Long-term outcomes of warfarin versus aspirin after Fontan surgery

Chantal Attard, BSc (Hons), PhD,[a,b] Paul T. Monagle, MBBS, MSc, MD, FRACP, FRCPA, FCCP,[a,b,c] Yves d'Udekem, MD, PhD,[a,b,c] Mark T. Mackay, MBBS, DRANZOG, FRACP, PhD,[a,b,c] Julie Briody, MBioMedEng,[d,e] Rachael Cordina, MBBS (HONS), PhD, FRACP,[f,g] Ebrahim Bani Hassan, DVSc, DVM, PhD,[h,i] Peter Simm, MBBS (Hons), MD, FRACP,[a,c,j] Kathryn Rice, MB, ChB, FRACP,[k] and Vera Ignjatovic, BSc (hons), PhD,[a,b] the ANZ Fontan Registry Research group

ABSTRACT

Objectives: Because of the nature of the Fontan physiology, patients are at an increased risk of thromboembolic complications. As such, warfarin or aspirin is generally prescribed lifelong for thromboprophylaxis. This study aimed to compare long-term rates of cerebrovascular injury, thrombosis, bleeding, bone mineral density, and quality of life in people living with Fontan circulation receiving warfarin compared with aspirin.

Methods: This was a multicenter study of a selected cohort from the Australia and New Zealand Fontan population. Participants underwent cerebral magnetic resonance imaging to detect the presence of cerebrovascular injury (n = 84) and dual-energy X-ray absorptiometry to assess bone mineral density (n = 120). Bleeding (n = 100) and quality of life (n = 90) were assessed using validated questionnaires: Warfarin and Aspirin Bleeding assessment tool and Pediatric Quality of Life Inventory, respectively.

Results: Stroke was detected in 33 participants (39%), with only 7 (6%) being clinically symptomatic. There was no association between stroke and Fontan type or thromboprophylaxis type. Microhemorrhage and white matter injury were detected in most participants (96% and 86%, respectively), regardless of thromboprophylaxis type. Bleeding rates were high in both groups; however, bleeding was more frequent in the warfarin group. Bone mineral density was reduced in our cohort compared with the general population; however, this was further attenuated in the warfarin group. Quality of life was similar between the warfarin and aspirin groups. Home international normalized ratio monitoring was associated with better quality of life scores in the warfarin group.

Conclusions: Cerebrovascular injury is a frequent occurrence in the Australia and New Zealand Fontan population regardless of thromboprophylaxis type. No benefit of long-term warfarin prophylaxis could be demonstrated over aspirin; however, consideration must be given to important clinical features such as cardiac function and lung function. Furthermore, the association of reduced bone health in children receiving warfarin warrants further mechanistic studies. (J Thorac Cardiovasc Surg 2021;162:1218-28)

Overview of long-term outcomes of warfarin versus aspirin after Fontan surgery.

CENTRAL MESSAGE

Stroke was frequent in the Fontan cohort regardless of thromboprophylaxis type. No benefit of long-term warfarin prophylaxis could be demonstrated over aspirin post-Fontan surgery.

PERSPECTIVE

Ongoing thromboprophylaxis is required post-Fontan surgery; however, long-term outcomes of such therapy are lacking. Randomized controlled trials of non–vitamin K oral anticoagulants in Fontan cohorts have recently begun. We provide important, long-term outcome data of conventional treatment in which we found asymptomatic stroke and brain injury are frequent occurrences in the Fontan population, regardless of thromboprophylaxis type.

See Commentaries on pages 1229, 1230, and 1231.

From the [a]Murdoch Children's Research Institute, Parkville, Australia; [b]The University of Melbourne, Parkville, Australia; [c]The Royal Children's Hospital, Parkville, Australia; [d]Nuclear Medicine, The Children's Hospital at Westmead, Westmead, Australia; [e]The University of Sydney Children's Hospital, Westmead Clinical School, Westmead, Australia; [f]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia; [g]Faculty of Medicine and Health Sciences, University of Sydney, Sydney, Australia; [h]Australian Institute for Musculoskeletal Science, The University of Melbourne and Western Health, Melbourne, Australia; [i]Department of Medicine-Western Health, The University of Melbourne, Melbourne, Australia; [j]Department of Paediatric Endocrinology and Diabetes, Monash Children's Hospital, Clayton, Australia; and [k]Paediatric and Congenital Cardiac Service, Starship Children's Hospital, Auckland, New Zealand.

