses

	Hazard ratio	95% CI	P-value
Model 1: Systemic thromboembolic event			
Extracardiac conduit[*]	0.20	0.04 - 0.97	0.039
Atriopulmonary connection[*]	1.77	0.42 - 7.40	0.435
Antiplatelet therapy	0.46	0.17 - 1.23	0.122
Anticoagulant therapy	1.13	0.44 - 2.93	0.797
Dual therapy	1.09	0.23 - 5.25	0.918
Development of atrial tachyarrhythmia	2.55	0.91 - 7.10	0.074
Model 2: Venous thromboembolic event			
Extracardiac conduit[*]	0.41	0.12 - 1.38	0.151
Atriopulmonary connection[*]	2.22	0.80 - 6.14	0.124
Antiplatelet therapy	0.59	0.32 - 1.10	0.099
Anticoagulant therapy	1.23	0.61 - 2.48	0.564
Dual therapy	1.71	1.71 - 0.61	0.308
Development of atrial tachyarrhythmia	1.32	0.48 - 3.61	0.593
Model 3: Any thromboembolic event			
Extracardiac conduit[*]	0.34	0.13 - 0.91	0.031
Atriopulmonary connection[*]	2.01	0.86 - 4.70	0.106
Antiplatelet therapy	0.54	0.32 - 0.92	0.023
Anticoagulant therapy	1.21	0.68 - 2.15	0.525
Dual therapy	1.52	0.63 - 3.69	0.352
Development of atrial tachyarrhythmia	1.75	0.86 - 3.60	0.125

[*]The hazard ratios provided are with respect to lateral tunnel Fontan as the reference category. Cause-specific competing-risk models were stratified by surgical decades as follows: <1970, 1970-1979, 1980-1989, 1990-2000 and >2000. CI = confidence interval.

3.1.9. Figures

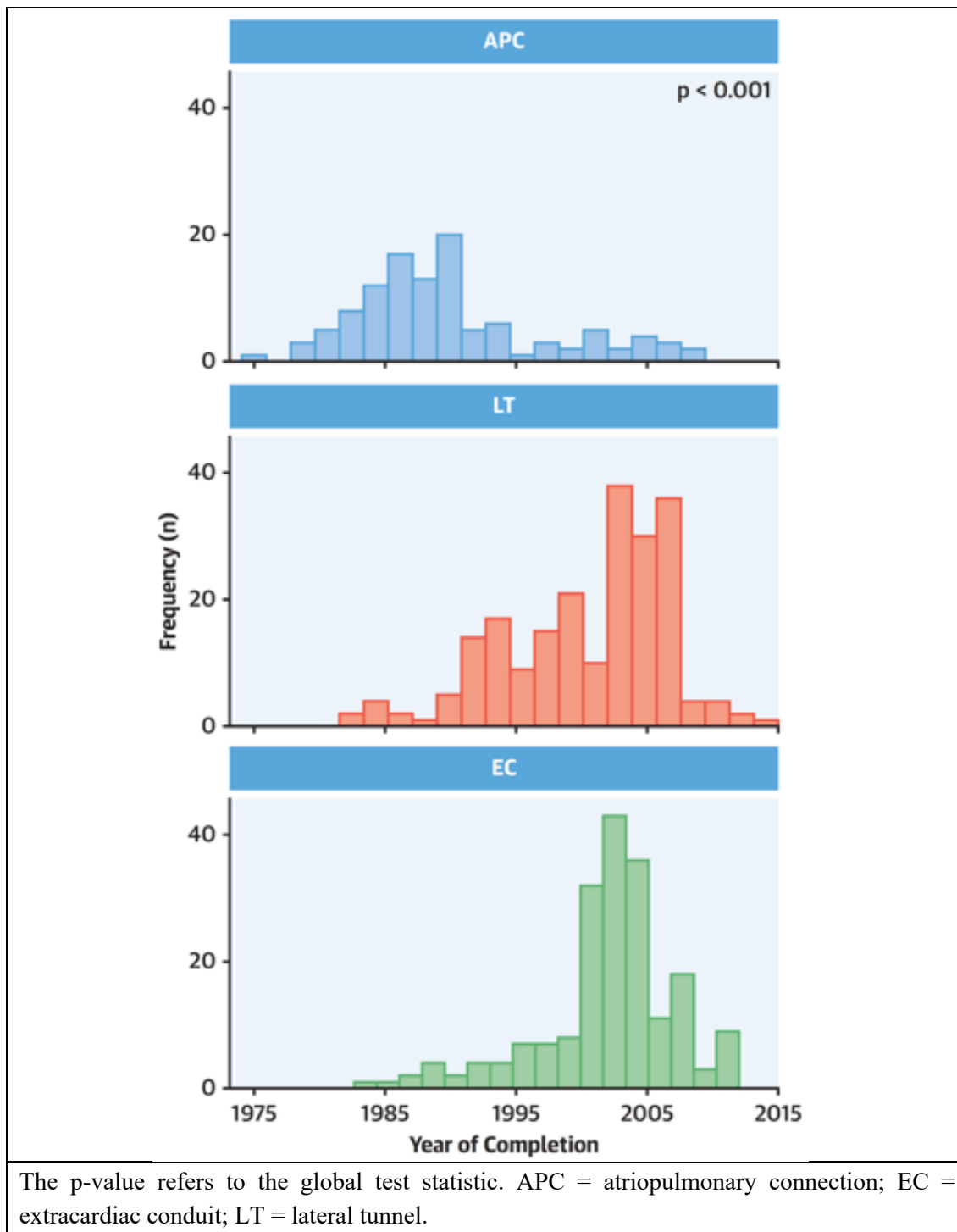**Figure 1.** Distribution of cases according to Fontan type and year of completion

The p-value refers to the global test statistic. APC = atriopulmonary connection; EC = extracardiac conduit; LT = lateral tunnel.

Figure 2. Freedom from conversion, transplantation and death according to Fontan type

The p-value refers to the global test statistic. Abbreviations as in Figure 1.
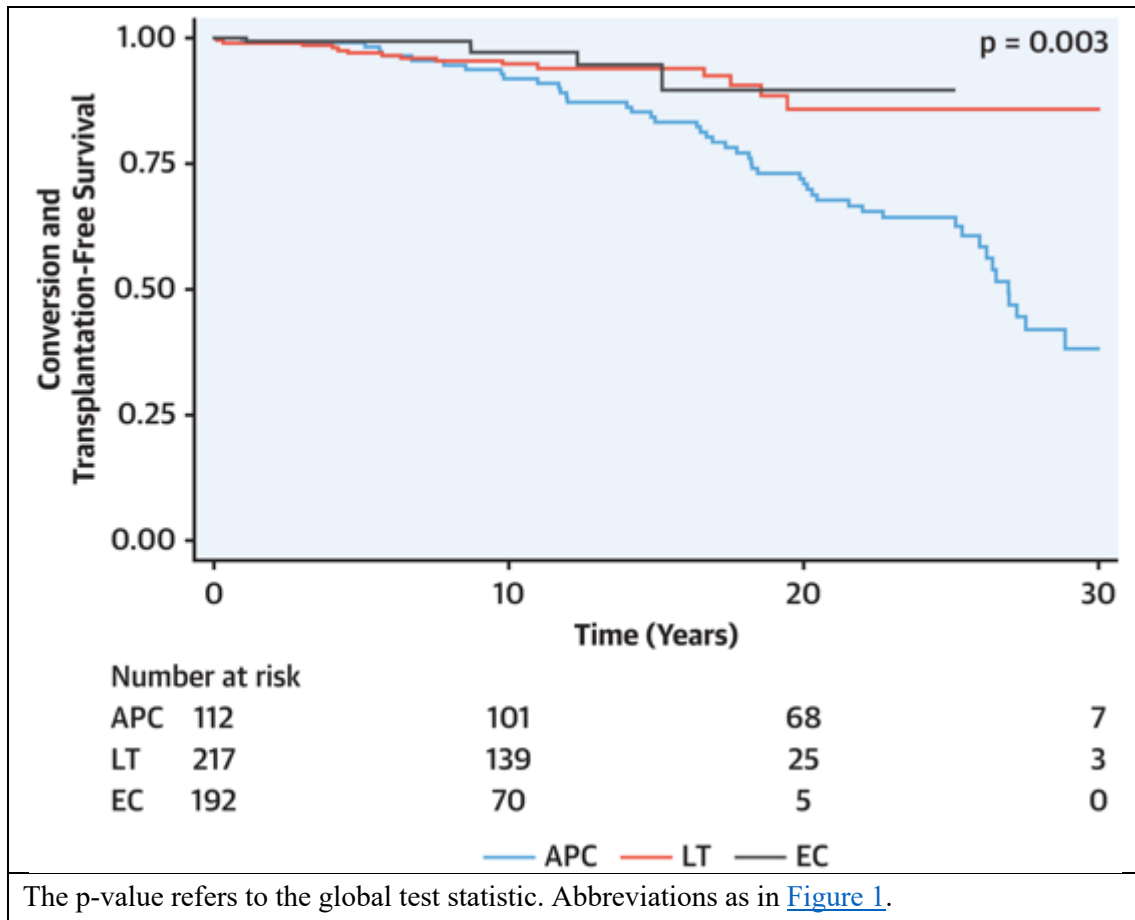
Figure 3. Cumulative incidence of atrial tachyarrhythmia according to Fontan type

The p-value refers to the global test statistic. Abbreviations as in Figure 1.
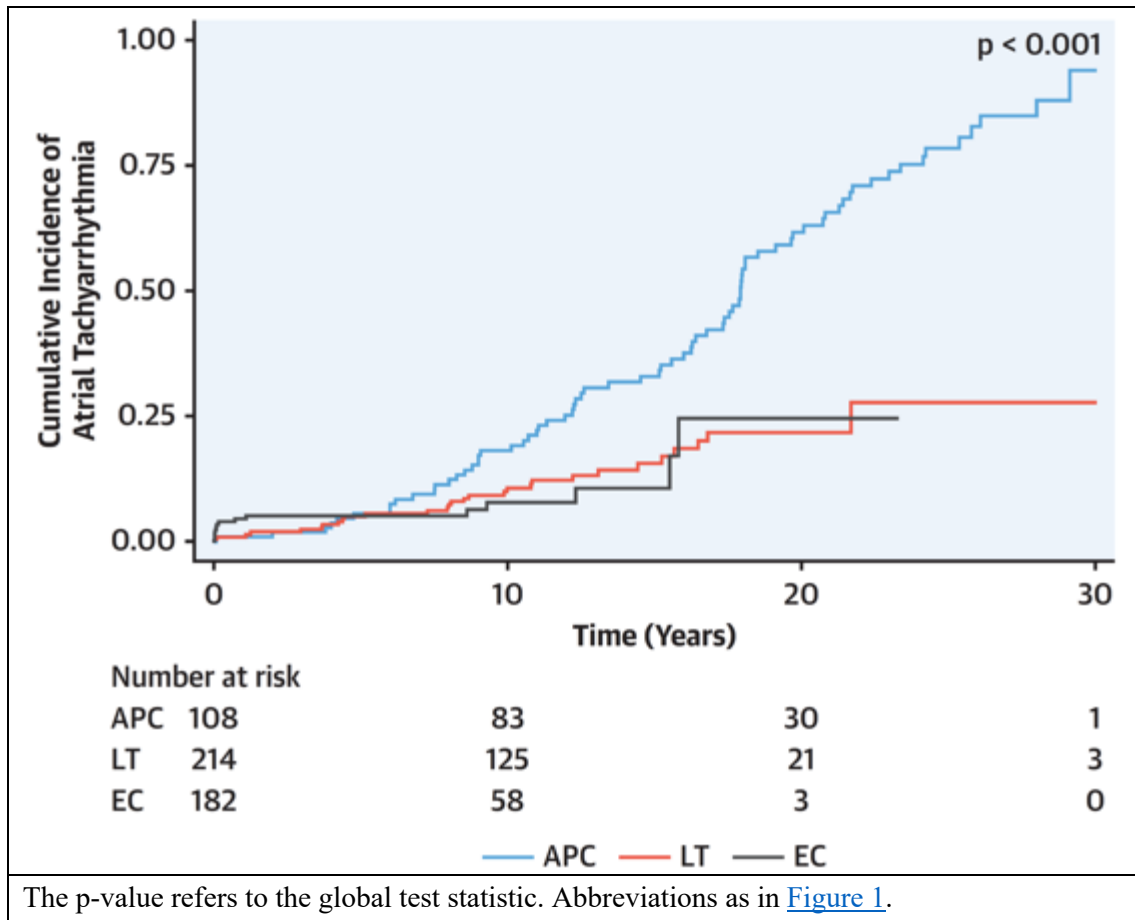
Figure 4. Trends in thromboprophylaxis use over time and according to Fontan type

Abbreviations as in Figure 1.
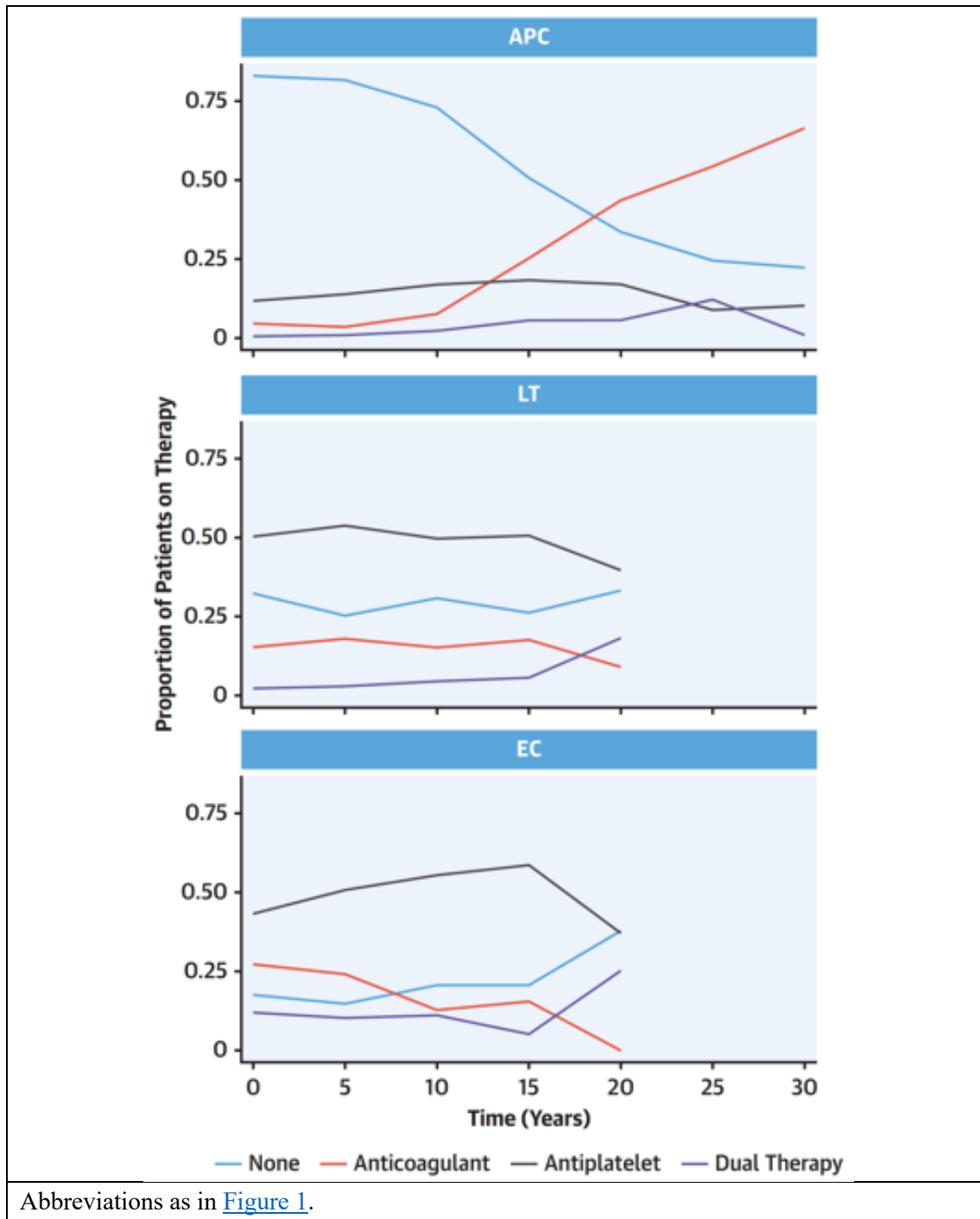
Figure 5. Cumulative incidence of thromboembolic events according to Fontan type

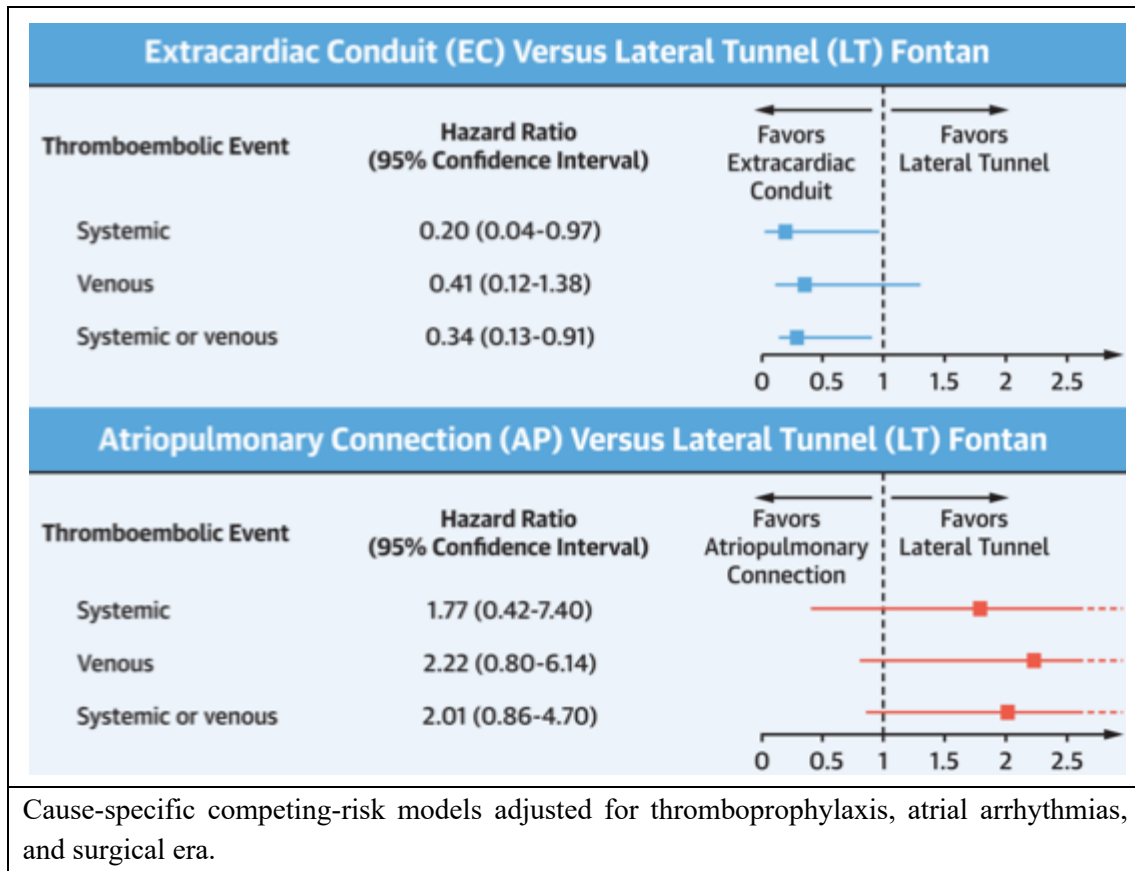The p-value refers to the global test statistic. Abbreviations as in Figure 1.
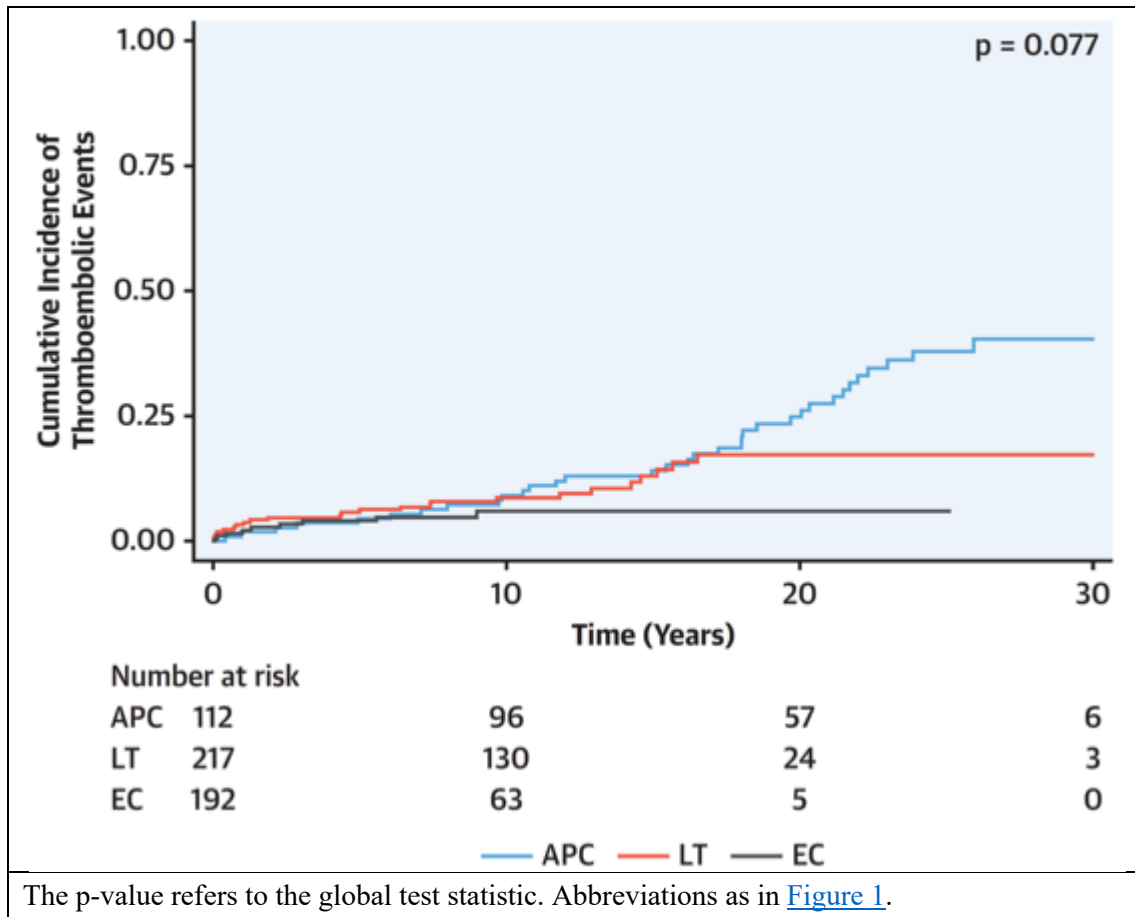
Figure 6. First thromboembolic event after atriopulmonary connection, lateral tunnel and extracardiac conduit Fontan surgery: adjusted hazard ratio

Cause-specific competing-risk models adjusted for thromboprophylaxis, atrial arrhythmias, and surgical era.

3.1.10. References

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3.2. Article 2: Tricuspid Intervention Following Pulmonary Valve Replacement in Adults with Congenital Heart Disease

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Contribution of the student: Dr. Deshaies designed the study protocol, coordinated ethics approvals, collected data, performed statistical analyses and wrote the article under the supervision of Drs. Trottier and Poirier.

Contribution of co-authors: Drs. Trottier and Poirier contributed to the design of the study, statistical analyses and interpretation of the findings. Drs. Khairy, Al-Aklabi, Beauchesne, Bernier, Dhillon, Gandhi, Haller, Horne, Hickey, Jacques, Kiess, Perron and Rodriguez participated in data acquisition. All co-authors reviewed, critically appraised and approved this work.

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3.2.1. Abstract

Background: Tricuspid regurgitation (TR) is common among adults with corrected tetralogy of Fallot (TOF) or pulmonary stenosis (PS) referred for pulmonary valve replacement (PVR). Yet, combined valve surgery remains controversial.