Funding: National Health and Medical Research Council (NHMRC) Grant APP1065794: Functional Outcomes After Fontan Surgery. C.A. was supported through an NHMRC postgraduate scholarship. Y.d'U. is a Clinician Practitioner Fellow of the NHMRC (1082186). Murdoch Children's Research Institute is supported by the Victorian Government's Operational Infrastructure Support Program.

ANZ Fontan Registry Research group: This research group includes the stated authors and the following individuals: Simone Mandelstam,[b,c,l] Craig Munns,[e,m] Thomas Gentles,[k] Leeanne Grigg,[b,n] David Winlaw,[g,o] and Joseph Yuan-Mou Yang[a,b,c]

Received for publication Aug 8, 2020; revisions received Nov 27, 2020; accepted for publication Dec 21, 2020; available ahead of print Jan 5, 2021.

Address for reprints: Chantal Attard, BSc (Hons), PhD, Murdoch Children's Research Institute, Royal Children's Hospital, Flemington Rd, Parkville 3052 Australia (E-mail: Chantal.attard@mcri.edu.au).

0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2020.12.102

Abbreviations and Acronyms

ANZ = Australia and New Zealand
BMD = bone mineral density
CI = confidence interval
DXA = dual-energy X-ray absorptiometry
INR = international normalized ratio
MRI = magnetic resonance imaging
OR = odds ratio
PedsQL = Pediatric Quality of Life Inventory
QoL = quality of life
REDCap = Research Electronic Data Capture
WA-BAT = Warfarin and Aspirin Bleeding assessment tool

Scanning this QR code will take you to the table of contents to access supplementary information.

The Fontan procedure is the culmination of a series of staged surgeries to treat patients with single-ventricle physiology by rerouting systemic venous blood flow directly to the lungs. Although the Fontan procedure is noncurative, the majority of Fontan-palliated patients are expected to survive well into adulthood. Because mortality post-Fontan has decreased dramatically in recent years, the focus of patient outcomes has now shifted to reducing Fontan-associated comorbidities such as arrhythmia, liver dysfunction, protein-losing enteropathy, and thrombosis.

Because of the nature of the Fontan physiology, patients are at an increased risk of thromboembolic complications. Abnormalities in all 3 aspects of Virchow's triad are present because of the presence of abnormal endothelium or prosthetic material, low flow, and intrinsic plasma protein changes most likely related to subtle derangement in liver synthetic function, which is more pronounced in those with protein-losing enteropathy. Cohort studies have reported an incidence of venous thrombosis from 4% to 19%[1-4] and stroke from 3% to 19%.[1,2,5-7] To mitigate the risk of thrombosis post-Fontan, patients are generally prescribed lifelong warfarin or aspirin. The American Heart Association Guidelines consider the long-term prophylactic use of either drug in the Fontan population as "reasonable," while acknowledging that the current evidence base for the optimal type or duration of antithrombotic therapy is limited.[8]

When determining antithrombotic therapy, it is important to consider the benefits and potential drawbacks. For warfarin, the primary considerations include the requirement of regular venous international normalized ratio (INR) monitoring, the increased risk of bleeding, and the potential for reduced bone mineral density (BMD).[9] For aspirin, although monitoring is not routinely performed and is considered controversial, the existence of a subpopulation of patients who may be aspirin resistant, putting these patients at an increased risk of thrombosis, needs to be considered.[9]

Although thrombosis in Fontan patients receiving warfarin and aspirin has been investigated to some extent previously, there are no comprehensive studies that compare thrombosis and stroke rates and assess complications of anticoagulant use such as bleeding (including minor bleeding), BMD levels, and quality of life (QoL) in this population.

This study aimed to compare cerebrovascular injury, BMD, bleeding, and QoL in Fontan patients receiving long-term warfarin or aspirin.

MATERIALS AND METHODS

Study Participants

Study participants were recruited for this cross-sectional study using the Australia and New Zealand (ANZ) Fontan Registry, with the specific registry design and enrollment procedures previously described.[10]

An overview of the recruitment procedure for this specific study is outlined in Figure 1. Specifically, potential participants were invited to participate if they satisfied all 3 of the following criteria: at least 13 years of age, minimum of 5 years post-Fontan surgery, and prescribed 5 consecutive years of thromboprophylaxis exclusively with warfarin or aspirin immediately before study enrollment. Patients receiving warfarin were titrated to a target INR of 2 to 3. Patients receiving aspirin were prescribed 3 to 5 mg/kg of aspirin capped at 150 mg. Aspirin levels were not measured using a clinical test. Low-molecular-weight heparin use was not included as a comparison because it is not used for more than 3 months in any patients.

For magnetic resonance imaging (MRI) and BMD investigations, potential participants were invited by mail and then screened for eligibility by phone. All study aspects were optional, and as such, during phone screening and the consent process, patients were able to opt out of some aspects of the study if they did not want to undergo all investigations (eg, undergo BMD screening without MRI). Baseline characteristics and follow-up data including history of thrombosis were obtained from the ANZ Fontan Registry database.[1]

For assessments performed online, a link to the questionnaire was emailed to all Fontan Registry members who met the eligibility criteria and for whom an email address was known. Consent was implied if questionnaires were completed.

Study Sites

This multicenter study was approved by the national and local hospital Ethics Committees of each study center. Victoria (Australia): Royal Children's Hospital; Australian Institute for Musculoskeletal Science and University of Melbourne; New South Wales (Australia): Children's Hospital at Westmead and Royal Prince Alfred Hospital; Auckland (New Zealand): Starship Children's Health.

Cerebrovascular Injury

Clinical history of stroke was collected for all participants undergoing MRI or BMD screening using the ANZ Fontan Registry database. Brain MRI was performed to quantify the presence of cerebrovascular injury on a 1.5 Tesla Siemens MRI in Victoria and Auckland, and on a Philips

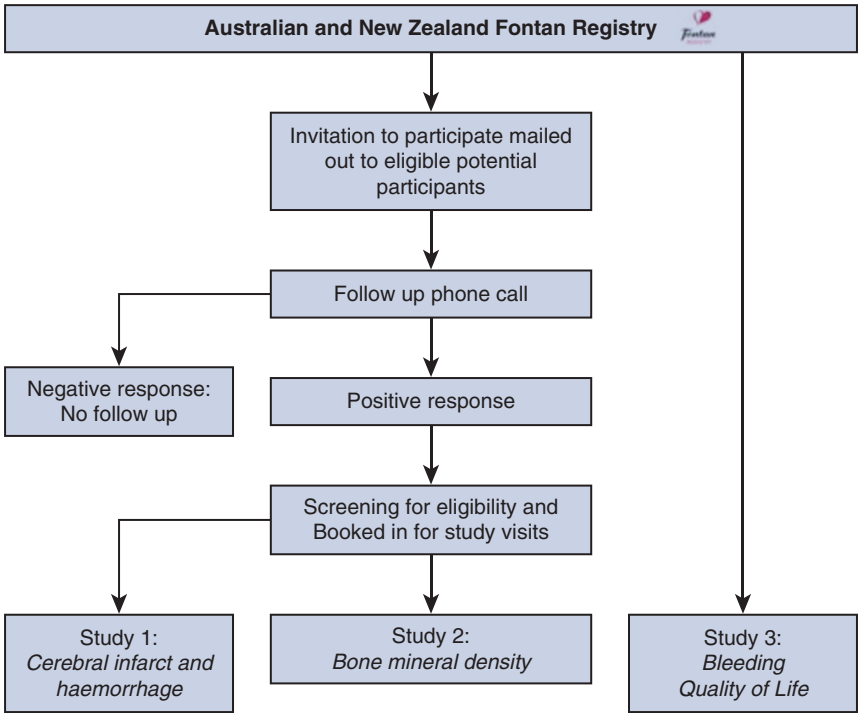

FIGURE 1. Patient recruitment strategy overview. Participants were recruited into the various study arms using the ANZ Fontan Registry.