Objectives: This study sought to evaluate the impact of concomitant tricuspid valve intervention (TVI) on postoperative TR, length of hospital stay and on a composite endpoint consisting of 7 early adverse events (death, reintervention, cardiac electronic device implantation, infection, thromboembolic event, hemodialysis and readmission).

Methods: The national Canadian cohort enrolled 542 patients with TOF or PS and mild to severe TR who underwent isolated PVR (66.8%) or PVR+TVI (33.2%). Outcomes were abstracted from charts and compared between groups using multivariable logistic and negative binomial regression.

Results: Median age at reintervention was 35.3 years. Regardless of surgery type, TR decreased by at least 1 echocardiographic grade in 35.4, 66.9 and 92.8% of patients with preoperative mild, moderate and severe insufficiency. In multivariable analyses, PVR+TVI was associated with an additional 2.3-fold reduction in TR grade (odds ratio [OR]: 0.44; 95% confidence interval [CI]: 0.25-0.77) without an increase in early adverse events (OR: 0.85; 95% CI: 0.46-1.57) or hospitalization time (incidence rate ratio: 1.17; 95% CI: 0.93-1.46). Preoperative TR severity and presence of trans-valvular leads independently predicted postoperative TR. In contrast, early adverse events were strongly associated with atrial tachyarrhythmia, extracardiac arteriopathy and a high body mass index.

Conclusions: In patients with TOF or PS and significant TR, concomitant TVI is safe and results in better early tricuspid valve competence than isolated PVR.

3.2.2. Condensed Abstract

A national Canadian cohort enrolled 542 adults with corrected tetralogy of Fallot or pulmonary stenosis who underwent pulmonary valve replacement (PVR) with mild to severe tricuspid regurgitation (TR) to assess the impact of concomitant tricuspid valve intervention (TVI) on early postoperative outcomes. There was no difference in adjusted risk of early adverse events or length of hospitalization between groups. PVR+TVI was independently associated with a 2.3-fold improvement in postoperative TR (odds ratio: 0.44; 95% confidence interval: 0.25-0.77). Thus, in this adult congenital population, combined surgery is safe and may represent a better treatment option than isolated PVR.

3.2.3. Introduction

At the time of pulmonary valve replacement (PVR), three-quarters of adults with repaired tetralogy of Fallot (TOF) or pulmonary stenosis (PS) present with at least mild tricuspid regurgitation (TR), and one-third present with at least moderate TR [1-4]. Although progressive annular dilatation and tethering of the subvalvular apparatus play a key role in the pathophysiology of the lesion, several primary malformations and iatrogenic injuries can further compromise valvular integrity [5-7]. Surgical exposure of the tricuspid valve at the time of PVR provides an ideal opportunity to accurately identify and address underlying mechanisms of regurgitation; however, the impact of an additional procedure on operative risk and valvular competence remains highly debated [3,4,8-12]. Thus, we conducted a national Canadian cohort study evaluating the early clinical and echocardiographic outcomes of adult congenital patients undergoing PVR with or without concomitant tricuspid valve intervention (TVI).

3.2.4. Methods

Study design and patient population

The Surgical Correction Of Tricuspid Insufficiency in Adult congenital patients requiring Pulmonary Valve Replacement (SCOTIA-PVR) study was designed and supported by the Canadian Congenital Cardiac Collaborative (4C). It is the first research initiative to involve surgeons from all 8 university centers across Canada routinely performing pediatric and adult congenital cardiac procedures. The multicenter retrospective observational cohort included all patients: 1) 18 years of age or older; 2) with previously corrected TOF or PS; 3) who underwent a first surgical pulmonary valve implant between January 1, 2000 and December 31, 2016; and 4) had more than trace TR on preoperative transthoracic echocardiography. Patients with pulmonary atresia and a history of right-ventricle-to-pulmonary-artery conduit, and those with complex intracardiac surgeries, such as complete atrioventricular septal defect and double-outlet right ventricle with noncommitted ventricular septal defect repairs, were excluded. At each collaborating site, eligible cases were identified using centralized procedural databases. Patients were ultimately divided into two groups based on their exposure to concomitant TVI. Tricuspid

intervention was defined as any surgical procedure purposefully applied to the valve to improve its competence and included both repairs and replacements.

Data collection and definition of outcomes

Research ethics board and institutional approvals were obtained in all recruiting adult sites before initiating enrollment. Approvals were also sought in four pediatric centers to retrieve old missing records and maximize data completeness. Data collection proceeded at each institution with a waiver of consent. It consisted of chart reviews and was highly standardized with a single abstractor and co-author (C.D.) performing data extraction at all sites.

Baseline characteristics, recorded at the time of PVR, included age; sex; congenital and acquired structural, coronary and arrhythmic diagnoses; components and timing of prior surgical and percutaneous cardiac procedures; preoperative transthoracic echocardiographic parameters; known genetic syndromes; and the presence of pulmonary, vascular, hepatic, renal and endocrine comorbidities. Operative details, procedural times, and urgency level were also collected. Preoperative atrial tachyarrhythmia was defined as any sustained atrial arrhythmia lasting >30 seconds, and ventricular arrhythmia, as any aborted sudden cardiac death or symptomatic episode lasting >30 seconds or requiring cardioversion or defibrillation. Urgency level, chronic lung disease and extracardiac arteriopathy were reported as per EuroScore definitions [13]. Glomerular filtration rates were estimated using the Cockroft-Gault formula [14]. Chronic liver disease included cirrhosis and any other condition causing, at the time of surgery, elevated transaminases for >6 months [15].

The first outcome of the study was a composite endpoint consisting of: 1) perioperative death; 2) readmission; 3) reintervention for bleeding; 4) implantation of a new cardiac electronic device; 5) major infection; 6) thromboembolic event; and 7) episode of acute renal failure leading to new-onset hemodialysis. Perioperative mortality was defined as any fatality occurring during the index admission or within 30 days of surgery. Readmissions were monitored for up to 30 days following hospital discharge. Other complications were also reported within 30 days of surgery. Reintervention for bleeding included surgical mediastinal or pleural re-exploration, as well as the insertion of a percutaneous pericardial drain. Implantation of a new cardiac

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electronic device was defined as any primary implant or upgrade to a different system type (e.g., pacemaker to defibrillator or resynchronization therapy). Major infections were categorized as respiratory (pneumonia), cardiac (endocarditis or device), surgical site (deep sternal wound or vascular harvest site), bloodstream (primary or central-line associated) or gastrointestinal (Clostridium difficile or intra-abdominal) in accordance with surveillance definitions from the Centers for Disease Control and Prevention [16]. Thromboembolic events included cardiac, neurologic, peripheral, renal and mesenteric arterial complications, as well as pulmonary embolisms and deep venous thromboses. With the exception of transient ischemic attacks, each of these events required appropriate confirmatory imaging [17-22].

The other two outcomes of the study were postoperative length of hospital stay and tricuspid regurgitation grade. Length of hospital stay was calculated in days in all patients surviving index admission from the date of surgery until discharge home or to a rehabilitation facility. Tricuspid regurgitation – graded as none/trivial, mild, moderate or severe – was directly abstracted from reports of transthoracic echocardiographic studies completed prior to discharge or within the first three months following PVR.

Quality control and study coordination

Two major layers of quality control were integrated into the SCOTIA-PVR study. Data collection was performed on spreadsheets with built-in systematic range and consistency checks, which automatically flagged invalid and inappropriately missing entries. On secure transfer and merging of databases, entries were again screened for implausible values. For continuous variables, observations found within the first and last fifth percentiles were verified against patient records. For categorical variables, outliers were identified through testing of conditional assumptions before being confirmed. The full project was coordinated from the Montreal Heart Institute, where data was also stored and analyzed.

Data analysis

Continuous baseline characteristics were expressed as mean ± standard deviation or median and interquartile range (25th-75th percentile). They were compared between patients with or without concomitant TVI using analyses of variance or Wilcoxon rank-sum tests, based on normality of distribution. Categorical variables were presented as frequencies and percentages and compared using chi-square tests.

The composite of all early adverse events and each of the seven separate endpoints were evaluated using multivariable logistic regression. Length of hospital stay and postoperative tricuspid regurgitation grades were respectively analyzed using multivariable negative binomial and ordered logistic regression. All cases (N=542) were included in the analysis of the composite endpoint and perioperative mortality. Other separate early adverse events were evaluated only in operative survivors (N=541); length of stay, in admission survivors (N=532); and tricuspid regurgitation, in live patients who underwent echocardiography within 3 months of surgery (N=498). The negative binomial regression model was also truncated to fit an observed minimum hospital stay of three days.

For each model, potential confounding variables were pre-selected based on available literature and suspected pathophysiological relevance. Relationships between variables were represented in directed acyclic graphs and variables likely to introduce a collider bias were excluded. The remaining confounders, listed in Appendix 1, were then tested in bivariable models with forced retention of exposure to TVI. For the 3 main study outcomes, final models were obtained through stepwise forward introduction of all variables leading to a >5% change in the odds ratio (OR) or incidence rate ratio (IRR) associated with TVI. To avoid overfitting, separate adverse events with an incidence between 5 and 10% were treated using a higher adjustment threshold of 10%. Events encountered in <5% of the cohort were adjusted only for baseline TR.

Finally, sensitivity analyses using the propensity-based matching weight method were carried for all study outcomes [23]. Matching weights were estimated from a non-parsimonious logistic regression model in which exposure to TVI was defined as the dependent variable and all variables listed in Appendix 2 were included as covariates. Balance after conditioning was

evaluated using the absolute standardized mean difference and deemed acceptable if the measure was <10% for all covariates. Marginal models were then fitted using generated weights. As propensity-based results did not differ from those obtained with conventional analyses, they were presented only as supplemental material. Two-tailed p-values <0.05 were considered statistically significant. All analyses were performed using STATA/SE software version 14.2 (StataCorp LP, College Station, Texas).

3.2.5. Results

Baseline and intraoperative characteristics

A total of 894 adults with corrected TOF or PS who underwent PVR were assessed for eligibility. Based on absent TR alone, 28.6% of otherwise eligible cases were excluded (Figure 1). Thus, 542 patients with mild, moderate or severe TR were enrolled of whom 362 (66.8%) received isolated PVR and 180 (33.2%), PVR+TVI. Baseline characteristics according to surgery type are presented in Table 1. The most common anatomical substrate was TOF corrected through a ventriculotomy with a transannular patch. Primary repair was only performed in 58.9% of cases, resulting in a high median age at complete correction. Prevalence of TVI in childhood was very low and similar between groups. At the time of PVR, the proportion of adults undergoing combined tricuspid surgery varied from 0 to 55.6% according to center. Besides institutional trends, TVI was associated with worse preoperative TR and right ventricular (RV) dilatation grades. Patients selected for a concomitant procedure were also slightly older and had more comorbidities, with a greater prevalence of chronic liver, lung and renal diseases, as well as diabetes, extracardiac arteriopathy, cardiac implantable electronic devices, and atrial tachyarrhythmia. There was no difference in the small proportion of urgent cases performed with or without TVI.

Group comparisons of intraoperative characteristics are displayed in Table 2. Tricuspid valve interventions included 165 (91.7%) repairs and 15 (8.3%) replacements. Ring, DeVega and Kay annuloplasties were respectively performed in 56.4, 13.3 and 7.3% of repairs. The remaining procedures (23.0%) involved a combination of leaflet and commisuro- plasties. With the exception of a single mechanical valve, all tricuspid valve replacements were bioprostheses.

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Pulmonary valve implant, branch arterioplasties, outflow tract remodeling, and residual atrial and ventricular septal defect closures were similarly carried with or without TVI. However, adding tricuspid surgery naturally translated in a greater proportion of patients with cardioplegic or fibrillatory arrests and longer procedural times.

Early adverse events

Early adverse events are summarized in Table 3. In the entire cohort, 11 patients (2.0%) died perioperatively. One death occurred during surgery following a clamp-related aortic dissection leading to almost eight hours of cardiopulmonary bypass, intractable biventricular failure and coagulopathy. Nine patients died within the index admission from heart failure (n=3), infection (n=3) or arrhythmia (n=3). The final patient died suddenly from a witnessed cardiac arrest four days after being discharged home following an uncomplicated hospital course. Twenty-nine survivors (5.5%) were readmitted within 30 days for fluid overload (n=12), infection (n=6), pericarditis (n=5), arrhythmia (n=3) and bleeding (n=3).

Combining all 7 types of early adverse events, 27.8% of patients with concomitant TVI suffered a complication – a crude risk 1.6 times that of subjects who had undergone PVR alone (OR: 1.60; 95% confidence interval [CI]: 1.06-2.44; p=0.027). However, in the adjusted multivariable analyses presented in Table 4, there was no significant difference observed in the composite endpoint between groups (OR: 0.85; 95% CI: 0.46-1.57; p=0.612). Factors independently associated with a higher combined risk of perioperative complications were body mass index (OR: 1.05; p=0.016), atrial tachyarrhythmia (OR: 3.64; P<0.001) and extracardiac arteriopathy (OR: 15.18; p=0.023). Consistently, concomitant TVI was not associated with any of the separate endpoints (Figure 2).

Length of hospital stay

Postoperative recovery time intervals are displayed in Table 5. Adults surviving their index admission were ventilated for a median of six hours, transferred out of intensive care a median of one day later, and discharged home a median of six days later. In univariable analyses, PVR+TVI was associated with a nearly 2-fold longer hospital stay than isolated PVR (IRR:

1.94; 95% CI: 1.26-2.99; p=0.003). However, in the final multivariable negative binomial model presented in Table 4, there was no longer a difference in hospitalization times measured between groups (IRR: 1.17; 95% CI: 0.93-1.46; p=0.181). As for adverse events, atrial tachyarrhythmia (IRR: 1.34; p=0.006) and extracardiac arteriopathy (IRR: 3.80; p=0.007) remained independently associated with an extended hospital stay.

Postoperative tricuspid regurgitation

The postoperative evolution of tricuspid insufficiency according to surgery type and preoperative TR grade is displayed in Figure 3. Regardless of the type of intervention performed, valvular competence improved by at least 1 grade in 35.4, 66.9 and 92.8% of patients with preoperative mild, moderate and severe TR, respectively. In the multivariable model presented in Table 4, concomitant TVI was independently associated with a 2.3-fold greater odds of improvement of TR by at least 1 grade as compared to PVR alone (OR: 0.44; 95% CI: 0.25-0.77; p=0.004). In contrast, higher grade of preoperative TR (OR: 3.75-9.46; P<0.001) and the presence of trans-valvular pacemaker or defibrillator leads (OR: 2.07; P<0.001) were the 2 factors independently associated with residual TR.

3.2.6. Discussion

The SCOTIA-PVR study, to the best of our knowledge, is the largest multicenter initiative to report on the short-term outcomes of combined pulmonary and tricuspid surgery in adults with corrected TOF and PS. In this national cohort, TR was ubiquitous – reported as mild, moderate or severe in more than 70% of all surgical referrals – and spontaneously decreased by at least one grade in fewer than half of isolated PVR cases. Still, in multivariable analyses, concomitant TVI was more than twice as likely to improve postoperative TR than PVR alone. Presence of trans-valvular leads independently contributed to residual TR. Finally, PVR+TVI was safe, resulting in comparable adjusted risk of early adverse events and length of hospital stay (Figure 4).

Spontaneous regression of TR in response to volume offloading was already documented after isolated surgical and transcatheter PVR and correlated with slight improvements in tricuspid annular diameter, coaptation distance, right ventricular size and systolic pressure [24-

27]. The current study is, however, the first to clearly demonstrate better early valvular competence with combined surgery, irrespective of preoperative TR grade and other comorbidities. Five observational cohorts published between 2010 and 2019 reported no difference in postoperative TR following PVR with or without TVI [3,8,10-12]. However, these studies were small (N=35-67), precluding multivariable analyses and carrying a high risk of a type 2 error. A larger cohort (N=129) published in 2015 alluded to an improvement in TR with PVR+TVI following a simple adjustment for baseline tricuspid insufficiency [4]. The reported odds ratio (OR: 0.67) was similar to that observed in our study (OR: 0.44), but it resulted from exploratory analyses without a clear approach to confounder control. Definitive conclusions could, therefore, not be drawn. In light of limited evidence, the SCOTIA-PVR cohort provides strong data confirming that TVI can improve tricuspid valve function beyond what is achieved with RV offloading.

Furthermore, the study raises awareness of lead-induced tricuspid insufficiency. At the time of PVR, 6.5% of our patients had 1, and 2.3%, between 2 and 3 right ventricular leads. Although this factor was not directly linked to preoperative TR, it is interesting to note that, in our cohort, for each trans-tricuspid lead, the risk of postoperative insufficiency more than doubled. This finding suggests that a component of lead-induced TR likely goes undetected in many patients with an intracardiac device, longstanding pulmonary regurgitation, and mixed functional TR [28]. Elective surgical PVR offers an ideal opportunity to evaluate and repair device-related injuries (e.g., leaflet perforation or fibrosis, chordal entrapment, etc.)[29], safely extract excess leads [30] and implant epicardial device systems if indicated [31,32]. In our national experience, interventions aimed at reducing trans-valvular lead burden have rarely been explored. These procedures may, therefore, merit a closer evaluation [33].

Regarding operative risk, presented results are consistent with those of other contemporary adult cohorts reporting low in-hospital mortality (1.1 to 4.6%) and rare complications causing long-term sequelae following pulmonary reintervention [34-37]. Yet, the SCOTIA-PVR study is the first to provide reassurance regarding safety concerns [9,10,12] by highlighting that TVI is commonly performed in late referrals – in patients displaying worse TR, low myocardial reserve and more comorbidities at the time of surgery. Naturally, this indication bias results in disproportionally higher crude rates of adverse events with TVI.

However, as also reported by studies evaluating the early outcomes of combined mitral and tricuspid surgery [38,39], these greater perceived risks do not withstand adjustment for confounders.

Taken together, findings from the SCOTIA-PVR study cast serious doubt on the appropriateness of conservative management of severe TR at the time of pulmonary reintervention in adults with repaired TOF and PS. They also confirm that concomitant TVI can safely improve moderate insufficiency beyond the effect of RV offloading – a strategy likely worthwhile to adopt in a population of young adults already at high risk for right heart failure. Additional research is required to explore the long-term clinical and echocardiographic impacts of combined surgery. Prospective mechanistic studies, using routine multimodal imaging and a standardized approach to reporting anatomic and functional tricuspid abnormalities, are also necessary to guide optimal patient and technique selection [40]. Meanwhile, based on our national experience, we advocate for the repair at a lower threshold of mechanisms unlikely to improve with RV offloading (e.g., leaflet entrapment in ventricular septal defect patch repairs, lead-related injuries, congenital malformations, and annular diameters >40mm) [41,42].

Limitations

The SCOTIA-PVR cohort is an observational study. Thus, its findings remain vulnerable to unmeasured confounders. Retrospective data collection resulted in a few missing postoperative echocardiographic studies (attrition rate: 6.4%), might have slightly underestimated the incidence of adverse events, and could not inform on the specific mechanisms of tricuspid regurgitation. A composite endpoint was reported, but its components were carefully selected to provide a comprehensive and clinically relevant depiction of surgical risk. Another limitation is that, despite the national experience, the sample size remained too small to allow for a comparison of specific TVI techniques. Last, patients requiring urgent PVR or diagnosed with complex pathologies were, respectively, underrepresented and excluded. Caution should, therefore, be exercised in generalizing results to these subgroups.

3.2.7. Conclusions

In the multicenter SCOTIA-PVR cohort of over 500 adults with repaired TOF or PS who presented for a first pulmonary valve implant with significant TR, PVR+TVI was associated with superior early tricuspid competence than isolated PVR. Moreover, in adjusted analyses, no increase in the risk of early adverse events was noted along with a similar hospital length of stay. Future research should explore the long-term outcomes of combined surgery and define optimal indications for TVI. Meanwhile, combined surgery can be considered safe and should be offered to young adults who display moderate to severe tricuspid valve insufficiency at the time of PVR.

Perspectives

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In adults with corrected tetralogy of Fallot or pulmonary stenosis, severe tricuspid regurgitation should be considered a relative contraindication to isolated pulmonary valve replacement, with concurrent replacement or repair of the tricuspid valve potentially improving postoperative tricuspid valve function.

TRANSLATIONAL OUTLOOK: Future studies should incorporate a systematic approach to classifying the structure and function of the tricuspid valve to clarify the indications for intervention and improve long-term clinical outcomes.

3.2.8. Tables

Table 1.   Baseline characteristics

	All cases N=542	PVR N=362	PVR+TVI N=180	P-value
Congenital surgical history				
Age at complete repair, years	4.6 (2.2-7.7)	4.1 (1.9-6.6)	5.8 (2.8-11.3)	<0.001
Tetralogy of Fallot, N (%)	433 (79.9)	304 (84.0)	129 (71.7)	0.001
Primary repair, N (%)	319 (58.9)	213 (58.8)	106 (58.9)	0.991
Ventriculotomy, N (%)	474 (87.5)	322 (89.0)	152 (84.4)	0.136
Transannular patch, N (%)	314 (57.9)	225 (62.2)	89 (49.4)	0.005
Tricuspid intervention, N (%)	11 (2.0)	6 (1.7)	5 (2.8)	0.384
Total number of sternotomies	1 (1-2)	1 (1-2)	1 (1-2)	0.249
Clinical parameters at reintervention				
Age at reintervention, years	35.3 (25.6-46.0)	33.7 (24.9-43.8)	39.6 (27.6-52.1)	<0.001
Female sex, N (%)	249 (45.9)	158 (43.7)	91 (50.6)	0.128
Body mass index, kg/m^2	25.6 (21.8-28.4)	24.8 (22.0-28.0)	25.1 (21.6-29.1)	0.322
Confirmed genetic syndrome, N (%)	60 (11.1)	44 (12.2)	16 (8.9)	0.254
Chronic liver disease, N (%)	9 (1.7)	2 (0.6)	7 (3.9)	0.004
Chronic lung disease, N (%)	25 (4.6)	11 (3.0)	14 (7.8)	0.013
Diabetes, N (%)	29 (5.4)	12 (3.3)	17 (9.4)	0.003
Extracardiac arteriopathy, N (%)	5 (0.9)	0 (0)	5 (2.8)	0.001
Glomerular filtration rate, mL/min	114 ± 36	118 ± 33	109 ± 41	0.001
Atrial tachyarrhythmia, N (%)	133 (24.5)	57 (15.8)	76 (42.2)	<0.001
Intra-atrial re-entry tachycardia	73 (13.5)	35 (9.7)	38 (21.1)	
Atrial fibrillation	60 (11.1)	22 (6.1)	38 (21.1)	
Ventricular arrhythmia, N (%)	38 (7.0)	25 (6.9)	13 (7.2)	0.892
Cardiac electronic device, N (%)	52 (9.6)	26 (7.2)	26 (14.4)	0.007
Number of trans-tricuspid leads[*]	1 (1-1)	1 (1-2)	1 (1-1)	0.269
Urgent admission, N (%)	33 (6.1)	19 (5.2)	14 (7.8)	0.342
Due to heart failure	16 (3.0)	8 (2.2)	8 (4.4)	
Due to ventricular arrhythmia	17 (3.1)	11 (3.0)	6 (3.3)	

Table 1. Baseline characteristics (…)

Transthoracic echocardiographic parameters at reintervention				
Tricuspid regurgitation, N (%)				<0.001
Moderate	192 (35.4)	102 (28.2)	90 (50.0)	
Severe	72 (13.3)	4 (1.1)	68 (37.8)	
Pulmonary regurgitation, N (%)				<0.001
Moderate	49 (9.0)	17 (4.7)	32 (17.8)	
Severe	481 (88.7)	337 (93.1)	144 (80.0)	
Pulmonary stenosis (>mild), N (%)	65 (12.0)	45 (12.4)	20 (11.1)	0.656
RV dilatation, N (%)				0.037
Mild	74 (13.7)	57 (15.8)	17 (9.4)	
Moderate	226 (41.7)	157 (43.4)	69 (38.3)	
Severe	237 (43.7)	144 (39.8)	93 (51.7)	
RV dysfunction (>mild), N (%)	130 (24.0)	84 (23.2)	46 (25.6)	0.546
LV ejection fraction, %	58 ± 6	58 ± 6	57 ± 7	0.279
Values are median (25th-75th percentile), n (%), or mean ± SD. *Calculations excluded device-free cases. LV = left ventricular; PVR = pulmonary valve replacement; PVR+TVI = pulmonary valve replacement with concomitant tricuspid intervention; RV = right ventricular.				