MRI in New South Wales, with equivalent sequences being used. Sequences included diffusion weighted imaging, T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery, susceptibility-weighted imaging, and magnetic resonance angiography.

All MRI scans were performed for the sole purpose of this study and were reported centrally and classified by consensus by a Senior Pediatric Neurologist (with subspecialty stroke expertise) and Pediatric Neuroradiologist, both of whom were blinded to all clinical information. Classification of brain injury followed the criteria used by Beca and colleagues,[11] who described MRI findings in a cohort of children with congenital heart disease.

Bone Mineral Density

BMD was measured using dual-energy X-ray absorptiometry (DXA). Data were converted to age-adjusted Z scores to allow for grouped comparisons. Z scores were calculated using reference population data provided by the respective DXA manufacturers, as per clinical practice. DXA was performed at each study site using available instrumentation (Table E1).

Height for age z score was calculated using the Centers for Disease Control growth chart.[12] Plain left-hand radiograph was used to determine bone age in participants aged less than 18 years. Pubertal stage was estimated in participants aged less than 18 years using self-reported tanner assessment.[13] Dietary calcium intake was evaluated using a validated food frequency questionnaire,[14] which is used clinically as standard practice by the endocrinology department at The Royal Children's Hospital, Melbourne, to estimate dietary calcium intake of their patients. Serum vitamin D was measured using the Liaison XL 25OH Vitamin D assay (DiaSorin S.p.A, Vercelli, Italy) per the manufacturer's instructions.

Assessment of Bleeding and Quality of Life

We used a Warfarin and Aspirin Bleeding assessment tool (WA-BAT) developed and previously validated by our team to specifically assess bleeding in individuals receiving oral thromboprophylaxis.[15] The WA-BAT consisted of 25 questions assessing the types, rates, and severity of bleeding. After validity and reliability testing, the questionnaire was administered electronically through Research Electronic Data Capture (REDCap).

To assess health-related QoL in our participants, age-appropriate versions of the Paediatric Quality of Life Inventory core scales (PedsQL; 23 items, version 4.0, 1998) were administered using REDcap, concurrently with the WA-BAT. The PedsQL Measurement Model is a modular approach to measure health-related QoL in children, adolescents, and adults.[16]

Data Storage and Statistical Analysis

Study data were collected and managed using REDCap. Statistical analyses were performed in STATA version 14 (StataCorp, LP, College Station, Tex). Values are reported as number (%) for proportions, mean (standard deviation) for normally distributed data, and median (interquartile range) for non-normally distributed data. Patient characteristics and outcome measures were compared between groups using chi-square tests, *t* tests, and rank-sum tests, where appropriate. Odds ratios (ORs) were used to quantify the strength of association between outcomes and variables. Where warfarin and aspirin were compared, the warfarin group was considered the reference cohort.

Where appropriate, logistic or linear regression models were used to quantify the relationship between thromboprophylaxis type with outcome measures and to adjust for potential confounding variables. Details of adjusted variables are shown in the relevant tables (Tables 1 and 2).

RESULTS

A summary of the results is presented in Figure 2.

Study Population

The ANZ Fontan Registry included 1186 active enrollees at the time of recruitment commencement. The characteristics of the registry participants are presented in Table 3. On

TABLE 1. Clinical stroke and radiologic findings by thromboprophylaxis type

	Total	Warfarin	Aspirin	*P* value*	OR†	Adjusted *P* value†	95% CI
Clinical stroke (%). All MRI and BMD participants‡ n = 121; 67w; 54a	7 (6)	3 (5)	4 (7)	.43			
Radiologic findings							
Infarct (%)	33 (39)	20 (44)	13 (34)	.39	0.87	.87	0.18-4.26
Infarct number (%) n = 45w; 37a				.710	1.11	.91	0.18-6.93
Single	19 (23)	11 (24)	8 (22)				
Multiple	14 (17)	9 (20)	5 (14)				
Macrohemorrhage (%) n = 45w; 38a	1 (1)	1 (2)	0 (0)	.357			
Microhemorrhage (%) n = 43w; 36a	76 (96)	40 (93)	36 (100)	.106			
Microhemorrhage severity (%) n = 40w; 36a				.332			
Mild	4 (5)	1 (3)	3 (8)				
Moderate	18 (24)	8 (20)	10 (28)				
Severe	54 (71)	31 (78)	23 (64)				
White matter injury (%) n = 45w; 38a	72 (86)	40 (87)	32 (84)	.72	0.99	.99	0.24-4.0