Table 2.   Intraoperative characteristics

	All cases N=542	PVR N=362	PVR+TVI N=180	P-value
Pulmonary prosthesis size, mm	29 (27-29)	29 (27-29)	29 (27-29)	0.669
Branch pulmonary arterioplasty, N (%)	109 (20.1)	81 (22.4)	28 (15.6)	0.062
Residual VSD closure, N (%)	38 (7.0)	28 (7.7)	10 (5.6)	0.349
Atrial ablation, N (%)	68 (12.6)	22 (6.1)	46 (25.6)	<0.001
Ventricular ablation, N (%)	70 (12.9)	51 (14.1)	19 (10.6)	0.248
Combined procedures, N (%)	43 (7.9)	22 (6.1)	21 (11.7)	0.074
Coronary bypass	18 (3.3)	10 (2.8)	8 (4.4)	
Mitral valve	8 (1.5)	2 (0.6)	6 (3.3)	
Aortic valve	7 (1.3)	4 (1.1)	3 (1.7)	
Thoracic aorta +/- aortic valve	5 (0.9)	4 (1.1)	1 (0.6)	
Other	5 (0.9)	2 (0.6)	3 (1.7)	
Cardiopulmonary bypass time, min	100 (71-137)	86 (65-117)	123 (105-163)	<0.001
Aortic clamping or fibrillation, N (%)	356 (65.7)	210 (58.0)	146 (81.1)	<0.001
Arrest time, min[*]	58 (42-82)	51 (40-73)	71 (46-91)	<0.001
Femoral cannulation due to injury, N (%)	41 (7.6)	26 (7.2)	15 (8.3)	0.633
Values are median (25th-75th percentile) or n (%). [*]Calculations excluded cases without aortic clamping or fibrillation. VSD = ventricular septal defect; other abbreviations as in Table 1.				

Table 3. Early adverse events according to surgery type

	All cases	PVR	PVR+TVI	P-value
Mortality, N (%)	**N=542**	**N=362**	**N=180**	
Within admission or 30 days of surgery	11 (2.0)	5 (1.4)	6 (3.3)	0.129
Other complications, N (%)	**N=541**	**N=362**	**N=179**	
Major infection*	49 (9.1)	26 (7.2)	23 (12.8)	0.031
Respiratory	37 (6.8)	21 (5.8)	16 (8.9)	
Bloodstream	11 (2.0)	4 (1.1)	7 (3.9)	
Surgical site	7 (1.3)	3 (0.8)	4 (2.2)	
Cardiac	5 (0.9)	4 (1.1)	1 (0.6)	
Gastrointestinal	4 (0.7)	1 (0.3)	3 (1.7)	
New cardiac electronic device	40 (7.4)	23 (6.4)	17 (9.5)	0.189
Secondary prevention defibrillator	14 (2.6)	7 (1.9)	7 (3.9)	
Primary prevention defibrillator	14 (2.6)	12 (3.3)	2 (1.1)	
Pacemaker or resynchronization therapy	12 (2.2)	4 (1.1)	8 (4.5)	
Reintervention for bleeding	25 (4.6)	14 (3.9)	11 (6.1)	0.235
New-onset hemodialysis	7 (1.3)	3 (0.8)	4 (2.2)	0.173
Thromboembolic or ischemic event*	6 (1.1)	3 (0.8)	3 (1.7)	0.376
Cerebrovascular accident	4 (0.7)	2 (0.6)	2 (1.1)	
Myocardial infarction	1 (0.2)	0 (0.0)	1 (0.6)	
Pulmonary embolism	1 (0.2)	1 (0.3)	0 (0.0)	
Deep venous thrombosis	1 (0.2)	0 (0.0)	1 (0.6)	
Readmission, N (%)	**N=532**	**N=358**	**N=174**	
Within 30 days of discharge	29 (5.5)	18 (5.0)	11 (6.3)	0.537
Composite endpoint, N (%)	**N=542**	**N=362**	**N=180**	
Any type of event	120 (22.1)	70 (19.3)	50 (27.8)	0.026

Values are n (%). *Subcategories are not mutually exclusive. Abbreviations as in Table 1.

Table 4. Factors associated with the main study outcomes in multivariable analyses

	Adjusted RR	95% CI	P-value
Model 1: Composite of 7 early adverse events (N=542)[*]			
Pulmonary valve replacement			
** With concomitant tricuspid intervention**	**0.85**	**0.46 – 1.57**	**0.612**
Comorbidities			
Atrial tachyarrhythmia	3.64	2.18 – 6.06	<0.001
Extracardiac arteriopathy	15.18	1.44 – 159.49	0.023
Body mass index (kg/m^2)	1.05	1.01 – 1.09	0.016
Preoperative tricuspid regurgitation grade			
Moderate	1.25	0.74 – 2.13	0.400
Severe	1.43	0.64 – 3.22	0.387
Model 2: Length of hospital stay (N=532)[*]			
Pulmonary valve replacement			
** With concomitant tricuspid intervention**	**1.17**	**0.93 – 1.46**	**0.181**
Comorbidities			
Atrial tachyarrhythmia	1.35	1.09 – 1.66	0.006
Extracardiac arteriopathy	3.80	1.44 – 10.08	0.007
Preoperative tricuspid regurgitation grade			
Moderate	1.10	0.93 – 1.31	0.253
Severe	1.85	0.92 – 3.70	0.083
Model 3: Residual postoperative tricuspid regurgitation (N=498)[*]			
Pulmonary valve replacement			
** With concomitant tricuspid intervention**	**0.44**	**0.25 – 0.77**	**0.004**
Preoperative tricuspid regurgitation grade			
Moderate	3.75	2.36 – 5.97	<0.001
Severe	9.46	4.20 – 21.33	<0.001
Cardiac electronic device			
Number of trans-tricuspid leads	2.07	1.39 – 3.09	<0.001
[*]The 3 models were also adjusted for center, but relative risks of collaborating institutions were omitted. CI = confidence interval; RR = relative risk.			

Table 5.   Recovery time intervals of admission survivors according to surgery type

	All cases N=532	PVR N=358	PVR+TVI N=174	P-value
Invasive ventilation, hours	6.0 (4.1-11.0)	6.0 (4.1-9.1)	7.4 (5.0-16.1)	<0.001
>48 hours, N (%)	19 (3.6)	9 (2.5)	10 (5.8)	0.019
Intensive care stay, days	1.0 (1.0-2.5)	1.0 (1.0-2.0)	2.0 (1.0-4.0)	<0.001
>4 days, N (%)	58 (10.9)	27 (7.5)	31 (17.8)	<0.001
Hospital stay, days	6.0 (5.0-8.0)	6.0 (5.0-7.0)	7.0 (5.0-10.0)	<0.001
>7 days, N (%)	151 (28.4)	80 (22.4)	71 (40.8)	<0.001
Values are median (25th-75th percentile) or n (%). Abbreviations as in Table 1.				

3.2.9. Figures

Figure 1. Cohort selection flowchart

This figure summarizes enrollment, treatment allocation, and reasons for exclusion. PS = pulmonary stenosis; PVR = pulmonary valve replacement; PVR+TVI = pulmonary valve replacement with concomitant tricuspid intervention; TOF = tetralogy of Fallot; TR = tricuspid regurgitation; TTE = transthoracic echocardiography.
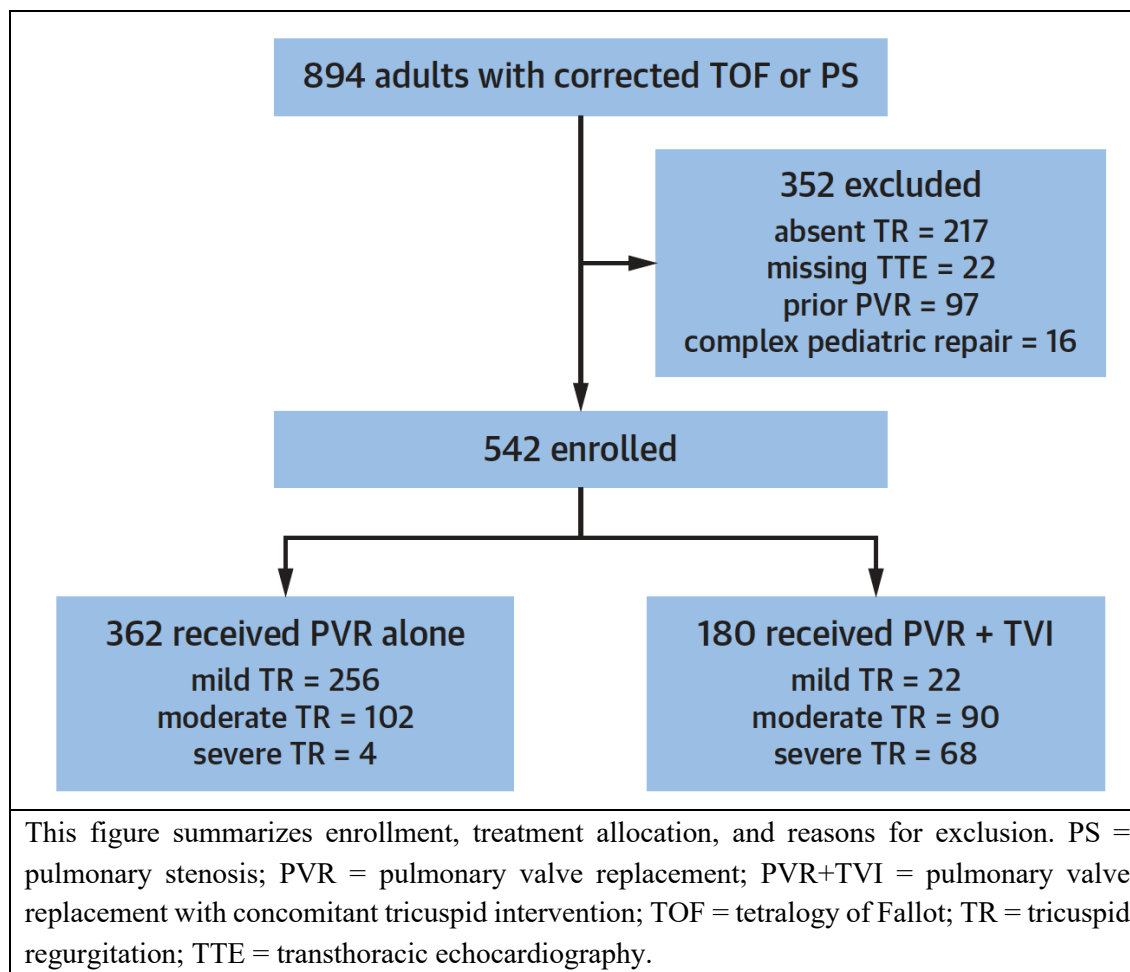
Figure 2. Crude and adjusted odds ratios of the 7 early adverse events and composite endpoint following concomitant tricuspid valve intervention
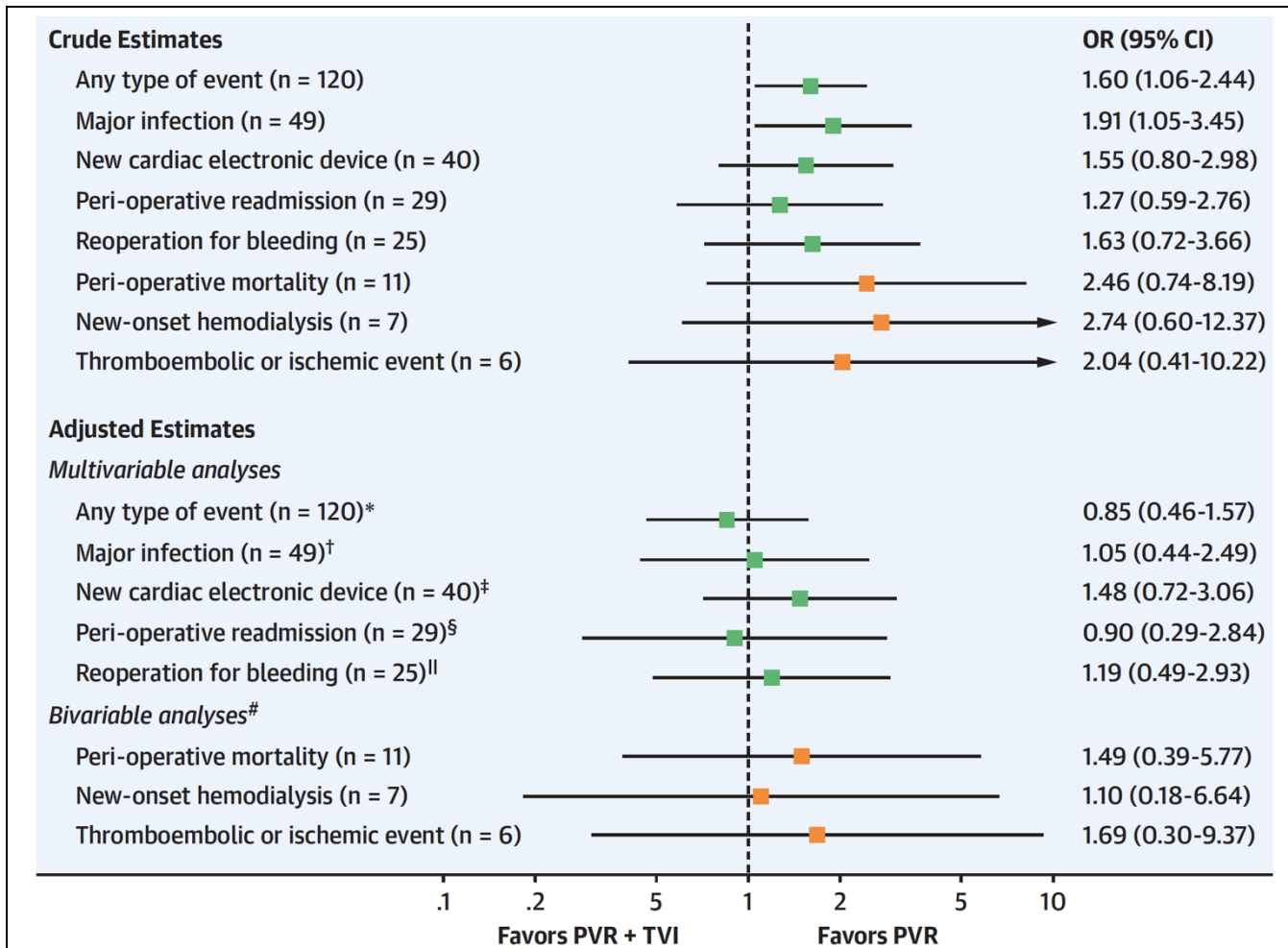
This figure depicts the crude and adjusted odds ratios associated with concomitant TVI for the 7 early adverse events and composite endpoint reported in the study. Outcomes in green were treated using multivariable and outcomes in orange, using bivariable analyses. Multivariable regression models were respectively adjusted for: *baseline tricuspid regurgitation grade, body mass index, center, extracardiac arteriopathy and atrial tachyarrhythmia; †age at intervention, baseline tricuspid regurgitation grade, body mass index and atrial tachyarrhythmia; ‡age at intervention, center and underlying congenital cardiac diagnosis; §baseline tricuspid regurgitation grade, center and atrial tachyarrhythmia; and ‖additional minutes spent or saved on cardiopulmonary bypass based on group-specific medians, other combined procedures and atrial tachyarrhythmia. #Bivariable models were only adjusted for baseline tricuspid regurgitation grade. CI = confidence interval; OR = odds ratio; TVI = tricuspid valve intervention; other abbreviations as in Figure 1.

Figure 3. Evolution of postoperative tricuspid regurgitation grade according to surgery type and baseline insufficiency

This figure presents the relative percentages of patients with improving, worsening, and stable postoperative tricuspid regurgitation according to the type of surgery received and the grade of insufficiency recorded before the procedure. Abbreviations as in Figure 1.
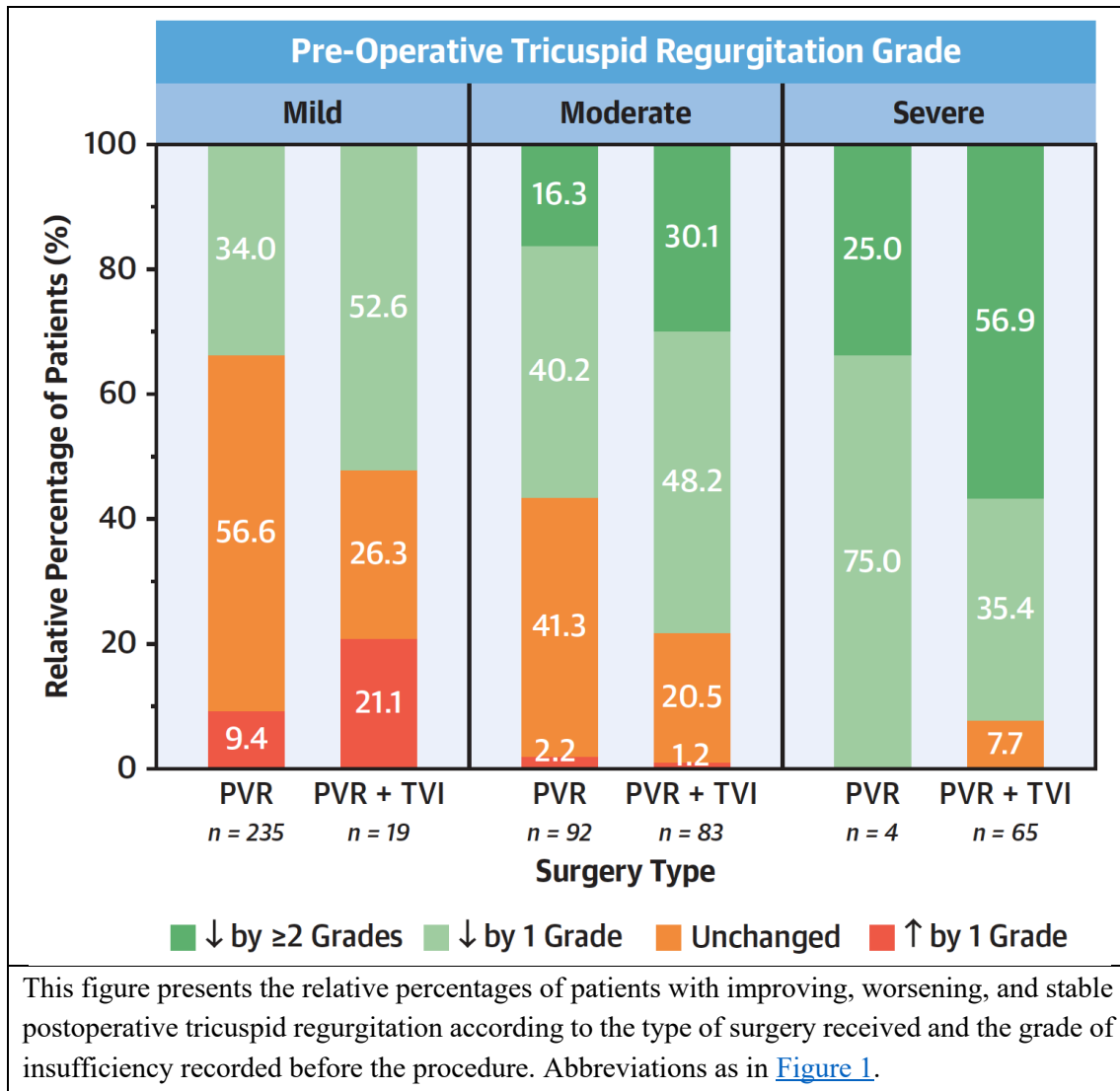
Figure 4. Adjusted relative risks of complications following concomitant tricuspid valve intervention

Outcome	Relative Risk (95% CI)	
Residual post-operative tricuspid regurgitation	0.44 (0.25-0.77)	
Composite of 7 early adverse events	0.85 (0.46-1.57)	
Length of hospital stay	1.17 (0.93-1.46)	

0.2   0.5   1   2

Favors PVR+TVI   Favors PVR

The main study findings are summarized. PVR = pulmonary valve replacement; PVR+TVI = pulmonary valve replacement with concomitant tricuspid intervention.
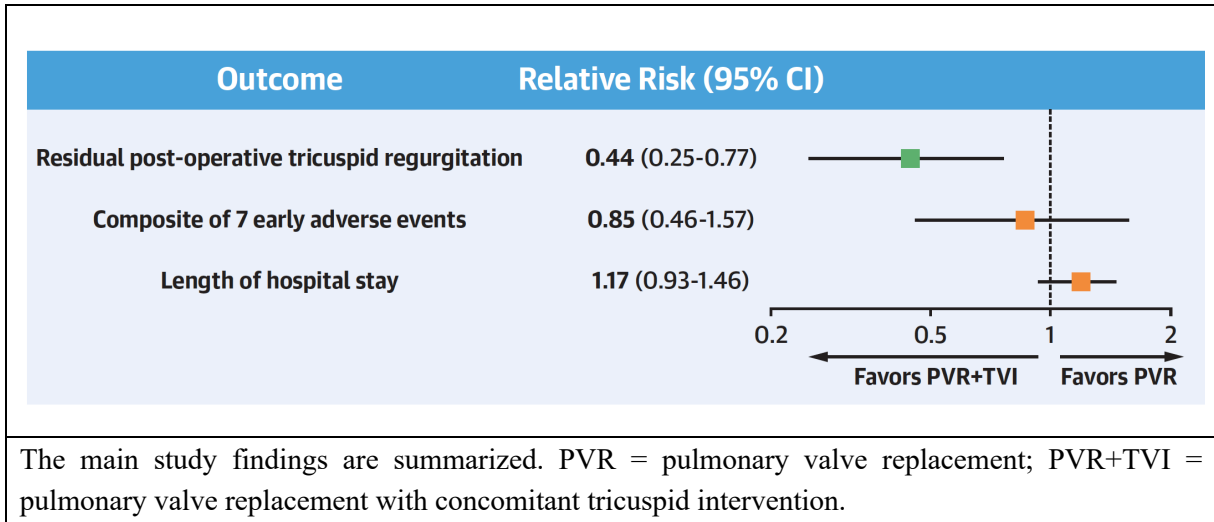
3.2.10. Supplemental material

Appendix 1. Confounding variables tested in multivariable analyses

Preoperative variables common to all models:

Age at reintervention (continuous); atrial tachyarrhythmia (yes/no); baseline right ventricular dilatation and dysfunction grades (none, mild, moderate, severe); body mass index (continuous); center (8 sites); chronic liver disease (yes/no); chronic lung disease (yes/no); combined procedures (aortic, mitral, coronary, thoracic aorta, other); diabetes (yes/no); estimated glomerular filtration rate (continuous); extracardiac arteriopathy (yes/no); femoral cannulation due to injury at sternotomy (yes/no); known genetic syndrome (yes/no).

Composite endpoint of all early serious adverse events:

+Additional preoperative variables introduced by the following separate endpoints.

Major infection and perioperative readmission:

Baseline tricuspid regurgitation grade (mild, moderate, severe); cardiac implantable electronic device (yes/no); left ventricular ejection fraction (continuous); urgency level (urgent/elective).

New cardiac implantable electronic device:

Age at complete repair (continuous); cardiac implantable electronic device (yes/no); prior tricuspid intervention (yes/no); prior ventriculotomy (yes/no); underlying congenital cardiac diagnosis (tetralogy of Fallot/pulmonary stenosis); ventricular arrhythmia (yes/no).

Reintervention for bleeding:

Additional minutes spent or saved on cardiopulmonary bypass based on group-specific medians (continuous); baseline tricuspid regurgitation grade (mild, moderate, severe); cardiac implantable electronic device (yes/no); left ventricular ejection fraction (continuous); urgency level (urgent/elective).

Length of hospital stay:

+Baseline tricuspid regurgitation grade (mild, moderate, severe); cardiac implantable electronic device (yes/no); left ventricular ejection fraction (continuous); urgency level (urgent/elective).

Postoperative tricuspid regurgitation grade:

+Age at complete repair (continuous); aortic cross-clamping or fibrillation (yes/no); baseline tricuspid regurgitation grade (mild, moderate, severe); number of trans-tricuspid leads (continuous); prior tricuspid intervention (yes/no); prior ventricular septal defect repair (none, muscular, perimembranous, mixed); repeated ventricular septal defect closure (yes/no); underlying congenital cardiac diagnosis (tetralogy of Fallot/pulmonary stenosis); ventricular arrhythmia (yes/no).

Appendix 2. Results from the propensity-based sensitivity analyses

Variables included in the non-parsimonious logistic model estimating matching weights:

Congenital surgical history:

+Age at complete repair (continuous); underlying congenital cardiac diagnosis (tetralogy of Fallot/pulmonary stenosis); primary repair (yes/no); prior ventriculotomy (yes/no); prior transannular patch (yes/no); prior ventricular septal defect repair (none, muscular, perimembranous, mixed); prior tricuspid intervention (yes/no); number of previous sternotomies (continuous).

Clinical evaluation at reintervention:

+Age at reintervention (continuous); center (8 sites); body mass index (continuous); known genetic syndrome (yes/no); chronic liver disease (yes/no); chronic lung disease (yes/no); diabetes (yes/no); estimated glomerular filtration rate (continuous); atrial tachyarrhythmia (yes/no); ventricular arrhythmia (yes/no); cardiac implantable electronic device (yes/no); number of trans-tricuspid leads (continuous); urgency level (urgent/ elective).

Transthoracic echocardiographic evaluation at reintervention:

+Baseline tricuspid regurgitation grade (mild, moderate, severe); baseline pulmonary regurgitation grade (mild, moderate, severe) baseline right ventricular dilatation and dysfunction grades (none/mild, >mild); baseline pulmonary stenosis grade (none/mild, >mild); baseline left ventricular dysfunction grade (none/mild, >mild).

Intraoperative characteristics:

+Pulmonary prosthesis size (continuous); branch pulmonary arterioplasty (yes/no); repeated ventricular septal defect closure (yes/no); aortic cross-clamping or fibrillation (yes/no); atrial cryoablation (yes/no); ventricular cryoablation (yes/no); combined procedures (aortic, mitral, coronary, thoracic aorta, other); femoral cannulation due to injury at sternotomy (yes/no); additional minutes spent or saved on cardiopulmonary bypass based on group-specific medians (continuous).

Figure 5. Love plot of absolute standardized mean differences
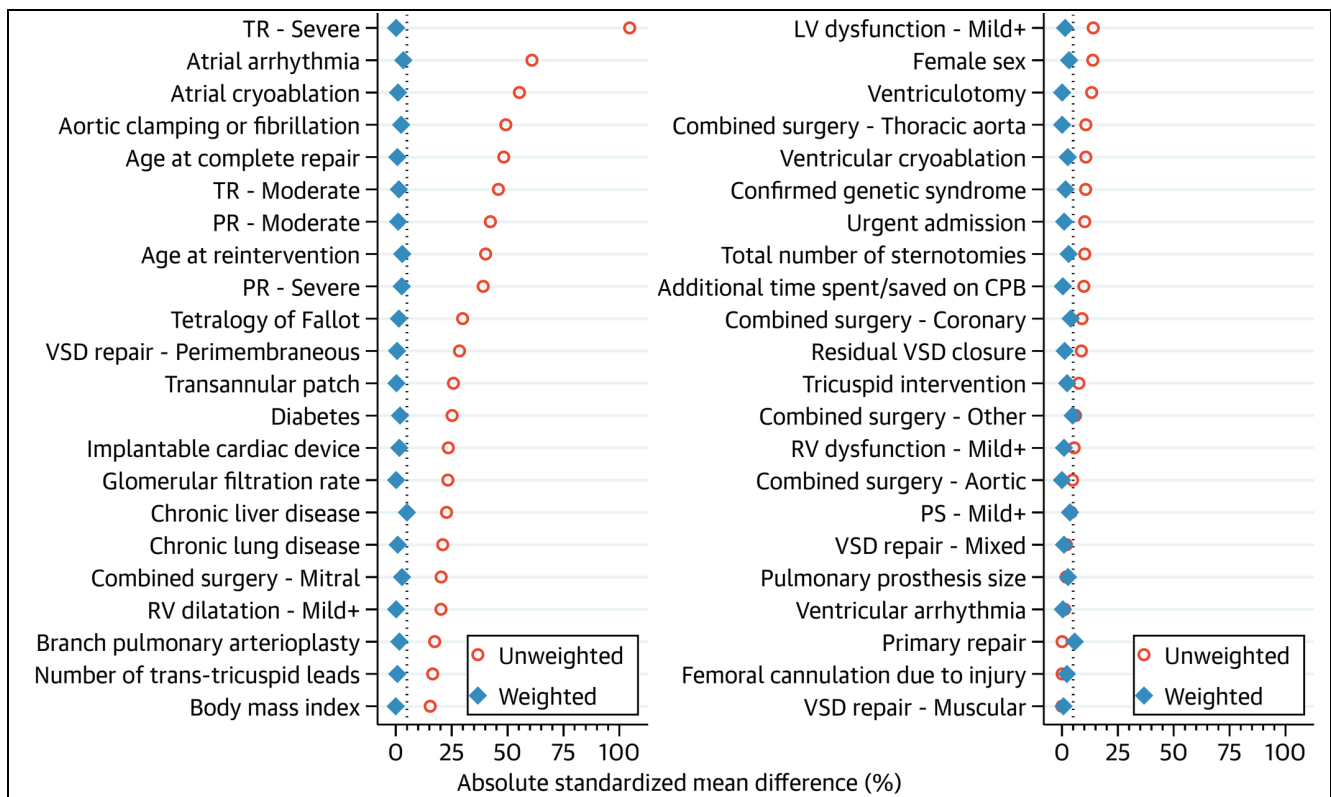
This summary plot depicts covariate balance before and after conditioning using matching weights. An absolute standardized mean difference <5% was obtained for all variables (including centers which were omitted from the graph) indicating excellent balance between groups. CPB = cardiopulmonary bypass; LV = left ventricular; PR = pulmonary regurgitation; PS = pulmonary stenosis; RV = right ventricular; TR = tricuspid regurgitation; VSD = ventricular septal defect.

Table 6.   Adjusted relative risks obtained with multivariable and propensity analyses

Study outcome	Multivariable analyses			Propensity analyses		
	RR	95% CI	P-value	RR	95% CI	P-value
Postoperative tricuspid regurgitation	0.44	0.25-0.77	0.004	0.46	0.27-0.77	0.003
Composite of 7 early adverse events	0.85	0.46-1.57	0.612	0.94	0.50-1.80	0.860
Major infection	1.05	0.44-2.49	0.909	0.89	0.35-2.23	0.798
New implantable cardiac device	1.48	0.72-3.06	0.291	1.34	0.47-3.80	0.586
Perioperative readmission	0.90	0.29-2.84	0.859	0.69	0.20-2.43	0.565
Reoperation for bleeding	1.19	0.49-2.93	0.698	1.25	0.32-3.50	0.934
Perioperative mortality	1.49	0.39-5.77	0.560	1.15	0.25-5.18	0.482
New-onset hemodialysis	1.10	0.18-6.64	0.916	1.03	0.16-2.61	0.567
Thromboembolic or ischemic event	1.69	0.30-9.37	0.549	1.46	0.32-8.67	0.446
Length of hospital stay	1.17	0.93-1.46	0.181	1.20	0.96-1.48	0.101
This table presents adjusted results obtained with propensity-based matching weight and standard multivariable analyses. Both approaches generated similar estimates and support the same conclusions. CI = confidence interval; RR = relative risk.						

3.2.11. References

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Chapter 4. Discussion and Conclusion

This last chapter summarizes thesis findings and provides an in-depth analysis of the strengths, limitations and clinical implications of the two presented articles. A concluding statement also emphasizes the general relevance and originality of the thesis.

4.1. The Fontan TACTIC Cohort (Article 1)

Findings of the international Fontan TACTIC cohort, which enrolled over 500 patients with a univentricular heart and Fontan palliation, can be summarized as follows: 1) our study is the first to document an independent association between extracardiac conduits and a lower risk of systemic (HR: 0.20; 95% CI: 0.04-0.97) and combined (HR: 0.34; 95% CI: 0.13-0.91) thromboembolic complications when compared to lateral tunnels; 2) we observed a lower incidence of combined events with antiplatelet therapy (HR: 0.54; 95% CI: 0.32-0.92), but not anticoagulation (HR: 1.21; 95% CI: 0.68-2.15); and 3) we identified a trend towards a higher risk of systemic events with the development of atrial arrhythmias (HR 2.55; 95% CI: 0.91-7.10).

4.1.1. Strengths

Our study displays several strengths. First, we identified and recruited patients using surgical rather than clinic databases. Opportunistic recruitment strategies based on outpatient registries are often used to explore late complications in repaired congenital heart disease. Unfortunately, while comparing surgical techniques, these methods may introduce a selection bias when survival, monitoring intensity or patient compliance varies between treatment groups. TACTIC, by virtue of its design, clearly avoided such a pitfall.

Second, the project integrated several layers of quality control. Data collection was performed using a common case report form. Critical events were blindly adjudicated. Data entry was also carefully monitored to detect aberrant values. Although these mechanisms could not prevent systematic differences to arise from initial patient management, they certainly

contributed to reduce random errors and differential misclassification. Generally speaking, accurate data collection optimizes study power and decreases the risk of information bias.

Third, data from TACTIC was not collected with the intention of comparing surgical techniques. Thus, there is no reason to believe that our findings may be influenced by the presence of observer bias.

Fourth, our cohort was the first to estimate thromboembolic risk across surgical techniques with more than 100 subjects per treatment arm. A large sample size, but most importantly balanced treatment groups, maximized power. In observational research, statistical power cannot be over-stated as it is of fundamental importance in performing the sophisticated analyses usually required to reach adequate confounding control.

Fifth, given the high level of details included in our database, we were able to treat atrial arrhythmia and thromboprophylaxis, two very important confounders, as time-dependent variables. The quality of these adjustments certainly contributed to reduce the risk of confounding bias.

Last, findings from our cohort, which involved a total of 12 North American university hospital centers, are definitely of greater generalizability than that of the majority of comparable studies, mostly single-centered initiatives (Table 2) [108-110,112,128,143].

4.1.2. Limitations

Although the Fontan TACTIC study resulted in higher-quality evidence than previously published data, it remains an observational cohort vulnerable to confounding, selection and information biases. A few aspects of its design may also limit generalizability.

Confounding Bias

A first concern is the potential presence of time-related bias. Atriopulmonary connections were introduced more than a decade before total cavopulmonary approaches. One could therefore assume that a growing awareness of the issue of thrombosis and progressive improvement in the quality of echocardiographic images, two factors leading to an increase in outcome detection over time, would disadvantage the lateral tunnel and extracardiac conduit, and that preventative strategies, such as thromboprophylaxis, staging and fenestration, would disadvantage the

atriopulmonary connection. In order to address the issue of time-related bias, we adjusted for 16 potential confounders reflecting changes in practice that could have impacted thromboembolic risk. However, since the full TACTIC project was not designed with the intention of comparing surgical techniques, other variables for which we would have liked to adjust could not be obtained from the database. To account for part of the unmeasured confounding, we stratified all of our analyses by surgical decade. We acknowledge that this indirect adjustment strategy is not ideal and that our comparison of the atriopulmonary connection to the lateral tunnel may remain biased. However, as the extracardiac conduit and lateral tunnel techniques were introduced around the same time, it would be surprising for our main study findings contrasting both procedures to be greatly influenced by the presence of residual time-related bias.

Selection Bias

Another threat to the internal validity of TACTIC is the potential presence of selection bias. While attrition was limited by recruiting only local patients, about 15% of our subjects were lost to follow-up, a state defined as more than 24 months without medical contact. Upon stratification by surgical decade, the baseline characteristics of our patients with complete follow-up did not significantly differ from those who were lost, so we performed survival analyses assuming independent censoring. Still, there is a small possibility that our estimates may be biased by the presence of underappreciated differential attrition between groups.

In the current study, we also treated outcomes precluding or modifying the occurrence of thromboembolic complications as competing events. We used a cause-specific modeling approach as it was the easiest technique to apply using commercially available software in the presence of time-varying covariates. An important caveat of most strategies for modelling competing risks is that they also assume independent censoring. Unfortunately, such a condition is impossible to validate. There is no doubt that a faulty assumption of independence could have triggered a selection bias influencing our results. However, given that the majority of deaths, transplantations and Fontan conversions occurred after a first thromboembolic episode and that censoring due to a competing event only affected about 5% of our cohort, we believe that such a risk is rather low.

Information Bias

Third, we were initially concerned that outcome surveillance in our cohort could have been influenced by surgical exposure. More specifically, we suspected that cases of acute graft thrombosis reported in the mid-1990s could have triggered more aggressive clinical and echocardiographic monitoring of patients with extracardiac conduits, disadvantaging the procedure [137-139]. However, since our final results favored this technique, such a problem appears unlikely.

External Validity

As mentioned earlier, TACTIC definitely yielded findings of greater generalizability than that of comparable studies. However, caution should still be exercised in generalizing its conclusions to all patients progressing along Fontan stages as it only included children who survived full palliation and remained followed in tertiary centers. Finally, we acknowledge that our results may need to be replicated outside of North America to gain wider acceptance.

4.1.3. Clinical implications of the findings and future perspectives

As stated in the discussion section of Article 1, our main study findings, concluding in a lower risk of systemic and combined thromboembolic events with extracardiac conduit as opposed to lateral tunnel Fontan surgery, are quite provocative as they cast doubt on the widely held notion that the former is potentially more thrombogenic by virtue of greater exposure to synthetic material and relative flow restriction through a fixed pathway.

Growth potential was historically regarded as a major advantage of the lateral tunnel. However, recent evidence suggests that maturation of this type of connection is seldom proportional to somatic growth. In the first 5 years following palliation, the indexed size of lateral tunnels tends to fall, driving resistance across the Fontan pathway up to measures comparable to those obtained across 16 to 18mm conduits [225]. A longitudinal observational study carried in older children also demonstrated a greater risk of pathway distortion with the intracardiac as compared to the extracardiac cavopulmonary connection [226]. Thus, although the lateral tunnel displays growth potential, this feature does not seem to translate into better

fluid dynamics. In contrast, a clear advantage of the extracardiac conduit is its unparalleled procedural flexibility. A lateral tunnel completed after a hemi-Fontan generally results in a T-shape construct prone to collision of superior and inferior vena cavae flows and steep dissipation of energy [227]. In comparison, the extracardiac conduit preceded by a Glenn procedure allows for 4 different modifications: caval offset, curving or flaring of the anastomoses, and Y-grafting (Figure 10) [227]. In computer modelization and in-vitro studies, these subtle changes in structure has been shown to promote conservation of energy [228-231]. While the current study does not provide insight into the exact mechanisms explaining differences in thrombogenicity observed across surgical techniques, it could be hypothesized that optimization of geometry and blood flow energetics may favor the extracardiac conduit. Indeed, laminar flow could limit chronic local activation of the coagulation cascade and, when combined with a slight reduction in portal pressure, translate in improved synthesis and metabolism of blood components.

With regards to the specific reasons that could explain a higher risk of arterial, as opposed to venous, thromboembolic events following lateral tunnel Fontan palliation, it is possible that suboptimal hemodynamics could preferentially trigger platelet activation, which, in turn, may promote intra-arterial thrombus formation [232]. Furthermore, a large proportion of systemic events diagnosed after univentricular palliation are caused by paradoxical emboli [72]. Thus, one could hypothesize that a higher incidence of underappreciated right-to-left shunts may disadvantage the lateral tunnel. Small baffle leaks, for example, a well-recognized technical problem associated with this type of repair, could certainly promote such a phenomenon. Pulmonary arteriovenous malformations may also trigger right-to-left shunting. However, as a lateral tunnel combined to a hemi-Fontan generally result in better hepatic factor distribution between lungs than other constructs [227], they are unlikely to play an important role here. Finally, a significant percentage of arterial thromboembolic events can usually be attributed to clot formation within the systemic atrium [72]. In the absence of fenestration, an extracardiac conduit only exposes venous blood to foreign surface. In contrast, the intracardiac baffle of a lateral tunnel also comes in contact with arterial, or systemic atrial, blood. In this context, one could assume that the presence of a small piece of intracardiac foreign material may be more dangerous for the systemic circulation than of a large synthetic tube placed outside of heart chambers.

Of course, all of these postulates remain to be validated. The interplay between operative technique, blood flow energetics, hepatic factor distribution, liver function, coagulation factor levels, platelet activation, and thromboembolic risk after univentricular palliation certainly warrants additional research. While the integration of fundamental and clinical knowledge remains challenging, the emergence of new imaging modalities, such as 4D flow cardiac magnetic resonance imaging, a technique enabling comprehensive assessment of in-vivo intracardiac flow patterns and reproducible quantification of energy loss, may soon facilitate this critical step [233-237].

Pending new advances in the field, findings from TACTIC support the use of antiplatelet therapy, as opposed to anticoagulation, in children undergoing univentricular palliation with an extracardiac conduit, provided that they remain free of additional risk factors for thrombosis [72,88]. In other words, based on our results, the extracardiac conduit should not be considered, in and of itself, a significant thrombogenic contributor (Table 1).

Figure 10. Modifications reducing energy losses in the extracardiac conduit
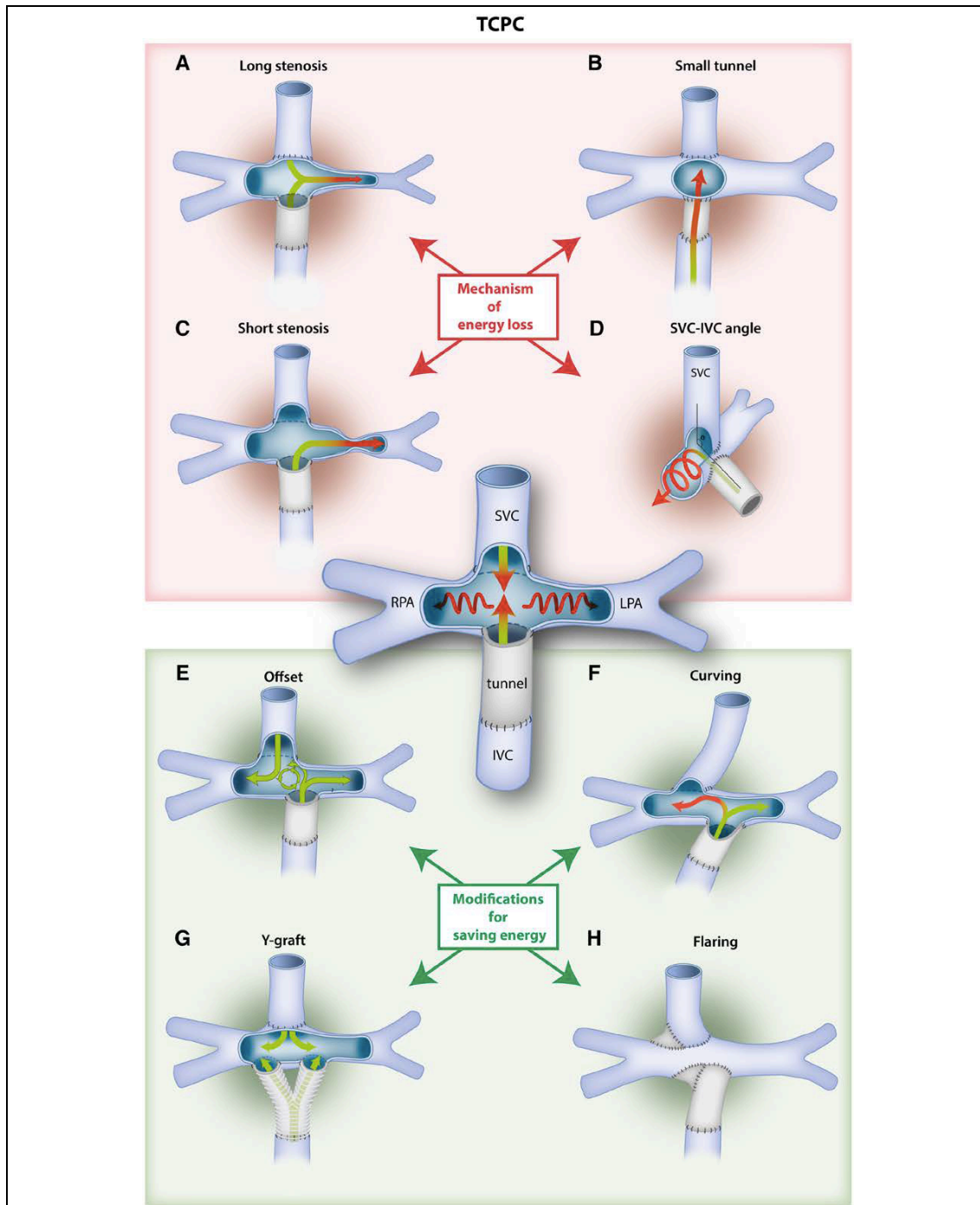
The central image represents a classic T-shape TCPC. Figures E-H represent modifications known to reduce energy losses in the extracardiac conduit. IVC = inferior vena cava; LPA = left pulmonary artery; RPA = right pulmonary artery; SVC = superior vena cava; TCPC = total cavopulmonary connections. Reproduced from Rijnberg et al. with permission from Wolters Kluwer Health [227; p.2396].

4.2. The SCOTIA-PVR Cohort (Article 2)

Findings of the national SCOTIA-PVR cohort, which enrolled over 500 adults with corrected tetralogy of Fallot or pulmonary stenosis undergoing a first pulmonary valve implant, include the following: 1) our study is the first to support the safety and effectiveness of combined pulmonary and tricuspid valve surgery when compared to isolated pulmonary valve replacement: in multivariable analyses, combined surgery was associated with a 2.3-fold reduction in tricuspid regurgitation grade (OR: 0.44; 95% CI: 0.25-0.77) without an increase in early adverse events (OR: 0.85; 95% CI: 0.46-1.57) or hospitalization time (IRR: 1.17; 95% CI: 0.93-1.46); 2) preoperative tricuspid regurgitation severity and presence of trans-valvular leads independently predicted postoperative regurgitation; and 3) early adverse events were strongly associated with atrial tachyarrhythmia, extracardiac arteriopathy and a high body mass index.

4.2.1. Strengths

Our study presents several strengths. First, although our aim was to compare interventions performed in adults, we dedicated considerable effort to reviewing the full course of illness of every recruited patient. Ethics approvals were obtained from all affiliated pediatric hospitals to access old medical records and accurately document diagnoses and past surgical exposures. Patients treated in multiple provinces were also tracked across collaborating institutions. Given those measures, with the exception of a handful of postoperative echographic parameters, all study variables were complete. Data completeness reduced the complexity of our analyses and the risk of selection bias.

Second, data collection was highly standardized. Variables were collected by a single person, following a detailed coding manual, and using spreadsheets designed to automatically flag aberrant values. Data accuracy likely optimized study power and decreased the risk of differential misclassification errors.

Third, we applied a meticulous plan to control for confounding. Unlike TACTIC, the SCOTIA-PVR study was specifically designed to compare surgical approaches. Thus, a lot of emphasis was placed on collecting the right potential confounders. In our analyses, we carefully explored relationships between variables to avoid conditioning on colliders. We also compared

two statistical approaches: one based on conventional multivariable modelling and another based on matching weights, an extension of inverse probability of treatment weighting. Our sensitivity analyses, which yielded comparable results, surely contributed to increase faith in the internal validity of our findings.

Fourth, our initiative resulted in a cohort almost twice the sum of all cases previously published on the topic of combined pulmonary and tricuspid valve surgery in adults with congenital heart disease. A large sample size was key in performing powered analyses and obtaining well-adjusted estimates of treatment effects.

Finally, our results were derived from a national experience. Thus, they should be easily generalizable to populations of other industrialized countries providing universal access to specialized congenital cardiac care.

4.2.2. Limitations

Similar to TACTIC, the observational SCOTIA-PVR cohort remains at risk of confounding, selection and information biases. Inclusion and exclusion criteria also affect its generalizability.