OR, Odds ratio; *CI*, confidence interval; *MRI*, magnetic resonance imaging; *BMD*, bone mineral density. *Chi-square *P* value of difference. †Adjusted for Fontan type, sex, age, fenestration and age at Fontan; mild = ≤3 foci and all ≤2 mm, Moderate = >3 and ≤10 foci or any >2 mm, severe = >10 foci. ‡NB: One participant had their thromboprophlaxis changed from aspirin to warfarin after a clinically diagnosed stroke and was thus designated to the aspirin group for our analysis.

the basis of our selection criteria, 490 patients were identified and invited to participate in our study. Of these, 137 potential participants agreed to be further screened by phone for eligibility for the MRI and BMD arms of our study. Reasons for ineligibility included not meeting the selection criteria, claustrophobia (for MRI), and unwilling/unable to attend study visit because of distance or work/study commitments. A total of 121 patients living with Fontan circulation underwent MRI, BMD screening, or both (Tables 4 and 5). Patient characteristics were similar between eligible registry participants and those who participated in our study (Tables 3-5). Table E1 demonstrates that there are specific regional preferences for fenestration and prophylaxis type.

TABLE 2. Bone mineral density, fracture rate, and vitamin D and calcium intake based on thromboprophylaxis type

	Total	Warfarin	Aspirin	Difference	95% CI	*P* value	Adjusted *P* value†
Z score*							
Total body (SD) n = 43w; 51a	−0.71 (1.18)	−0.94 (1.15)	−0.52 (1.17)	−0.42	−1.18-0.03	.09	.064
Left femoral neck (SD) n = 67w; 52a	−0.67 (1.03)	−0.91 (0.97)	−0.36 (1.04)	−0.55	−1.16-0.23	.004	.004
Right femoral neck (SD) n = 58w; 41a	−0.56 (1.09)	−0.89 (1.03)	−0.1 (1.0)	−0.79	−1.51-0.54	.0002	<.0001
Lumbar spine (SD) n = 63w; 50a	−1.08 (1.07)	−1.23 (1.08)	−0.90 (1.03)	−0.33	−1.01-0.04	.09	.07
Clinically significant reduced BMD (participants with z score <−2)							
Total body (%) n = 43w; 51a	13 (13.4)	7 (16.3)	6 (11.8)	-		.53	
Left femoral neck (%) n = 67w; 52a	11 (9.2)	8 (11.9)	3 (5.8)	-		.25	
Right femoral neck (%) n = 58w; 41a	7 (7.1)	5 (8.7)	2 (4.9)	-		.47	
Lumbar spine (%) n = 63w; 50a	19 (16.8)	12 (19.1)	7 (14)	-		.48	
Fractures							
Individuals who had fracture (%) n = 60w; 46a	45 (43)	27 (45)	18 (39)	-	0.64-4.70	.55	.28
Total fractures n = 60w; 46a	60	28	32	-	0.39-3.0	.06	.87
No. of fractures (%) n = 60w; 46a							
1	26 (25)	18 (30)	8 (17)	-			-
2	11 (10)	5 (8)	6 (13)	-			-
3	4 (4)	0 (0)	4 (8)	-			-
Height for age z score (SD)	−0.44 (1.07)	−0.51 (1.03)	−0.33 (1.13)	−0.18	−0.63-0.57	.36	-
Vitamin D (SD) n = 35w; 39a	61.75 (24.28)	59.38 (25.73)	63.86 (23.04)	−4.48	−6.81-15.79	.43	-
Calcium intake mg/d (SD) n = 58w; 46a	1160 (649)	1153 (700)	1168 (586)	−15	−240-271	.91	-

CI, Confidence interval; *SD*, standard deviation; *BMD*, bone mineral density. *Adjusted for age and gender. †Adjusted for vitamin D and calcium intake.