Confounding Bias

A first concern is the potential presence of residual confounding by indication. In our study, concomitant tricuspid valve intervention was generally offered at the time of pulmonary valve replacement to patients with significant tricuspid regurgitation and symptoms, who were most likely to benefit from an additional procedure, or those with severe comorbidities, who might not be candidate for reintervention in the event of treatment failure. There is no doubt that such indications, which also correlate with a high risk of complications, likely disadvantaged combined surgery. To limit bias, we controlled for the main factors suspected to influence treatment allocation. While we doubt that important variables were overlooked, it is possible that some of our covariates were too imprecise to fully control for confounding. For example, we adjusted for baseline tricuspid valve competence and right ventricular size and function using echocardiographic grades as opposed to continuous and highly reproducible magnetic resonance imaging parameters. Although greater precision would have been desirable, we knew that

magnetic resonance imaging measures would only be available in about a third of patients. Ultimately, with echocardiographic variables, we favored data completeness and a lower risk of selection bias over tighter confounding control. This decision, we think, was the most appropriate. Even with better adjustments, we doubt that the direction of measured associations would actually change.

Selection Bias

Second, with regards to the risk of selection bias, 6.4% of our subjects were lost to follow-up before undergoing a repeat echocardiographic study measuring postoperative tricuspid regurgitation. We believe that the main reason for immediate postoperative attrition was long home-to-hospital travel distances, and doubt that this factor could have directly or indirectly influenced the relationship between surgical treatment and residual tricuspid regurgitation. However, we did not collect variables allowing us to measure geographic proximity and to test this hypothesis. A comparison of baseline characteristics of complete and incomplete cases yielded no significant differences between surgical groups. Imputation methods, such as multiple imputation and the next observation carried backward method, were also tested and offered no advantage over listwise deletion, with absolutely no influence on the calculated estimate and its confidence interval. Thus, we concluded in a low risk of selection bias and simply carried a complete-case analysis. Nevertheless, there is still a small possibility that underappreciated differences in attrition between treatment groups might have biased our echocardiographic results.

Information Bias

A third common threat to the internal validity of observational studies is information bias, an issue which arises when inaccurate variable measurements cause a distortion in the association between exposure and outcome. In the SCOTIA-PVR cohort, data collection was highly standardized, which reduced the risk of non-differential misclassification. However, the fact that the PhD candidate abstracted data herself increased the potential for observer bias, a form of differential misclassification triggered by the tendency of investigators to observe and report what they expect to see. In the hope to prevent observer bias, we systematically collected

outcome data and treatment allocation on different days and using separate spreadsheets. Still, we recognize that this approach was not perfect. In a few charts, surgical exposure was indicated on so many documents that it was virtually impossible to remain blinded to treatment.

External Validity

Finally, as previously stated, our study, which represents a national experience, displays excellent external validity. However, as it only included adults who were operated in centers with recognized expertise in congenital cardiac surgery, our findings should not be extrapolated to settings in which general cardiac surgeons occasionally perform congenital interventions.

4.2.3. Clinical implications and future perspectives

As described in the discussion section of Article 2, findings from the SCOTIA-PVR study bear important clinical implications. They challenge the appropriateness of conservative management of severe tricuspid regurgitation in patients over the age of 18 with repaired tetralogy of Fallot or pulmonary stenosis undergoing repeat surgery. Furthermore, they highlight that, in this population, concomitant tricuspid valve intervention can safely improve moderate insufficiency beyond the effect of right ventricular offloading – a strategy likely worthwhile to adopt in young adults already at high risk of right heart failure.

Although our conclusions provide new insight on the surgical management of tricuspid regurgitation in congenital patients, they also raise additional questions. First, one could ask: which tricuspid regurgitation mechanisms respond best to surgery, and is there a specific repair technique outperforming others? Unfortunately, our study lacks the granularity required to comment on these specific matters. For cause, we identified, in the entire cohort, only a handful of detailed pre- or intra-operative anatomic assessments of the tricuspid valve. Baseline annular diameter was reported in less than 5% of subjects, and only 1 surgeon systematically described in his operative notes the mechanisms of regurgitation encountered at the time of repair (n=4). Although we gathered a huge amount of technical data on every procedure carried in the operating room, commenting on the effectiveness of individual techniques will be virtually impossible without a clearer understanding of the precise indications for their use. To palliate

this gap, one could suggest reinterpreting available 2D transthoracic echocardiographic images. However, we would argue that this approach, in addition to being time-consuming and expensive, might be risky. The anatomy of the tricuspid valve is more complex and variable, and its leaflets are thinner and more difficult to visualize within the same plane than that of the mitral valve, so the potential for error while reinterpreting images would be high [238]. Furthermore, tricuspid regurgitation was, for decades, considered inconsequential, so many studies might be incomplete, especially in patients displaying low-grade insufficiency – a phenomenon likely to result in both selection and detection biases. These observations emphasize that, going forward, routine multimodal imaging and a systematic approach to reporting abnormal tricuspid valve structure and function will be required to better define surgical indications and optimize patient care. At a Canadian level, the uptake of preoperative 3D transthoracic echocardiography could represent a cost-effective way of improving the quality of both current clinical decisions and future research projects [239].

Another fundamental question raised by the SCOTIA-PVR study is: does an improvement in tricuspid regurgitation translate into long-term benefits for patients? Although a few studies carried in other cardiac populations already support this statement, evidence in adults with congenital heart disease is lacking [213-216]. As part of the current initiative, we collected data on late mortality, readmissions due to heart failure or arrhythmia, reinterventions and functional capacity. Unfortunately, attrition in our cohort was very high after 5 years (>40%) and missing data was clearly not random. The healthiest patients, often exposed to isolated pulmonary valve replacement, were also those most likely to abandon local follow-up – an issue likely to cause under-detection of adverse events in this particular subgroup. Given a high potential for irremediable bias, we did not embark into additional analyses and concluded that a study based on provincial administrative health data, as opposed to information extracted from individual hospital records, would probably be best suited for exploring the long-term outcomes of patients following pulmonary valve replacement with or without tricuspid valve intervention.

In summary, findings from the SCOTIA-PVR study support that, in adults with corrected tetralogy of Fallot or pulmonary stenosis, pulmonary valve replacement combined with tricuspid intervention is safe and more than twice as likely to improve postoperative tricuspid

regurgitation than pulmonary valve surgery alone. While additional research is required to optimize indications for surgery, we advocate for the repair at a lower threshold of tricuspid regurgitation mechanisms unlikely to improve with right ventricular offloading. Examples of such mechanisms include leaflet entrapment in ventricular septal defect patch repairs, lead-related injuries, congenital malformations, and annular diameters over 40mm. Finally, we would argue that, pending long-term outcome data, severe tricuspid regurgitation should remain a relative contraindication to isolated surgical or transcatheter pulmonary valve replacement.

4.3. Conclusion

Over the last 60 years, outstanding advances in the field of cardiac surgery have made possible for a growing number of infants to survive with severe heart malformations [10]. Once seen as a problem of the young, complex congenital heart disease affects now two adults for one child and this gap will continue to widen for several decades [14]. Thus, the burden of complications experienced by older patients is increasing. Several research and quality-improvement initiatives have already contributed to a better understanding of this demographic shift, resource planning, and centralization of services [53-57]. Unfortunately, standardization of care is still poor as the level of evidence guiding most clinical decisions remains low [58,59,61]. This issue is particularly true in surgery, a field in which powered high-quality comparative studies are more the exception than the norm. The current thesis, comprising two impactful stand-alone multicenter observational studies, exemplifies the importance of nurturing collaboration, as opposed to competitiveness, among surgical divisions in order to rapidly bridge residual knowledge gaps and help optimizing patient outcomes using the right operative techniques.

As previously mentioned, the Fontan TACTIC study was carried in collaboration with the Alliance for Adult Research in Congenital Cardiology. This North American non-profit organization specializes in the conduct of multicenter observational research using protocol-driven data collection. Over the last 15 years, it carried 13 projects and published over 20 influential papers. In 2014, the Alliance surveyed members of the Adult Congenital Heart Association to prioritize research topics in the field. This survey revealed that patients were particularly concerned by the effects of surgery on their life, ranking this topic at the top of all

priorities [66]. Interestingly, the Fontan TACTIC project was the first initiative of the AARCC to focus on a pure surgical question. As a surgeon in training, my experience among this group of cardiologists was very positive. Despite different perspectives on care, my opinion was valued, and I certainly felt empowered to explore new research ideas. These observations highlight the importance for young surgeons to show a vested interest in all kinds of collaborative networks if they wish to be at the forefront of meaningful discoveries. My experience also emphasizes that it makes no sense for cardiologists and surgeons to work in silos when both medical and surgical projects can be conducted together at little extra cost.

The SCOTIA-PVR study was supported by the Canadian Congenital Cardiac Collaborative. It was the first initiative to involve all congenital cardiac surgery centers across the country. There is no doubt that our collaboration brought up interesting challenges. However, in hindsight, our group faced very few major hurdles while carrying the presented project. First, our study was completed in less than three years. Second, research ethics boards, which were initially concerned by the fact that an external data abstractor would carry the work at each site, were ultimately pleased with our approach and confirmed that they would again approve similar projects in the future. Third, the study, which capitalized on my cardiac surgery residency academic enrichment years, costed very little (~$5,000). Low incurred costs allowed us to include all centers, regardless of their operative volume or ability to financially contribute to the initiative. Considering all of these aspects, the SCOTIA-PVR study proves that Canadian congenital cardiac surgeons can effectively collaborate provided the right research question. Hopefully, this fruitful experience will pave the way for many other research initiatives supported by the 4C.

In conclusion, the presented findings demonstrate that preconceptions in congenital cardiac surgery are common and that rigorous multicenter observational research remains key in improving patient outcomes. Furthermore, this thesis proves that – with dedication, patience, humility and the right mentors – it is possible for trainees to actively partake in large collaborations and significantly contribute to the advancement of evidence-based surgical management of congenital heart disease.

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Appendices

Appendix 1. The Fontan TACTIC Cohort – Case Report Form

SECTION 1

SCREENING FORM

DATE OF SCREENING: ❑❑❑❑-❑❑-❑❑
YEAR - MO- DAY

DATE OF BIRTH: ❑❑❑❑-❑❑
YEAR - MO

SEX: ❑$_0$ FEMALE   ❑$_1$ MALE

TYPE OF CONGENITAL HEART DISEASE (please indicate most appropriate primary diagnosis; if diagnosis not listed, please select "other" and complete):

Complexity	Predominant type of congenital heart disease*	
Simple	*Native disease* ❑$_1$ Isolated congenital aortic valve disease ❑$_2$ Isolated mitral valve disease (exclude parachute valve, clef leaflet) ❑$_3$ Small atrial septal defect (ASD) ❑$_4$ Isolated small VSD (no associated lesions) ❑$_5$ Mild pulmonary stenosis ❑$_6$ Small patent ductus arteriosus	*Repaired condition* ❑$_7$ Previously ligated or occluded PDA ❑$_8$ Repaired secundum ASD (without residua) ❑$_9$ Repaired sinus venosus ASD (no residua) ❑$_{10}$ Repaired VSD without residua
Moderate	❑$_{11}$ Aorto-left ventricular fistula ❑$_{12}$ Anomalous pulmonary venous drainage ❑$_{13}$ Ostium primim ASD/partial AVSD ❑$_{14}$ Complete AVSD ❑$_{15}$ Aortic coarctation ❑$_{16}$ Ebstein's anomaly ❑$_{17}$ Infundibular RVOT obstruction of significance ❑$_{18}$ Unrepaired patent ductus arteriosus ❑$_{19}$ Pulmonary regurgitation (moderate/severe) ❑$_{20}$ Pulmonic stenosis (moderate/severe) ❑$_{21}$ Sinus of Valsalva fistula/aneurysm	❑$_{22}$ Sinus venosus ASD ❑$_{23}$ Subvalvar AS or SupraAS (except HOCM) ❑$_{24}$ Tetralogy of Fallot *Ventricular septal defect with:* ❑$_{25}$ Absent valve or valves ❑$_{26}$ Aortic regurgitation ❑$_{27}$ Aortic coarctation ❑$_{28}$ Mitral disease ❑$_{29}$ Right ventricular outflow tract obstruction ❑$_{30}$ Straddling tricuspid/mitral valve ❑$_{31}$ Subaortic stenosis
Severe	❑$_{26}$ Eisenmenger syndrome ❑$_{27}$ Congenitally corrected TGA (L-TGA) ❑$_{23}$ Complete TGA (D-TGA) ❑$_{24}$ Truncus arteriosus/hemitruncus ❑$_{24}$ Heterotaxy syndrome	❑$_{32}$ Single ventricle physiology: morphologic RV ❑$_{33}$ Single ventricle physiology: morphologic LV ❑$_{34}$ Other form of cyanotic heart disease Please specify:

❑$_{99}$ Other: _____

TO QUALIFY, THE PATIENT MUST HAVE HAD FONTAN PALLIATION OR AT LEAST ONE EPISODE OF ATRIAL TACHYARRHYTHMIA OR FIBRILLATION.

DID THE PATIENT HAVE FONTAN SURGERY?:　❑₁ YES ❑₀ NO

    IF YES, please indicate date(s) and type(s) of Fontan surgery in Section 2, column 2

      Was the Fontan fenestrated?　❑₁ YES ❑₀ NO

      If fenestrated, was it subsequently closed?

      ❑₀ NO　　❑₁ YES-spontaneously　❑₂ YES-intervention (indicate date in section 2, column 2)

      Has the patient had protein-losing enteropathy (PLE)?　❑₁ YES ❑₀ NO

    If YES, date of PLE:　❑❑❑❑-❑❑-❑❑

                  YEAR - MO- DAY

HAS THE PATIENT HAD ONE OF THE FOLLOWING SUSTAINED ATRIAL TACHYARRHYTHMIA OR ATRIAL FIBRILLATION (please indicate all that apply):

    ❑₁ YES ❑₀ NO　　If YES, complete Section 4

Atrial tachyarrhythmia	*Date of first diagnosis* YEAR-MO-DAY	*Atrial cycle length* (ms)	*Venricular rate* (bpm)
❑₁ Atrial fibrillation	❑❑❑❑-❑❑-❑❑		❑❑❑
❑₂ Focal atrial tachycardia	❑❑❑❑-❑❑-❑❑	❑❑❑❑	❑❑❑

Intra-atrial reentrant tachycardia (IART)

❑₃ Typical atrial flutter	❑❑❑❑-❑❑-❑❑	❑❑❑❑	❑❑❑
❑₄ Reverse typical atrial flutter	❑❑❑❑-❑❑-❑❑	❑❑❑❑	❑❑❑
❑₅ Scar-based macroreentry	❑❑❑❑-❑❑-❑❑	❑❑❑❑	❑❑❑
❑₆ Lower-loop flutter	❑❑❑❑-❑❑-❑❑	❑❑❑❑	❑❑❑
❑₇ Double wave reentry	❑❑❑❑-❑❑-❑❑	❑❑❑❑	❑❑❑
❑₈ RA free wall (no atriotomy)	❑❑❑❑-❑❑-❑❑	❑❑❑❑	❑❑❑
❑₉ LA macroreentrant tachycardia	❑❑❑❑-❑❑-❑❑	❑❑❑❑	❑❑❑
❑₁₀ IART; subtype unknown	❑❑❑❑-❑❑-❑❑	❑❑❑❑	❑❑❑

RA denotes right atrial; LA, left atrial

❖ For the purpose of adjudication, please attach denominalized photocopies of the documented atrial tachyarrhythmia (e.g., 12-lead ECG, rhythm strip, Holter or event monitor, intracardiac electrograms) and results of electrophysiological studies, if applicable.

SECTION 2

CARDIAC CATHETER AND SURGICAL INTERVENTIONS

CARDIAC SURGERY: ❏₁ YES ❏₀ NO

NUMBER OF CARDIAC SURGERIES: ❏❏

CATHETER INTERVENTIONS (excluding diagnostic studies and arrhythmia interventions):

❏₁ YES ❏₀ NO

NUMBER OF CATHETER INTERVENTIONS: ❏❏

PLEASE INDICATE ALL THAT APPLY

	Year	Month			Year	Month
❏₁ ASD closure	❏❏❏❏	-❏❏				
❏₂ VSD closure	❏❏❏❏	-❏❏	❏₂₀ Fenestration closure	❏❏❏❏	-❏❏
❏₃ PDA closure	❏❏❏❏	-❏❏	❏₂₁ Fontan: RA to PA	❏❏❏❏	-❏❏
❏₄ Atrial septostomy	❏❏❏❏	-❏❏	❏₂₂ Fontan: RV to PA	❏❏❏❏	-❏❏
❏₅ Blalock-Taussig shunt	❏❏❏❏	-❏❏	❏₂₃ Fontan: lateral tunnel	❏❏❏❏	-❏❏
❏₆ Glenn shunt	❏❏❏❏	-❏❏	❏₂₄ Fontan: extracardiac	❏❏❏❏	-❏❏
❏₇ Potts anastomosis	❏❏❏❏	-❏❏	❏₂₅ Hemi-Fontan	❏❏❏❏	-❏❏
❏₈ Waterston anastomosis	❏❏❏❏	-❏❏	❏₂₆ MV repair/replacement	❏❏❏❏	-❏❏
❏₉ TOF repair	❏❏❏❏	-❏❏	❏₂₇ TV repair/replacement	❏❏❏❏	-❏❏
❏₁₀ Ao coarctation repair	❏❏❏❏	-❏❏	❏₂₈ PV repair/replacement	❏❏❏❏	-❏❏
❏₁₁ Ross procedure	❏❏❏❏	-❏❏	❏₂₉ Relief RVOTO	❏❏❏❏	-❏❏
❏₁₂ Repair Ao-LV fistula	❏❏❏❏	-❏❏	❏₃₀ Relief LVOTO	❏❏❏❏	-❏❏
❏₁₃ Mustard or Senning	❏❏❏❏	-❏❏	❏₃₁ Unifocaliz. MAPCAs	❏❏❏❏	-❏❏
❏₁₄ Brock procedure	❏❏❏❏	-❏❏			
❏₁₅ Rastelli operation	❏❏❏❏	-❏❏	❏₃₂ Cardiac transplantation	❏❏❏❏	-❏❏
❏₁₆ REV procedure	❏❏❏❏	-❏❏			
❏₁₇ Double switch	❏❏❏❏	-❏❏	❏₉₉ Other (specify)	❏❏❏❏	-❏❏
❏₁₈ Arterial switch	❏❏❏❏	-❏❏	❏₉₉ Other (specify)	❏❏❏❏	-❏❏
❏₁₉ Norwood	❏❏❏❏	-❏❏	❏₉₉ Other (specify)	❏❏❏❏	-❏❏

ASD denotes atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; TOF, tetralogy of Fallot; Ao, aortic; LV, left ventricle; RA, right atrium; PA, pulmonary artery; RV, right ventricle; MV, mitral valve; TV, tricuspid valve; PV, pulmonic valve; RVOT, right ventricular outflow tract obstruction; LVOTO, left ventricular outflow tract obstruction; Unifocaliz., unifocalization; MAPCAS, major aorto-pulmonary collaterals

SECTION 3

BASELINE CHARACTERISTICS
(time of first documented sustained atrial arrhythmia)

HEIGHT: ❑❑❑ CM   WEIGHT: ❑❑❑ KG

BODY SURFACE AREA: ❑❑❑ M^2 BODY MASS INDEX : ❑❑❑

NEW YORK HEART ASSOCIATION CLASS: ❑$_0$ I   ❑$_1$ II   ❑$_2$ III   ❑$_3$ IV

COMORBIDITIES:

❑$_0$ None   ❑$_{10}$ Obstructive lung disease

❑$_1$ Congestive heart failure   ❑$_{11}$ Asthma

❑$_2$ Hypertension   ❑$_{12}$ Liver cirrhosis

❑$_1$ Diabetes   ❑$_{13}$ Dyslipidemia

❑$_3$ Prior stroke   ❑$_{14}$ Current cigarette smoker

❑$_4$ Prior transient ischemic attack   ❑$_{15}$ Past cigarette smoker

❑$_5$ Chronic renal failure   ❑$_{16}$ Alcoholism

❑$_6$ Coronary artery disease   ❑$_{17}$ Affective mood disorder

❑$_7$ Hyperthyroidism   ❑$_{18}$ Illicit drug use

❑$_8$ Hyopthyroidism   ❑$_{19}$ Cancer, specify

❑$_9$ Restrictive lung disease   ❑$_{99}$ Other

_____

MEDICAL THERAPY AT TIME OF DIAGNOSIS OF ATRIAL TACHYARRHYTHMIA:

Beta-blocker	❑$_1$ YES	❑$_0$ NO
Digoxin	❑$_1$ YES	❑$_0$ NO
Amiodarone	❑$_1$ YES	❑$_0$ NO
Sotalol	❑$_1$ YES	❑$_0$ NO
Dofetilide	❑$_1$ YES	❑$_0$ NO
Dronedarone	❑$_1$ YES	❑$_0$ NO
Class IA or IC antiarrhythmic agent	❑$_1$ YES	❑$_0$ NO
ACE-inhibitor or ARB	❑$_1$ YES	❑$_0$ NO
Diuretic	❑$_1$ YES	❑$_0$ NO
Statin	❑$_1$ YES	❑$_0$ NO
Antiplatelet agent	❑$_1$ YES	❑$_0$ NO
Oral vitamin K antagonist	❑$_1$ YES	❑$_0$ NO
Direct thrombin inhibitor	❑$_1$ YES	❑$_0$ NO

(Please specify:)

_____

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BIOCHEMISTRY:

Arterial oxygen saturation on room air: ❑❑❑ (%)

Hemoglobin level: ❑❑❑   ❑ g/dL ❑ g/L

Hematocrit level: 0.❑❑

Platelet count: ❑❑❑   ❑ 1000/mL ❑x10E9/L

Serum creatinine ❑❑❑   ❑ μmol/L ❑ mg/dL

Serum potassium ❑.❑ (mEq/L)

Serum sodium ❑❑❑ (mEql/L)

International Normalized Ratio (INR): ❑❑.❑❑

NOTE: FOR THE FOLLOWING DIAGNOSTIC TESTS, PLEASE INDICATE FINDINGS FROM THE MOST RECENT STUDIES (i.e., NO MORE THAN 2 YEARS PRIOR TO THE FIRST QUALIFYING ARRHYTHMIA OR WITHIN 1 YEAR FOLLOWING ARRHYTHMIA ONSET):

                                                                  Year   Month

A) *ELECTROCARDIOGRAM (in sinus rhythm, if possible)* ❑❑❑❑   ❑❑

Underlying rhythm: ❑₁ Sinus   ❑₂ Atrial escape rhythm ❑₃ Atrial tachycardia

❑₄ Atrial fibrillation ❑₅ Junctional ❑₆ Atrial paced   ❑₉₉ Other

Is there a ventricular-paced underlying rhythm? ❑₁ YES   ❑₀ NO

Bundle branch block? ❑₀ NO ❑₁ RBBB ❑₂ LBBB ❑₃ Intraventricular conduction delay

Longest dominant QRS duration   ❑❑❑ MSEC

R-R interval   ❑❑❑❑ MSEC

P-R interval   ❑❑❑❑ MSEC

P-wave duration   ❑❑❑❑ MSEC

QT in lead II   ❑❑❑ MSEC

- -

                                                                  Year   Month

B) *24-HOUR HOLTER MONITOR* ❑ NOT DONE ❑❑❑❑   ❑❑

Number of PVCs in 24 hours: ❑❑❑❑❑

Sustained atrial tachyarrhythmia: ❑₁ YES   ❑₀ NO

Non-sustained SVT (≥3 beats, <30 seconds): ❑₁ YES   ❑₀ NO

If yes, longest run (number of beats) ❑❑

Runs of atrial fibrillation (≥3 beats, <30 seconds): ❑₁ YES   ❑₀ NO

Number of premature atrial beats in 24 hours: ❑❑❑❑❑

Non-sustained VT (≥3 beats, <30 seconds): ❑₁ YES   ❑₀ NO

Longest pause ❑❑.❑ SEC

                                            Year   Month

C) *ECHOCARDIOGRAM*   ☐ NOT DONE   ☐☐☐☐   ☐☐

Systemic ventricular (SV) dimensions:

     SVEDD ☐☐.☐ mm   SVESD ☐☐.☐ mm

     Method of assessment: ☐$_0$ 2D   ☐$_1$ M-mode

Systemic ventricular ejection fraction: ☐☐%

Systemic ventricular diastolic function:

☐$_0$ Normal   ☐$_1$ Mildly impaired   ☐$_2$ Moderately impaired   ☐$_3$ Severely impaired

     If known, E/e':   ☐☐.☐

Subpulmonary ventricular (SPV) systolic function:

☐$_0$ Normal   ☐$_1$ Mildly impaired   ☐$_2$ Moderately impaired   ☐$_3$ Severely impaired

     If known, calculated ejection fraction: ☐☐%

Subpulmonary ventricular dilation: ☐$_0$ None   ☐$_1$ Mild   ☐$_2$ Moderate   ☐$_3$ Severe

     If known, indexed SPVED area (apical 4 chamber view) ☐☐.☐ cm^2/m^2

     Method of assessment: ☐$_0$ 2D   ☐$_1$ M-mode

     If known, length of subpulmonary ventricle in 2D mode:

         Apical ☐☐.☐ mm   Inlet ☐☐.☐ mm

Right atrial dimension: ☐☐.☐ mm   Left atrial dimension: ☐☐.☐ mm

Systolic pulmonary arterial pressure: ☐$_0$ Unknown   ☐$_1$ Known

     If known, systolic pulmonary arterial pressure: ☐☐☐ mmHg

Systemic AV valve regurgitation: ☐$_0$ None   ☐$_1$ Mild   ☐$_2$ Moderate   ☐$_3$ Severe

Subpulmonary AV valve regurgitation: ☐$_0$ None   ☐$_1$ Mild   ☐$_2$ Moderate   ☐$_3$ Severe

Pulmonary regurgitation: ☐$_0$ None   ☐$_1$ Mild   ☐$_2$ Moderate   ☐$_3$ Severe

Aortic regurgitation: ☐$_0$ None   ☐$_1$ Mild   ☐$_2$ Moderate   ☐$_3$ Severe

Subpulmonary outflow tract obstruction: ☐$_0$ None   ☐$_1$ Mild   ☐$_2$ Moderate   ☐$_3$ Severe

     If known, gradient across subpulmonary outflow tract: ☐☐☐ mmHg

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Year Month

D) *CARDIAC MRI* ❑ NOT DONE ❑❑❑❑ ❑❑

Systemic ventricular systolic function:

❑$_0$ Normal ❑$_1$ Mildly impaired ❑$_2$ Moderately impaired ❑$_3$ Severely impaired

If known, calculated ejection fraction: ❑❑%

Subpulmonary ventricular systolic function:

❑$_0$ Normal ❑$_1$ Mildly impaired ❑$_2$ Moderately impaired ❑$_3$ Severely impaired

If known, calculated ejection fraction: ❑❑%

Systolic pulmonary arterial pressure: ❑$_0$ Unknown ❑$_1$ Known

If known, systolic pulmonary arterial pressure: ❑❑❑ mmHg

Systemic AV valve regurgitation: ❑$_0$ None ❑$_1$ Mild ❑$_2$ Moderate ❑$_3$ Severe

Subpulmonary AV valve regurg.: ❑$_0$ None ❑$_1$ Mild ❑$_2$ Moderate ❑$_3$ Severe

Pulmonary regurgitation: ❑$_0$ None ❑$_1$ Mild ❑$_2$ Moderate ❑$_3$ Severe

Aortic regurgitation: ❑$_0$ None ❑$_1$ Mild ❑$_2$ Moderate ❑$_3$ Severe

Pulmonary regurgitation volume: ❑❑.❑ mL

Pulmonary regurgitation fraction: ❑❑.❑ %

Subpulmonary ventricular (SPV) dilation: ❑$_0$ None ❑$_1$ Mild ❑$_2$ Moderate ❑$_3$ Severe

If known: SPVEDV ❑❑❑.❑ mL SPVESV ❑❑❑.❑ mL

Systemic ventricular (SV) dilation: ❑$_0$ None ❑$_1$ Mild ❑$_2$ Moderate ❑$_3$ Severe

If known: SVEDV ❑❑❑.❑ mL SVESV ❑❑❑.❑ mL

Was late gadolinium enhancement performed? ❑$_1$ YES ❑$_0$ NO

Presence of late-gadolinium enhancements? ❑$_1$ YES ❑$_0$ NO

Please specify location: _____

E) *HEMODYNAMIC STUDY*   ❏ NOT DONE

Year ❏❏❏❏   Month ❏❏

Subpulmary ventricular systolic pressure   ❏❏❏ mmHg

Subpulmonary EDP   ❏❏❏ mmHg

Systemic ventricular systolic pressure   ❏❏❏ mmHg

Systemic ventricular EDP   ❏❏❏ mmHg

PAP   ❏❏❏/❏❏❏/❏❏❏ mmHg

Systolic   Diastolic   Mean

- -

F) *EXERCISE STRESS TEST WITH OR WITHOUT VO2 MAX*

Year ❏❏❏❏   Month ❏❏

❏ NOT DONE

Exercise METS performed   ❏❏.❏ METS

Maximum heart rate   ❏❏❏ bpm

% Maximum predicted heart rate   ❏❏❏.❏ %

Maximum VO2   ❏❏.❏ mL/kg/min

Non-sustained VT (3 beats or more, <30 seconds):   ❏₁ YES   ❏₀ NO

Sustained VT (≥30 seconds):   ❏₁ YES   ❏₀ NO

- -

SECTION 4

ARRHYTHMIA HISTORY

ATRIAL TACHYARRHYTHMIAS WERE ASSOCIATED WITH (indicate all that apply):

❑$_1$ Palpitations

❑$_2$ Pre-syncope

❑$_3$ Syncope

❑$_4$ Chest pain

❑$_5$ Shortness of breath

❑$_6$ Fatigue

❑$_7$ Increase in troponin levels

❑$_8$ Reduction in systemic ventricular function

❑$_9$ Pulmonary edema

❑$_{10}$ Hypotension

❑$_{11}$ Right-sided heart failure

❑$_{12}$ Resuscitated cardiac arrest

❑$_{13}$ Death

❑$_0$ None of the above

PREDOMINANT PATTERN OF ATRIAL TACHYARRHYTHMIAS AT TIME OF SCREENING:

Terminology	Clinical features
❑$_0$ Paroxysmal	• Spontaneous termination <7 days
❑$_1$ Persistent	• Lasting >7 days with spontaneous termination or terminated by cardioversion
❑$_2$ Permanent	• Failed cardioversion or no attempt to terminate, or terminated but with subsequent relapse and decision to abandon attempts to terminate

HOSPITALIZATIONS: Year-Mo-Day

Date of first diagnosis of atrial tachyarrhythmia: ❑❑❑❑-❑❑-❑❑

Date of first recurrence following initial diagnosis: ❑❑❑❑-❑❑-❑❑

    Total number of ER visits/hospitalizations for atrial tachyarrhythmias: ❑❑❑

    Total number of hospitalization days for atrial tachyarrhythmias: ❑❑❑

Date of first pharmacologic cardioversion: ❑❑❑❑-❑❑-❑❑

    Total number of attempted pharmacologic cardioversions: ❑❑❑

    Number of successful pharmacologic cardioversions: ❑❑❑

Date of first electrical cardioversion: ❑❑❑❑-❑❑-❑❑

    Total number of attempted electrical cardioversions: ❑❑❑

    Number of successful electrical cardioversions   ❑❑❑

Date of first transesophageal echocardiogram prior to cardioversion: ❑❑❑❑-❑❑-❑❑

    Total number of transesophageal echocardiograms: ❑❑❑

    Number of transesophageal echocardiograms demonstrating thrombus: ❑❑❑
(If thrombus identified, complete Section 7)

ARRHYTHMIA INTERVENTION

CATHETER ABLATION PROCEDURE   ☐$_1$ YES   ☐$_0$ NO

<div align="right">Year-Mo-Day</div>

If YES, date of first ablation procedure   ☐☐☐☐-☐☐-☐☐

Total number of catheter ablation procedures: ☐☐☐

Total number of atrial arrhythmias targeted: ☐☐☐

Number of atrial arrhythmias successfully ablated acutely: ☐☐☐

Type(s) of atrial tachyarrhythmia ablated:

☐$_1$ Atrial fibrillation   ☐$_6$ Lower-loop flutter

☐$_2$ Focal atrial tachycardia   ☐$_7$ Double wave reentry

☐$_3$ Typical atrial flutter   ☐$_8$ RA free wall (no atriotomy)

☐$_4$ Reverse typical atrial flutter   ☐$_9$ LA macroreentrant tachycardia

☐$_5$ Scar-based macroreentry   ☐$_{10}$ IART; subtype unknown

----

PACEMAKER IMPLANTATION   ☐$_1$ YES   ☐$_0$ NO

<div align="right">Year-Mo-Day</div>

If YES, date of first pacemaker procedure   ☐☐☐☐-☐☐-☐☐

Approach: ☐$_0$ Transvenous   ☐$_1$ Epicardial   ☐$_1$ Hybrid (transvenous/epicardial)

Type of pacemaker:

       ☐$_0$ Atrial only

       ☐$_1$ Ventricular only

       ☐$_2$ Dual chamber

       ☐$_3$ Cardiac resynchronization therapy

ICD IMPLANTATION   ☐$_1$ YES   ☐$_0$ NO

<div align="right">Year-Mo-Day</div>

If YES, date of first ICD procedure   ☐☐☐☐-☐☐-☐☐

Approach: ☐$_0$ Transvenous   ☐$_1$ Epicardial   ☐$_1$ Hybrid (transvenous/epicardial)

Type of ICD:

       ☐$_0$ Ventricular only

       ☐$_1$ Dual chamber

       ☐$_2$ Cardiac resynchronization therapy

ANTIARRHYTHMIC THERAPY

No	Yes	Medication	Date of initiation	Date of termination
☐$_0$	☐$_1$	Beta-blocker	☐☐☐☐-☐☐-☐☐	☐☐☐☐-☐☐-☐☐ ***Reason(s) for termination*** ☐$_0$ Inefficacy ☐$_4$ Proarrhythmia/↑QT ☐$_1$ Intolerance ☐$_5$ Post ablation ☐$_2$ Extracardiac toxicity ☐$_{99}$ Other (specify): ☐$_3$ Bradyarrhythmia
☐$_0$	☐$_1$	Calcium channel blocker	☐☐☐☐-☐☐-☐☐	☐☐☐☐-☐☐-☐☐ ***Reason(s) for termination*** ☐$_0$ Inefficacy ☐$_4$ Proarrhythmia/↑QT ☐$_1$ Intolerance ☐$_5$ Post ablation ☐$_2$ Extracardiac toxicity ☐$_{99}$ Other (specify): ☐$_3$ Bradyarrhythmia
☐$_0$	☐$_1$	Digoxin	☐☐☐☐-☐☐-☐☐	☐☐☐☐-☐☐-☐☐ ***Reason(s) for termination*** ☐$_0$ Inefficacy ☐$_4$ Proarrhythmia/↑QT ☐$_1$ Intolerance ☐$_5$ Post ablation ☐$_2$ Extracardiac toxicity ☐$_{99}$ Other (specify): ☐$_3$ Bradyarrhythmia
☐$_0$	☐$_1$	Sotalol	☐☐☐☐-☐☐-☐☐	☐☐☐☐-☐☐-☐☐ ***Reason(s) for termination*** ☐$_0$ Inefficacy ☐$_4$ Proarrhythmia/↑QT ☐$_1$ Intolerance ☐$_5$ Post ablation ☐$_2$ Extracardiac toxicity ☐$_{99}$ Other (specify): ☐$_3$ Bradyarrhythmia
☐$_0$	☐$_1$	Flecainide	☐☐☐☐-☐☐-☐☐	☐☐☐☐-☐☐-☐☐ ***Reason(s) for termination*** ☐$_0$ Inefficacy ☐$_4$ Proarrhythmia/↑QT ☐$_1$ Intolerance ☐$_5$ Post ablation ☐$_2$ Extracardiac toxicity ☐$_{99}$ Other (specify): ☐$_3$ Bradyarrhythmia

No	Yes	Medication	Date of initiation	Date of termination
☐$_0$	☐$_1$	Propafenone	☐☐☐☐-☐☐-☐☐	☐☐☐☐-☐☐-☐☐ ***Reason(s) for termination*** ☐$_0$ Inefficacy ☐$_4$ Proarrhythmia/↑QT ☐$_1$ Intolerance ☐$_5$ Post ablation ☐$_2$ Extracardiac toxicity ☐$_{99}$ Other (specify): ☐$_3$ Bradyarrhythmia
☐$_0$	☐$_1$	Amiodarone	☐☐☐☐-☐☐-☐☐	☐☐☐☐-☐☐-☐☐ ***Reason(s) for termination*** ☐$_0$ Inefficacy ☐$_4$ Proarrhythmia/↑QT ☐$_1$ Intolerance ☐$_5$ Post ablation ☐$_2$ Extracardiac toxicity ☐$_{99}$ Other (specify): ☐$_3$ Bradyarrhythmia
☐$_0$	☐$_1$	Dronedarone	☐☐☐☐-☐☐-☐☐	☐☐☐☐-☐☐-☐☐ ***Reason(s) for termination*** ☐$_0$ Inefficacy ☐$_4$ Proarrhythmia/↑QT ☐$_1$ Intolerance ☐$_5$ Post ablation ☐$_2$ Extracardiac toxicity ☐$_{99}$ Other (specify): ☐$_3$ Bradyarrhythmia
☐$_0$	☐$_1$	Dofetilide	☐☐☐☐-☐☐-☐☐	☐☐☐☐-☐☐-☐☐ ***Reason(s) for termination*** ☐$_0$ Inefficacy ☐$_4$ Proarrhythmia/↑QT ☐$_1$ Intolerance ☐$_5$ Post ablation ☐$_2$ Extracardiac toxicity ☐$_{99}$ Other (specify): ☐$_3$ Bradyarrhythmia
☐$_0$	☐$_1$	Other (specify):	☐☐☐☐-☐☐-☐☐	☐☐☐☐-☐☐-☐☐ ***Reason(s) for termination*** ☐$_0$ Inefficacy ☐$_4$ Proarrhythmia/↑QT ☐$_1$ Intolerance ☐$_5$ Post ablation ☐$_2$ Extracardiac toxicity ☐$_{99}$ Other (specify): ☐$_3$ Bradyarrhythmia

SECTION 5

ANTIPLATELET/ANTICOAGULATION THERAPY

A) ACETYLSALICILC ACID (ASA):

Was ASA therapy ever received?   ☐₁ YES   ☐₀ NO

    If YES, date of initiation: ☐☐☐☐-☐☐-☐☐
                                          Year-Mo-Day

    Daily dose prescribed:
    ☐₀ 75-81 mg   ☐₁ 150-162.5 mg   ☐₂ 325 mg qday   ☐₃ ≥650 mg

Was ASA therapy discontinued?   ☐₁ YES   ☐₀ NO

    If YES, date of discontinuation: ☐☐☐☐-☐☐-☐☐
                                            Year-Mo-Day

    Reason(s) for discontinuation:
    ☐₁ Thromboembolic event
    ☐₂ Minor bleed
    ☐₃ Major bleed
    ☐₄ Allergy
    ☐₅ Intolerance or side-effect
    ☐₆ Deemed no longer necessary
    ☐₇ Non-compliance

B) ORAL VITAMIN K ANTAGONIST (VKA):

Was VKA therapy ever received?   ☐₁ YES   ☐₀ NO

    If YES, date of initiation: ☐☐☐☐-☐☐-☐☐
                                            Year-Mo-Day

    Initial INR target range:
    ☐₀ 1.5-2.0 ☐₁ 2.0-2.5 ☐₂ 2.0-3.0 ☐₃ 2.5-3.0 ☐₄ 2.5-3.5 ☐₅ ≥3.0

    Was the targeted INR range ever increased?   ☐₁ YES   ☐₀ NO
    If YES, to what range
    ☐₀ 2.0-2.5 ☐₁ 2.0-3.0 ☐₂ 2.5-3.0 ☐₃ 2.5-3.5 ☐₄ ≥3.0

Was VKA therapy ever discontinued?   ☐₁ YES   ☐₀ NO

    If YES, date of discontinuation: ☐☐☐☐-☐☐-☐☐
                                            Year-Mo-Day

Reason(s) for discontinuing VKA (indicate all that apply):

- ❏₁ Thromboembolic event
- ❏₂ Minor bleed
- ❏₃ Major bleed
- ❏₄ Allergy
- ❏₅ Intolerance or side-effect
- ❏₆ Deemed no longer necessary
- ❏₇ Non-compliance

INR levels: Please select the most accurate statement

- ❏₁ The INR level was seldomly in the targeted range
- ❏₂ Major fluctuations in INR levels occurred requiring frequent dose adjustments
- ❏₃ INR levels were stable on the whole but required occasional dose adjustments
- ❏₄ The INR level was nearly always therapeutic

Patient compliance: Please select the most accurate statement regarding VKA

- ❏₁ No compliance/adherence issue was encountered
- ❏₂ On the whole, the patient was compliant with therapy and recommendations
- ❏₃ Compliance/adherence issues were encountered on more than one occasion
- ❏₄ Compliance/adherence was problematic

C) OTHER:

Was another oral antiplatelet/anticoagulant agent ever received?   ❏₁ YES   ❏₀ NO

If YES, date of initiation: ❏❏❏❏-❏❏-❏❏
                          Year-Mo-Day

Please specify agent and dose: _____

If the agent was a direct thrombin inhibitor, why was it prescribed?

- ❏₀ First-line therapy due to patient/physician preference
- ❏₁ Crossover from vitamin K antagonist due to patient/physician preference
- ❏₂ Allergy/intolerance to vitamin K antagonist
- ❏₃ Thromboembolic event despite vitamin K antagonist
- ❏₄ Major bleed on vitamin K antagonist
- ❏₅ Difficulty with access to anticoagulation checks
- ❏₆ Other (specify): _____

Was this therapy discontinued?   ❑$_1$ YES   ❑$_0$ NO

If YES, date of discontinuation: ❑❑❑❑-❑❑-❑❑

                                         Year-Mo-Day

Reason(s) for discontinuing therapy (indicate all that apply):
- ❑$_1$ Thromboembolic event
- ❑$_2$ Minor bleed
- ❑$_3$ Major bleed
- ❑$_4$ Allergy
- ❑$_5$ Intolerance or side-effect
- ❑$_6$ Deemed no longer necessary
- ❑$_7$ Non-compliance

SECTION 6

HEMORRHAGIC EVENT

❖ Please complete a separate Section 6 form for each hemorrhagic event. Please provide copies of supportive documentation for the purpose of adjudication.

DATE OF HEMORRHAGIC EVENT: ❏❏❏❏-❏❏-❏❏
YEAR - MO- DAY

CLASSIFICATION OF HEMORRHAGE:

❏₁ MAJOR (Requires one or more of the following):

    ❏₁ Reduction in hemoglobin level of ≥20 g/L

    ❏₂ Transfusion of at least 2 units of blood

    ❏₃ Symptomatic bleeding in a critical area or organ

        Specify area or organ: _____

❏₂ MINOR

    ❏₁ Spontaneous skin hematoma

    ❏₂ Spontaneous nose bleed

    ❏₃ Macroscopic hematuria

    ❏₄ Spontaneous rectal bleeding (more than spotting on toilet paper)

    ❏₆ Gingival bleeding for more than 5 minutes

    ❏₇ Bleeding leading to hospitalization and/or requiring surgical treatment

    ❏₈ Bleeding leading to transfusion of <2 units of whole blood or red cells

    ❏₉₉ Other bleeding event considered clinically relevant by the investigator

        Please specify: _____

ANTIPLATELET/ANTICOAGULANT THERAPY AT TIME OF EVENT:
Average daily dose

❏₀ None

❏₁ ASA   ❏❏❏ mg

❏₂ Vitamin K antagonist   ❏❏.❏ mg

❏₉₉ Other   ❏❏❏

_____   _____

BIOCHEMISTRY:

Oxygen saturation on room air: ❏❏❏ (%)   Creatinine: ❏❏❏ ❏ μmol/L ❏ mg/dL

Hemoglobin (lowest): ❏❏❏ ❏g/dL ❏ g/L   Serum potassium: ❏.❏ (mEq/L)

Hematocrit level (lowest): 0.❏❏   Serum sodium: ❏❏❏ (mEql/L)

Platelet count: ❏❏❏ ❏1000/mL ❏x10E9/L   INR: ❏❏.❏❏

SECTION 7

THROMBOEMBOLIC EVENT

❖ Please complete a separate Section 7 form for each thromboembolic event. Please provide copies of supportive documentation for the purpose of adjudication.

DATE OF THROMBOEMBOLIC EVENT: ☐☐☐☐-☐☐-☐☐
                                         YEAR - MO- DAY

CLASSIFICATION OF THROMBOEMBOLIC EVENT:

☐$_1$ SYSTEMIC

     ☐$_1$ Neurologic

         ☐$_1$ Transient ischemic attack (TIA; complete recovery ≤24 hours)

         ☐$_2$ Reversible ischemic neurological defect (RIND; complete recover >24 hrs)

         ☐$_3$ Cerebrovascular accident (deficit remains)

     ☐$_2$ Renal (confirmed by angiography, IVP, renal scan, or MRI)

     ☐$_3$ Peripheral arterial emboli (diagnosis may be based on clinical presentation)

     ☐$_3$ Mesenteric (angiographically confirmed)

     ☐$_{99}$ Other _____

     METHOD OF DOCUMENTATION (indicate all that apply):

     ☐$_1$ Clinical   ☐$_2$ CT scan   ☐$_3$ MRI   ☐$_4$ PET scan   ☐$_5$ Angiographic

☐$_2$ PULMONARY (Indicate all applicable supportive diagnostic tests):

     ☐$_1$ Elevated plasma D-dimers   ☐$_2$ Ultrasonography   ☐$_3$ V/Q lung scintigraphy

     ☐$_4$ CT scan   ☐$_5$ Pulmonary angiography   ☐$_{99}$ Other _____

                                             Specify:

☐$_3$ INTRACARDIAC THROMBUS:

     ☐$_1$ Fontan pathway (including right atrium in RA-PA connection Fontan)

     ☐$_2$ Systemic venous atrium

     ☐$_3$ Pulmonary venous atrium

     ☐$_4$ Systemic ventricle

     ☐$_5$ Subpulmonary ventricle

     ☐$_{99}$ Other (e.g., valve) _____

     METHOD OF DOCUMENTATION (indicate all that apply):

     ☐$_1$ Transthoracic echo   ☐$_2$ Transesophageal echo   ☐$_3$ CT scan   ☐$_4$ MRI

     ☐$_5$ Angiography   ☐$_5$ Surgery   ☐$_5$ Other _____

ANTIPLATELET/ANTICOAGULANT THERAPY AT TIME OF EVENT:

Average daily dose

☐$_0$ None

☐$_1$ ASA   ☐☐☐ mg

☐$_2$ Vitamin K antagonist   ☐☐.☐ mg

☐$_{99}$ Other _____   ☐☐☐ ____

BIOCHEMISTRY:

Oxygen saturation on room air: ☐☐☐ (%)

Hemoglobin level: ☐☐☐ (g/dL)

Hematocrit level: 0.☐☐

Platelet count: ☐☐☐ (1000/mL)

Serum creatinine: ☐☐☐ (µmol/L)

Serum potassium: ☐.☐ (mEq/L)

Serum sodium: ☐☐☐ (mEql/L)

INR: ☐☐.☐☐

RHYTHM AT TIME OF EVENT:

☐$_0$ Normal sinus rhythm

☐$_1$ Atrial fibrillation

☐$_2$ Focal atrial tachycardia

☐$_3$ Typical atrial flutter

☐$_4$ Reverse typical atrial flutter

☐$_5$ Scar-based macroreentry

☐$_6$ Lower-loop flutter

☐$_7$ Double wave reentry

☐$_8$ RA free wall (no atriotomy)

☐$_9$ LA macroreentrant tachycardia

☐$_{10}$ IART; subtype unknown

☐$_{11}$ Atrial paced rhythm

☐$_{99}$ Other _____

SECTION 8

DEATH REPORT

❖ Please provide copies of supportive documentation for the purpose of adjudication.

DATE OF DEATH: ☐☐☐☐-☐☐-☐☐
                             YEAR - MO- DAY

PRIMARY CAUSE OF DEATH (mark only one):

☐₁ CARDIOVASCULAR
- ☐₁ Thromboembolic
  - ☐₁ Ischemic stroke
  - ☐₂ Other systemic embolism, specify site: _____
  - ☐₃ Pulmonary embolism
- ☐₂ Hemorrhagic
  - ☐₁ Hemorrhagic stroke
  - ☐₂ Non-CNS hemorrhage, specify site: _____
- ☐₃ Stroke of unknown etiology
- ☐₄ Myocardial infarction/acute ischemia
- ☐₅ Presumed or documented arrhythmic death (mark all that apply)
  - ☐₁ Witnessed
  - ☐₂ During sleep
  - ☐₃ Out-of-hospital
  - ☐₄ Monitored bradyarrhythmia
  - ☐₅ Monitored tachyarrhythmia
- ☐₆ Congestive heart failure
- ☐₇ Aortic dissection/ruptured aortic aneurysm
- ☐₈ Procedure-related
  - ☐₁ Cardiac surgery
  - ☐₂ Percutaneous transcoronary intervention
  - ☐₃ Pacemaker/ICD/CRT implantation
  - ☐₄ Catheter ablation
  - ☐₅ Other (specify): _____
- ☐₉ Other (specify): _____

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❑₂ NON-CARDIOVASCULAR

     ❑₁ Cancer, specify type:

     ❑₂ Sepsis

     ❑₃ Trauma

     ❑₄ Pulmonary, specify:

         ❑₁ Amiodarone pulmonary toxicity

         ❑₂ Not related to amiodarone

     ❑₅ Non-cardiac surgery

     ❑₆ Suicide

     ❑₇ Other, specify: _____

ANTIPLATELET/ANTICOAGULANT THERAPY AT TIME OF EVENT:

Average daily dose

❑₀ None

❑₁ ASA   ❑❑❑ mg

❑₂ Vitamin K antagonist   ❑❑.❑ mg

❑₉₉ Other _____   ❑❑❑ _____

BIOCHEMISTRY PRECEEDING DEATH:

     Hemoglobin level: ❑❑❑   ❑ g/dL ❑ g/L

     Hematocrit level: 0.❑❑

     Platelet count: ❑❑❑   ❑ 1000/mL ❑x10E9/L

     Serum creatinine   ❑❑❑   ❑ μmol/L ❑ mg/dL

     Serum potassium   ❑.❑ (mEq/L)

     Serum sodium   ❑❑❑ (mEql/L)

     INR: ❑❑.❑❑

RHYTHM AT TIME OF EVENT:

     ❑₀ Normal sinus rhythm

     ❑₁ Atrial tachyarrhythmia

     ❑₂ Atrial fibrillation

     ❑₃ Atrial paced rhythm

     ❑₄ Ventricular tachycardia/fibrillation

     ❑₉₉ Other _____

SECTION 9

STUDY TERMINATION

DATE OF LAST FOLLOW-UP: ☐☐☐☐-☐☐-☐☐
YEAR - MO- DAY

OR

DATE OF CARDIAC TRANSPLANTATION: ☐☐☐☐-☐☐-☐☐
YEAR - MO- DAY

OR

DATE OF DEATH: ☐☐☐☐-☐☐-☐☐
YEAR - MO- DAY

NEW YORK HEART ASSOCIATION CLASS: ☐$_0$ I   ☐$_1$ II   ☐$_2$ III   ☐$_3$ IV

MEDICAL THERAPY AT LAST FOLLOW-UP:

Beta-blocker	☐$_1$ YES	☐$_0$ NO
Digoxin	☐$_1$ YES	☐$_0$ NO
Amiodarone	☐$_1$ YES	☐$_0$ NO
Sotalol	☐$_1$ YES	☐$_0$ NO
Dofetilide	☐$_1$ YES	☐$_0$ NO
Dronedarone	☐$_1$ YES	☐$_0$ NO
Class IA or IC antiarrhythmic agent	☐$_1$ YES	☐$_0$ NO
ACE-inhibitor or ARB	☐$_1$ YES	☐$_0$ NO
Diuretic	☐$_1$ YES	☐$_0$ NO
Statin	☐$_1$ YES	☐$_0$ NO
Antiplatelet agent	☐$_1$ YES	☐$_0$ NO
Oral vitamin K antagonist	☐$_1$ YES	☐$_0$ NO
Direct thrombin inhibitor	☐$_1$ YES	☐$_0$ NO

BIOCHEMISTRY AT LAST FOLLOW-UP:

Arterial oxygen saturation on room air:	☐☐☐ (%)	
Hemoglobin level:	☐☐☐	☐ g/dL ☐ g/L
Hematocrit level:	0.☐☐	
Platelet count:	☐☐☐	☐ 1000/mL ☐ x10E9/L
Serum creatinine	☐☐☐	☐ μmol/L ☐ mg/dL
Serum potassium	☐.☐ (mEq/L)	
Serum sodium	☐☐☐ (mEql/L)	
International Normalized Ratio (INR):	☐☐.☐☐	

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RHYTHM AT LAST FOLLOW-UP:
   ❑₀ Normal sinus rhythm
   ❑₁ Atrial tachyarrhythmia
   ❑₂ Atrial fibrillation
   ❑₃ Atrial paced rhythm
   ❑₉₉ Other _____

		Year	Month
A) *ELECTROCARDIOGRAM (preferably sinus)*		❑❑❑❑	❑❑

Is there a ventricular-paced underlying rhythm?   ❑₁ YES   ❑₀ NO

Bundle branch block? ❑₀ NO ❑₁ RBBB ❑₂ LBBB ❑₃ Intraventricular conduction delay

Longest dominant QRS duration   ❑❑❑ MSEC

R-R interval   ❑❑❑❑ MSEC

P-R interval   ❑❑❑❑ MSEC

P-wave duration   ❑❑❑❑ MSEC

QT in lead II   ❑❑❑ MSEC

		Year	Month
B) *24-HOUR HOLTER MONITOR* ❑ NOT DONE		❑❑❑❑	❑❑

Number of PVCs in 24 hours: ❑❑❑❑❑

Sustained atrial tachyarrhythmia: ❑₁ YES   ❑₀ NO

Non-sustained SVT (≥3 beats, <30 seconds):   ❑₁ YES   ❑₀ NO

   If yes, longest run (number of beats)   ❑❑

Runs of atrial fibrillation (≥3 beats, <30 seconds):   ❑₁ YES   ❑₀ NO

Number of premature atrial beats in 24 hours: ❑❑❑❑❑

Non-sustained VT (≥3 beats, <30 seconds):   ❑₁ YES   ❑₀ NO

Longest pause   ❑❑.❑ SEC

Year   Month

C) *ECHOCARDIOGRAM*   ☐ NOT DONE   ☐☐☐☐   ☐☐

Systemic ventricular (SV) dimensions:

SVEDD ☐☐.☐ mm   SVESD ☐☐.☐ mm

Method of assessment: ☐$_0$ 2D   ☐$_1$ M-mode

Systemic ventricular ejection fraction: ☐☐%

Systemic ventricular diastolic function:

☐$_0$ Normal   ☐$_1$ Mildly impaired   ☐$_2$ Moderately impaired   ☐$_3$ Severely impaired

If known, E/e':   ☐☐.☐

Subpulmonary ventricular (SPV) systolic function:

☐$_0$ Normal   ☐$_1$ Mildly impaired   ☐$_2$ Moderately impaired   ☐$_3$ Severely impaired

If known, calculated ejection fraction: ☐☐%

Subpulmonary ventricular dilation: ☐$_0$ None   ☐$_1$ Mild   ☐$_2$ Moderate   ☐$_3$ Severe

If known, indexed SPVED area (apical 4 chamber view) ☐☐.☐ cm^2/m^2

Method of assessment: ☐$_0$ 2D   ☐$_1$ M-mode

If known, length of subpulmonary ventricle in 2D mode:

Apical ☐☐.☐ mm   Inlet ☐☐.☐ mm

Right atrial dimension: ☐☐.☐ mm   Left atrial dimension: ☐☐.☐ mm

Systolic pulmonary arterial pressure: ☐$_0$ Unknown   ☐$_1$ Known

If known, systolic pulmonary arterial pressure: ☐☐☐ mmHg

Systemic AV valve regurgitation: ☐$_0$ None   ☐$_1$ Mild   ☐$_2$ Moderate   ☐$_3$ Severe

Subpulmonary AV valve regurgitation: ☐$_0$ None   ☐$_1$ Mild   ☐$_2$ Moderate   ☐$_3$ Severe

Pulmonary regurgitation: ☐$_0$ None   ☐$_1$ Mild   ☐$_2$ Moderate   ☐$_3$ Severe

Aortic regurgitation: ☐$_0$ None   ☐$_1$ Mild   ☐$_2$ Moderate   ☐$_3$ Severe

Subpulmonary outflow tract obstruction: ☐$_0$ None   ☐$_1$ Mild   ☐$_2$ Moderate   ☐$_3$ Severe

If known, gradient across subpulmonary outflow tract: ☐☐☐ mmHg

                                        Year   Month

D) *CARDIAC MRI*   ❑ NOT DONE   ❑❑❑❑   ❑❑

Systemic ventricular systolic function:

❑$_0$ Normal   ❑$_1$ Mildly impaired   ❑$_2$ Moderately impaired   ❑$_3$ Severely impaired

     If known, calculated ejection fraction: ❑❑%

Subpulmonary ventricular systolic function:

❑$_0$ Normal   ❑$_1$ Mildly impaired   ❑$_2$ Moderately impaired   ❑$_3$ Severely impaired

     If known, calculated ejection fraction: ❑❑%

Systolic pulmonary arterial pressure: ❑$_0$ Unknown   ❑$_1$ Known

     If known, systolic pulmonary arterial pressure: ❑❑❑ mmHg

Systemic AV valve regurgitation: ❑$_0$ None   ❑$_1$ Mild   ❑$_2$ Moderate   ❑$_3$ Severe

Subpulmonary AV valve regurg.:   ❑$_0$ None   ❑$_1$ Mild   ❑$_2$ Moderate   ❑$_3$ Severe

Pulmonary regurgitation: ❑$_0$ None   ❑$_1$ Mild   ❑$_2$ Moderate   ❑$_3$ Severe

Aortic regurgitation: ❑$_0$ None   ❑$_1$ Mild   ❑$_2$ Moderate   ❑$_3$ Severe

Pulmonary regurgitation volume: ❑❑.❑ mL

Pulmonary regurgitation fraction: ❑❑.❑ %

Subpulmonary ventricular (SPV) dilation: ❑$_0$ None ❑$_1$ Mild ❑$_2$ Moderate ❑$_3$ Severe

     If known: SPVEDV ❑❑❑.❑ mL   SPVESV ❑❑❑.❑ mL

Systemic ventricular (SV) dilation: ❑$_0$ None ❑$_1$ Mild ❑$_2$ Moderate ❑$_3$ Severe

     If known: SVEDV ❑❑❑.❑ mL   SVESV ❑❑❑.❑ mL

Was late gadolinium enhancement performed?   ❑$_1$ YES   ❑$_0$ NO

     Presence of late-gadolinium enhancements?   ❑$_1$ YES   ❑$_0$ NO

     Please specify location: _____

E) *HEMODYNAMIC STUDY*   ❏ NOT DONE

	Year	Month
	❏❏❏❏	❏❏

Subpulmary ventricular systolic pressure ❏❏❏ mmHg

Subpulmonary EDP ❏❏❏ mmHg

Systemic ventricular systolic pressure ❏❏❏ mmHg

Systemic ventricular EDP ❏❏❏ mmHg

PAP ❏❏❏/❏❏❏/❏❏❏ mmHg

Systolic   Diastolic   Mean

- -

F) *EXERCISE STRESS TEST WITH OR WITHOUT VO2 MAX*

	Year	Month
❏ NOT DONE	❏❏❏❏	❏❏

Exercise METS performed ❏❏.❏ METS

Maximum heart rate ❏❏❏ bpm

% Maximum predicted heart rate ❏❏❏.❏ %

Maximum VO2 ❏❏.❏ mL/kg/min

Non-sustained VT (3 beats or more, <30 seconds):   ❏₁ YES   ❏₀ NO

Sustained VT (≥30 seconds):   ❏₁ YES   ❏₀ NO

- -

Appendix 2. The SCOTIA-PVR Cohort – Coding Manual

SCOTIA-PVR STUDY – VARIABLE DEFINITION AND CODING

Spreadsheet 1. Preoperative & Operative Data (1/3)

Baseline Demographic Characteristics

Col.	Name	Label	Type	Variable Definition/Coding	Missing	N/A	Format
A	id	Unique identification number	Continuous	=(site*100+ids)	-	-	0
B	site	Center	Discrete	Halifax=1; McGill=2; Quebec=3; Ottawa=4; Montreal=10; Toronto=20; Edmonton=30; Vancouver=40	-	-	0
C	ids	Patient count	Continuous	-	-	-	0
D	sex	Gender[**2]	Discrete	Male=0; Female=1	-	-	0
E	dob	Date of birth	Date	-	-	-	yyyy-mm-dd

Source: most recent hospital facesheet.
[**]Variable included in the EuroScore II risk model.

Pediatric Surgical History

F	dx	Underlying diagnosis	Discrete	PS=0; TOF=1	-	-	0
G	palshunt	Palliative shunts	Discrete	None=0; Peripheral=1; Central=2; Cavopulmonary=3	999	-	0
H	palint	Palliative pulmonary interventions	Discrete	None=0; Open=1; Closed=2; Percutaneous=3	999	-	0
I	dac	Date of pediatric correction	Date	-	1902-09-25	-	yyyy-mm-dd
J	aac	Age at correction (months)	Continuous	=(dac-dob)	9999	-	0
K	rep	Primary repair	Discrete	No, 2-stage=0; Yes, 1-stage=1	999	-	0
L	repvent	Ventriculotomy	Discrete	No=0; Yes=1	999	-	0
M	repinf	Infundibulectomy	Discrete	No=0; Yes=1	999	-	0
N	reppaug	Pulmonary artery augmentation	Discrete	None=0; Non-transannular patch=1; Transannular patch=2	999	-	0
O	reppvs	Pulmonary valve resection	Discrete	No=0; Yes=1	999	-	0
P	repvsd	Type of ventricular septal defect	Discrete	None=0; Muscular=1; Perimembranous=2; Mixed=3	999	-	0
Q	reptvd	Tricuspid valve detachment	Discrete	No=0; Yes=1	999	-	0
R	reptvr	Attempted or completed TV repair	Discrete	No=0; Yes=1	999	-	0
S	redosx	# of surgical reinterventions	Continuous	-	9999	-	0
T	redopci	# of percutaneous reinterventions	Continuous	-	9999	-	0

Source: pediatric operative and procedural reports (if unavailable, clinic notes and imaging reports).

Spreadsheet 1. Preoperative & Operative Data (2/3)

Preoperative Comorbidites

Col.	Name	Label	Type	Coding Scheme	Missing	N/A	Format
U	dapvr	Date of PVR	Date	-	-	-	yyyy-mm-dd
V	aapvr	Age at PVR (years)[**1]	Continuous	=(dapvr-dob)	-	-	0
W	synd	Known genetic syndrome	Discrete	None=0; T21=1; DGS=2; Noonan=3; Goldenhar=4; RTS=5; Beckwick=6; DGS and Evans=7; FAS=8; VACTERL=9; MRKH=10; Diastrophic dysplasia=11; Klippel-Trenaunay=12; Kallman=13	999	-	0
X	idis	Intellectual disability	Discrete	No=0; Yes=1	999	-	0
Y	hapvr	Height (m)	Continuous	-	0	-	0.00
Z	wapvr	Weight (kg)	Continuous	-	0	-	0.0
AA	cr	Preoperative serum Cr (umol/L)	Continuous	-	0	-	0
AB	egfr_c	CG CrCl corrected for low weight (mL/min/1.73m^2)	Continuous	=(140-aapvr)*(wapvr)*(coef) / (0.814480*cr*coef2)	0	-	0.0
AC	egfr	CG CrCl (mL/min/1.73m^2)	Continuous	=(140-aapvr)*(wapvr)*(coef) / (0.814480*cr)	0	-	0.0
AD	mcgf	CG-BSA CrCl (mL/min/1.73m^2)	Continuous	=1.73*(egfr_c) / ((wapvr$^{0.425}$)*((hapvr*100)$^{0.725}$)*0.007184)	0	-	0.0
AE	coef	CG correction factor for sex	Discrete	If male=1; If female=0.85	-	-	0.00
AF	coef2	CG correction factor for weight	Discrete	If (wapvr/hapvr^2)<18.5=0.69; Otherwise=1	-	-	0.00
AG	hd	Preoperative hemodialysis	Discrete	No=0; Yes=1	999	-	0
AH	crf	Chronic renal failure[**3]	Discrete	Normal=0 (egfr_c>85); Mild-to-moderate=1 (50-85); Severe=2 (<50); Very severe=3 (hd=1)	999	-	0
AI	copd	Chronic lung disease[**7]	Discrete	No=0; Yes=1	999	-	0
AJ	dm	Diabetes[**10]	Discrete	No=0; Yes, on insulin=1; Yes, on oral agents=2	999	-	0
AK	pvd	Extracardiac arteriopathy[**4]	Discrete	No=0; Yes=1	999	-	0
AL	mob	Poor mobility[**5]	Discrete	No=0; Yes=1	999	-	0
AM	cirrh	Chronic hepatic failure	Discrete	No=0; Yes=1	999	-	0
AN	icu	Critical preoperative state[**9]	Discrete	No=0; Yes=1	999	-	0
AO	pcvs	Previous cardiac surgery[**6]	Discrete	=1 by definition for everyone	-	-	0
AP	endo	Active endocarditis[**8]	Discrete	No=0; Yes=1	999	-	0
AQ	acs	ACS in the last 90 days[**14]	Discrete	No=0; Yes=1	999	-	0
AR	euros	EuroScore (%)	Continuous	=(euros); Spreadsheet 4, variable AQ	-	-	0.00
AS	qrs	QRS duration (ms)	Continuous	-	999	-	0
AT	svt	Chronic atrial fibrillation	Discrete	None=0; Afib=1; A-flutter=2; Other=3	999	-	0
AU	eps	Electrophysiologic status	Discrete	No EPS=0; Not inducible=1; Inducible=2; Dx of VT/VF=3	999	-	0
AV	icd	Cardiac device	Discrete	None=0; Primary ICD=1; Secondary ICD=2; PM=3; CRT=4	999	-	0
AW	lead	# of leads across the TV	Continuous	-	999	888	0

Source: adult clinic, consultation, and admission notes; and operative, procedural and laboratory reports. Preoperative assessment considered valid up to 12 months before surgery.
[**]*Variables included in the EuroScore II risk model.*

Spreadsheet 1. Preoperative & Operative Data (3/3)

Operative Characteristics

Col.	Name	Label	Type	Coding Scheme	Missing	N/A	Format
AX	level	Operative urgency[**16]	Discrete	Elective=0; Urgent=1; Emergent=2; Salvage=3	999	-	yyyy-mm-dd
AY	pvrtype	Pulmonary prosthesis type	Discrete	Carbomedics=140; Mosaic=211; CE Classic/RSR=220; CE Magna/Magna Ease=221; Epic=231; Sorin=240; Contegra=310; Freestyle=311; Homograft=400	999	-	0
AZ	pvrsize	Pulmonary prosthesis size (mm)	Continuous	-	999	-	0
BA	mplast	Infundibular patch	Discrete	None=0; Bovine pericardium=1; Autologous pericardium=2; Synthetic material=3; Decellularized matrix=4	999	-	0
BB	bplast	Branch arterioplasty	Discrete	None=0; Unilateral=1; Bilateral=2	999	-	0
BC	vsdc	Closure of residual VSD	Discrete	None=0; Patch=1; Primary closure:2	999	-	0
BD	vsdt	Type of residual VSD	Discrete	None=0; Muscular=1; Perimembranous=2; Mixed=3	999	-	0
BE	tvdet	Tricuspid leaflet detachment	Discrete	No=0; Yes=1	999	-	0
BF	tvrep	Tricuspid valve repair	Discrete	No=0; Yes=1; Attempted=2	999	-	0
BG	tvleaf	Tricuspid leaflet plasty	Discrete	No=0; Yes=1	999	888	0
BH	tvtech	Tricuspid repair technique	Discrete	None=0; Ring annuloplasty=1; Stitch annuloplasty=2; Bicuspidization=3	999	888	0
BI	tvringt	Tricuspid ring type	Discrete	Contour 3D=110; CE Classic=120; CE MC3=121; CG Future=210; Duran AnCore=211; CE Physio =220	999	888	0
BJ	tvrings	Tricuspid ring size (mm)	Continuous	-	999	888	0
BK	tvr	TV replacement	Discrete	No=0; Yes=1; Attempted=2	999	-	0
BL	tvrtype	Type of TVR prosthesis	Discrete	SJ Bileafleat=130; Hancock=210; Mosaic=211; CE Theon/Plus=220; CE Magna=221	999	888	0
BM	tvrsize	TV prosthesis size (mm)	Continuous	-	999	888	0
BN	cryo	Cryoablation	Discrete	None=0; Atrial=1; Ventricular=2; Combined=3	999	-	0
BO	csx	Combined procedures	Discrete	None=0; Aortic=1; Coronary=2; Mitral=3; Other=4	999	-	0
BP	eusx1	Weight of the intervention[**17]	Discrete	=2 procedures by definition for everyone	-	-	0
BQ	eusx2	Surgery of the thoracic aorta[**18]	Discrete	No=0; Yes=1	999	-	0
BR	aoxt	Aortic cross-clamp time (min)	Continuous	-	9999	0	0
BS	fib	Arrest technique	Discrete	Aortic cross-clamping=0; Fibrillation=1	999	888	0
BT	cpbt	CPB time (min)	Continuous	-	9999	-	0
BU	femcan	Femoral cannulation	Discrete	No=0; Yes=1	999	-	0
BV	injury	Femoral access due to injury	Discrete	No=0; Yes=1	999	888	0
BW	pump	Femoral initiation of CPB	Discrete	No=0; Yes=1	999	888	0

Source: adult operative, perfusion and intraoperative nursing reports.

[**]Variable included in the EuroScore II risk model.

Spreadsheet 2. Longitudinal Clinical & Echographic Outcomes (1/1)

Patient/Visit Identifiers

Col.	Name	Label	Type	Coding Scheme	Missing	N/A	Format
A	id	Unique identification number	Continuous	-	-	-	0
B	fui	Follow-up interval (years)	Discrete	=0 (preop), 0.5 (postop), 1, 3, 5, 7, 10 and 15 years	-	-	0
C	maxf	Maximum follow-up	Discrete	No=0; Yes=1	-	-	0

Clinical Assessment

Col.	Name	Label	Type	Coding Scheme	Missing	N/A	Format
D	nyha	NYHA class[**11]	Discrete	Class I=1; Class II=2; Class III=3; Class IV=4	999	888	0
E	ccs	CCS class 4[**12]	Discrete	No=0; Yes=1	999	888	0
F	nyhaccs_d	Date of clinical follow-up	Date	-	1902-09-25	1902-06-06	yyyy-mm-dd
G	mets	Maximal oxygen uptake (mets)	Continuous	-	999	888	0.0
H	mets_d	Date of exercise stress test	Date	-	1902-09-25	1902-06-06	yyyy-mm-dd

Source: adult clinic notes and exercise stress test reports.
[**]Variables included in the EuroScore II risk model.

Echographic Assessment

Col.	Name	Label	Type	Coding Scheme	Missing	N/A	Format
I	d_e	Date of the echographic study	Date	-	1902-09-25	-	yyyy-mm-dd
J	ar_e	Aortic regurgitation	Discrete	Absent/trace=0; Mild=1; Moderate=2; Severe=3	999	-	0
K	ag_e	Mean aortic gradient (mmHg)	Continuous	-	999	-	0.0
L	as_e	Aortic stenosis	Discrete	Absent/trace=0; Mild=1; Moderate=2; Severe=3	999	-	0
M	mr_e	Mitral regurgitation	Discrete	Absent/trace=0; Mild=1; Moderate=2; Severe=3	999	-	0
N	mg_e	Mean mitral gradient (mmHg)	Continuous	-	999	-	0.0
O	ms_e	Mitral stenosis	Discrete	Absent/trace=0; Mild=1; Moderate=2; Severe=3	999	-	0
P	pr_e	Pulmonary insufficiency	Discrete	Absent/trace=0; Mild=1; Moderate=2; Severe=3	999	-	0
Q	pg_e	Peak pulm. gradient (mmHg)	Continuous	-	999	-	0.0
R	ps_e	Pulmonary stenosis	Discrete	Absent/trace=0; Mild=1; Moderate=2; Severe=3	999	-	0
S	tr_e	Tricuspid regurgitation	Discrete	Absent/trace=0; Mild=1; Moderate=2; Severe=3	999	-	0
T	tg_e	Mean tricuspid gradient (mmHg)	Continuous	-	999	-	0.0
U	ts_e	Tricuspid stenosis	Discrete	Absent/trace=0; Mild=1; Moderate=2; Severe=3	999	-	0
V	spap_e	Systolic PA pressure (mmHg)	Continuous	-	999	-	0.0
W	mpap_e	Mean PA pressure (mmHg)	Continuous	=0.61*(spap_e)+2	999	-	0.0
X	phtn_e	Pulmonary artery hypertension[**15]	Discrete	None=0 (mpap_e<31); Moderate=1 (31-55); Severe=2 (>55)	999	-	0
Y	tad_e	TV ED annular diameter (mm)	Continuous	-	999	-	0
Z	rvdil_e	RV dilatation	Discrete	Absent/trace=0; Mild=1; Moderate=2; Severe=3	999	-	0
AA	rvef_e	RV ejection fraction (%)	Continuous	-	999	-	0
AB	rvsd_e	RV systolic dysfunction	Discrete	Absent/trace=0; Mild=1; Moderate=2; Severe=3	999	-	0
AC	lvef_e	LV ejection fraction (%)	Continuous	-	999	-	0
AD	lvsd_e	LV systolic dysfunction	Discrete	Absent/trace=0; Mild=1; Moderate=2; Severe=3	999	-	0
AE	lveu_e	LV function as per Euroscore II[**13]	Discrete	Good=0 (lvef_e>50); Moderate=1 (31-50); Poor=2 (21-30); Very poor=3 (<21)	999	-	0

Source: adult transthoracic echographic reports (if unavailable, clinic notes)..
[**]Variable included in the EuroScore II risk model.

Spreadsheet 3. Cross-Sectional Clinical Outcomes (1/2)

Patient Identifier

Col.	Name	Label	Type	Coding Scheme	Missing	N/A	Format
A	id	Unique identification number	Continuous	-	-	-	0

Duration of Follow-Up and Mortality

Col.	Name	Label	Type	Coding Scheme	Missing	N/A	Format
B	loicus	Length of intensive care stay (days)	Continuous	-	-	888	0
C	dov	Duration of ventilation (days)	Continuous	-	-	888	0.0
D	dodc	Date of discharge	Date	-	-	-	yyyy-mm-dd
E	lohs	Length of hospital stay (days)	Continuous	=(dodc-dapvr)	-	888	0
F	death	Status at last follow-up	Discrete	Alive=0; Dead=1	-	-	0
G	deathcause	Cause of death	Free text	-	-	N/A	abc
H	dolf	Date of last follow-up	Date	-	-	-	yyyy-mm-dd

Source: intensive care flowsheets, discharge summaries and most recent hospital facesheet.

Short-Term Outcomes (within 30 days of PVR)

Col.	Name	Label	Type	Coding Scheme	Missing	N/A	Format
I	tamp	Re-exploration for bleeding	Discrete	No=0; Yes=1	-	888	0
J	tee	Major thromboembolic event	Discrete	No=0; Yes=1	-	888	0
K	teetype	First thromboembolic event type	Free text	-	-	N/A	abc
L	teetype2	Second thromboembolic event type	Free text	-	-	N/A	abc
M	infect	Major infection	Discrete	No=0; Yes=1	-	888	0
N	infectype	First infection type	Free text	-	-	N/A	abc
O	infectype2	Second infection type	Free text	-	-	N/A	abc
P	infectype3	Third infection type	Free text	-	-	N/A	abc
Q	devi	New cardiac device implantation	Discrete	No=0; Yes=1	-	888	0
R	devitype	New cardiac device type	Free text	-	-	N/A	abc
S	readm30	Readmission	Discrete	No=0; Yes=1	-	888	0
T	readmtype	Cause of readmission	Free text	-	-	N/A	abc
U	readm30d	Date of readmission	Date	-	-	1902-06-06	yyyy-mm-dd
V	hd0	Postoperative hemodialysis	Discrete	No=0; Yes=1	-	888	0

Source: operative, procedural, laboratory and imaging reports; intensive care and hemodialysis flowsheets; transfusion records; prescriptions; and discharge summaries.

Definitions:

All complications will be reported within 30 days of surgery. Deaths which occurred passed 30 days but within index admission will also be reported.

1. Re-exploration for bleeding: operative pericardial or pleural re-exploration, or percutaneous insertion of an additional pericardial drain due to bleeding.
2. Major thromboembolic event: neurologic (ischemic stroke, transient ischemic attack, spinal infarct), cardiopulmonary (myocardial infarction, pulmonary embolism) or peripheral vascular (acute arterial, deep venous, intra-abdominal thrombosis) event.
3. Major infection: culture-proven respiratory (upper or lower tract), wound (superficial or deep), hematologic (sepsis), neurologic (meningitis, abscess), cardiac (endocarditis, device-related) or gastrointestinal (C diff colitis, intraabdominal) infection requiring antibiotic therapy. Urinary tract infections are excluded.
4. New cardiac device implantation: insertion of a first cardiac device or upgrade to a different system. Battery change and lead revision are excluded.
5. Readmission: hospital readmission within the first 30 days of surgery or ER visit leading to > than 12 hours of planned observation.
6. Postoperative hemodialysis: new-onset temporary or permanent hemodialysis upon transfer to the ICU. Ultrafiltration while on CPB is excluded.

Spreadsheet 3. Cross-Sectional Clinical Outcomes (2/2)

Long-Term Outcomes (PVR until last follow-up)

W	chf	Readmission for heart failure	Discrete	No=0; Yes=1	-	888	0
X	dochf	Date of readmission for HF	Date	-	-	1902-06-06	yyyy-mm-dd
Y	newsvt	Readmission for new-onset SVT	Discrete	No=0; Yes=1	-	888	0
Z	newsvtd	Date of readmission for SVT	Date	-	-	1902-06-06	yyyy-mm-dd
AA	newvt	Readmission for new-onset VT	Discrete	No=0; Yes=1	-	888	0
AB	newvtd	Date of readmission for VT	Date	-	-	1902-06-06	yyyy-mm-dd
AC	cr1	Serum creatinine at 1 yr (umol/L)	Continuous	-	0	0	0
AD	cr1d	Date of creatinine at 1 yr	Date	-	1902-09-25	1902-06-06	yyyy-mm-dd
AE	hd1	Ongoing hemodialysis at 1 yr	Discrete	No=0; Yes=1	-	888	0
AF	reop	Cardiac reintervention after PVR	Discrete	No=0; Yes=1	-	888	0
AG	redotvi	Reintervention on the TV	Discrete	No=0; Yes=1	-	888	0
AH	reopd	Date of reintervention	Date	-	-	1902-06-06	yyyy-mm-dd
AI	reoptype	Type of reintervention	Free text	-	-	N/A	abc

Source: operative, procedural, laboratory and imaging reports; clinic notes; and discharge summaries.

Definitions:

1. Readmission for heart failure: signs and symptoms of fluid overload or low cardiac output resulting in hospital admission or administration in the ER for intravenous diuretics +/- ionotropic support. Presentation for uncomplicated postoperative pleural effusion is excluded.
2. Readmission for new-onset supraventricular tachycardia: new documented supraventricular tachycardia or symptoms of palpitations with inducible SVT on EPS resulting in hospital admission or chemical or electrical cardioversion in ER. Inapplicable situation for patients with preoperative atrial tachyarrhythmia.
3. Readmission for new-onset ventricular tachycardia: documented ventricular tachycardia or fibrillation or syncope with inducible VT on EPS. Inapplicable situation for patients with a symptomatic event or implantation of a secondary ICD prior to surgery.
4. Cardiac reintervention: any open-heart surgery or percutaneous cardiac intervention, excluding coronary and peripheral pulmonary artery stenting.

Spreadsheet 4. EuroScore II Calculator (1/2)

Patient Identifier

Col.	Name	Label	Equation	Imported Data
A	id	Unique identification number	=(id)	Sheet 1, variable A

Logistic Regression Variables

Col.	Name	Label	Equation	Imported Data
B	constant	Regression constant	=(-5.324537)	-
C	age	Age at PVR (years)[**1]	=(aapvr)	Sheet 1, variable V
D	agecat	Categorized age	=if(C2<=60;1;(C2-59))	-
E	Bagecat*x	Regression term 1	=(0.0285181*D2)	-
F	sex	Gender[**2]	=(sex)	Sheet 1, variable D
G	Bsex*x	Regression term 2	=(0.2196434*F2)	-
H	crf	Chronic renal failure[**3]	=(crf)	Sheet 1, variable AH
I	Bcrf*x	Regression term 3	=if(H2=3;0.6421508;if(H2=0;0;if(H2=1;0.303553;0.8592256)))	-
J	pvd	Extracardiac arteriopathy[**4]	=(pvd)	Sheet 1, variable AK
K	Bpvd*x	Regression term 4	=(0.5360268*J2)	-
L	mob	Poor mobility[**5]	=(mob)	Sheet 1, variable AL
M	Bmob*x	Regression term 5	=(0.2407181*L2)	-
N	pcvs	Previous cardiac surgery[**6]	=(pcvs)	Sheet 1, variable AO
O	Bpcvs*x	Regression term 6	=(1.118599*N2)	-
P	copd	Chronic lung disease[**7]	=(copd)	Sheet 1, variable AI
Q	Bcopd*x	Regression term 7	=(0.1886564*P2)	-
R	endo	Active endocarditis[**8]	=(endo)	Sheet 1, variable AP
S	Bendo*x	Regression term 8	=(0.6194522*R2)	-
T	icu	Critical preoperative state[**9]	=(icu)	Sheet 1, variable AN
U	Bicu*x	Regression term 9	=(1.086517*T2)	-
V	dm	Diabetes[**10]	=(dm)	Sheet 1, variable AJ
W	Bdm*x	Regression term 10	=if(V2=2;0.3542749;0)	-
X	nyha t=0	Preoperative NYHA class[**11]	=(nyha) at fui=0	Sheet 2, variable D
Y	Bnyha*x	Regression term 11	=if(X2=4;0.5597929;if(X2=1;0;if(X2=3;0.2958358;0.1070545)))	-
Z	ccs t=0	Preoperative CCS class 4[**12]	=(ccs) at fui=0	Sheet 2, variable E
AA	Bccs*x	Regression term 12	=(0.2226147*Z2)	-
AB	lveu t=0	Preoperative LV function[**13]	=(lveu_e) at fui=0	Sheet 2, variable AE
AC	Blveu*x	Regression term 13	=if(AB2=3;0.9346919;if(AB2=0;0;if(AB2=1;0.3150652;0.8084096)))	-
AD	acs	ACS in the last 90 days[**14]	=(acs)	Sheet 1, variable AQ
AE	Bacs*x	Regression term 14	=(0.1528943*AD2)	-
AF	phtn t=0	Preoperative PHTN[**15]	=(phtn_e) at fui=0	Sheet 2, variable X
AG	Bphtn*x	Regression term 15	=if(AF2=0;0;if(AF2=1;0.1788899;if(AF2=2;0.3491475;999)))	-
AH	level	Operative urgency[**16]	=(level)	Sheet 1, variable AX
AI	Blevel*x	Regression term 16	=if(AH2=0;0;if(AH2=1;0.3174673;if(AH2=2;0.7039121;1.362947)))	-
AJ	wgtsx	Weight of the intervention[**17]	=(eusx1)	Sheet 1, variable BP
AK	Bwgtsx*x	Regression term 17	=(0.2760739*AJ2)	-

Spreadsheet 4. EuroScore II Calculator (2/2)

Logistic Regression Variables […]

Col.	Name	Label	Equation	Imported Data
AL	thoao	Surgery of the thoracic aorta[18]	=(eusx2)	Sheet 1, variable BQ
AM	Bthoao*x	Regression term 18	=(0.6527205*AL2)	-
AN	β0 + ∑ βi*xi	NYHA class[11]	=(B2+E2+G2+I2+K2+M2+O2+Q2+S2+U2+W2+Y2+AA2+AC2+AE2+AG2+AI2+AK2+AM2)	-
AO	e^(β0 + ∑ βi*xi)	CCS class 4[12]	=(exp(AN2))	-
AP	Pmortality	Probability of death	=(AO2/(1+AO2))	-
AQ	euros	EuroScore (%)	=(100*AP2)	-

[EuroScore II risk model*: Eur J Cardiothorac Surg. 2012 Apr;41(4):734-44; discussion 744-5. doi:10.1093/ejcts/ezs043. http://www.euroscore.org/calc.html

Appendix 3. Directed Acyclic Graphs

Objective 1: Evaluate the association between Fontan surgery type and the risk of a first thromboembolic event
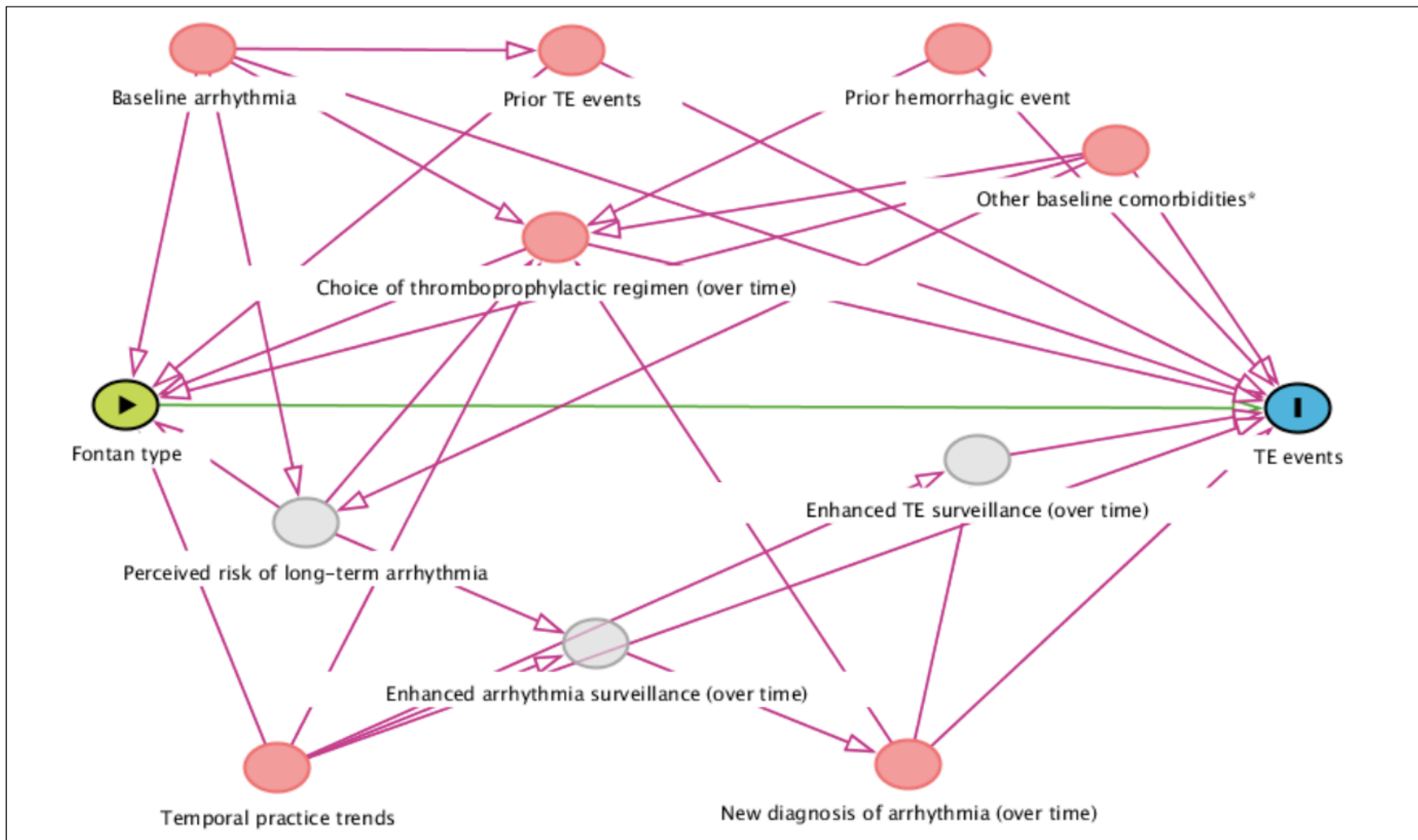

*Other baseline comorbidities include: age at Fontan palliation, staged palliation, congestive heart failure, pulmonary hypertension, renal failure, chronic lung disease, cirrhosis, thyroid disorder, baseline hematocrit, and baseline saturation.
Created using DAGitty Online v3.0

Objective 2: Evaluate the early safety of performing pulmonary valve replacement with concomitant tricuspid valve intervention
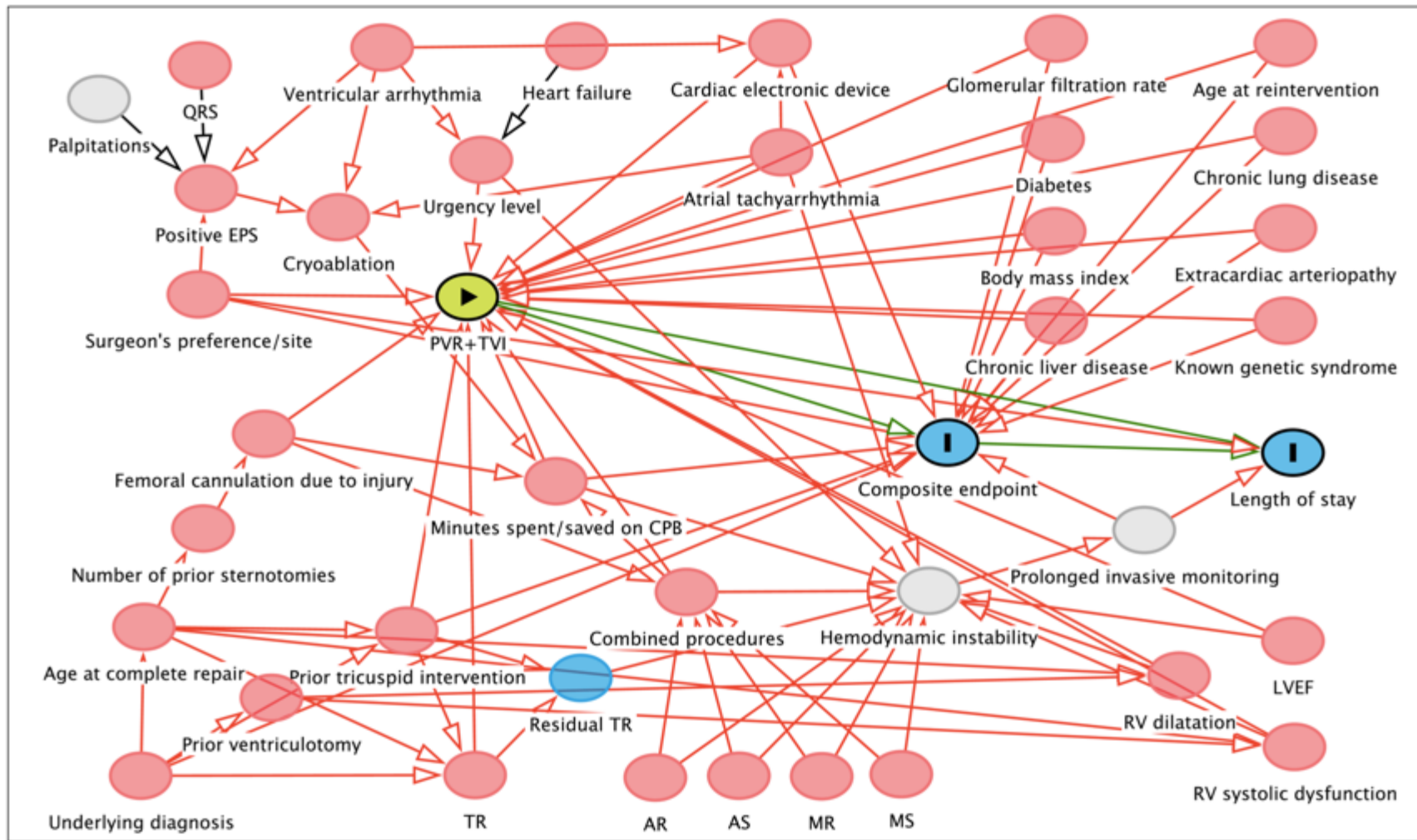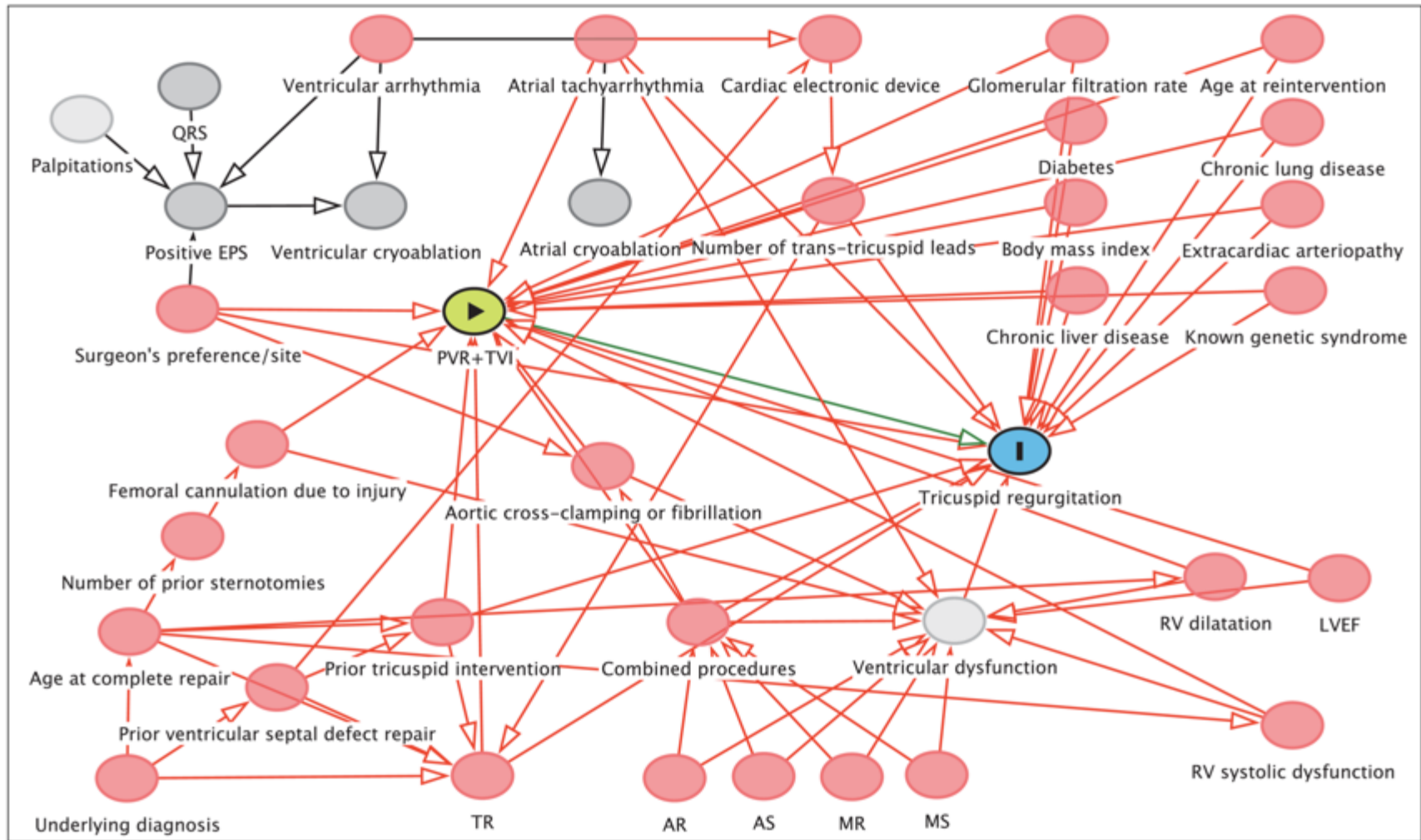

Created using DAGitty Online v2.3

Objective 3: Evaluate the early effectiveness of performing pulmonary valve replacement with concomitant tricuspid valve intervention

Created using DAGitty Online v2.3