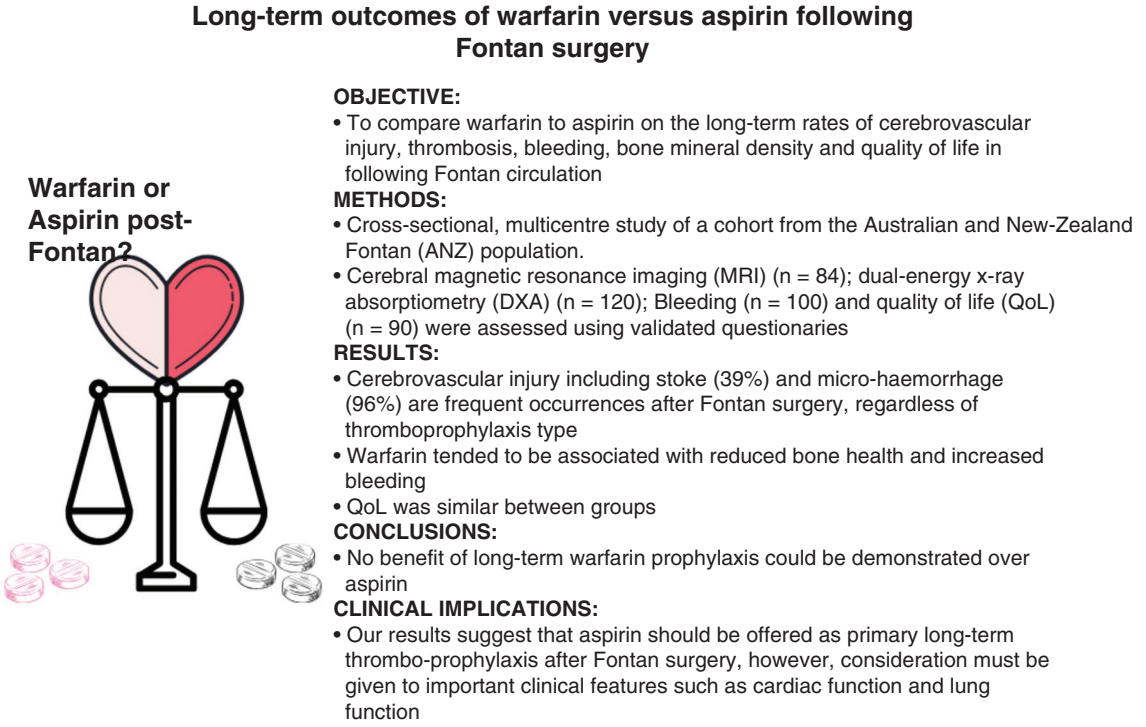

FIGURE 2. Long-term outcomes of warfarin versus aspirin after Fontan surgery. A summary of the key findings of a cross-sectional study of the ANZ Fontan Registry.

Cerebrovascular Injury

Of the potential participants who agreed to be further screened, 84 participants were deemed eligible and consented for brain MRI. The characteristics of the cohort are presented in Table 3. Rates of stroke and hemorrhage are presented in Table 1

High rates of focal and generalized brain abnormalities were observed, with all participants (100%) presenting with abnormal brain images. Figure E1 demonstrates the broad spectrum of brain injury as observed in a single patient and included parietal cortical and subcortical infarct, hemorrhagic transformation, and microhemorrhages.

Evidence of ischemic infarction was detected in 39% of participants, but only 15% of these (overall 6%) had a clinically recognized event (diagnosed on MRI at time of the event). There were no differences between warfarin and aspirin groups for stroke and hemorrhage in terms of incidence, type, or severity (number of infarcts/micro- or macrohemorrhages) (Table 1). Furthermore, there was no statistical association between Fontan type or cardiac morphology and stroke (atriopulmonary connection 33%, lateral tunnel 10%, extracardiac conduit 6%, *P* value .52; left 46%, right 28%, biventricular 20%, indeterminate 40%, *P* value .4).

All participants in the aspirin group and 93% of the warfarin group had evidence of microhemorrhage, with only 1 participant (1%) having evidence of macrohemorrhage. There was no statistical association between Fontan type or cardiac morphology and microhemorrhage (atriopulmonary connection 89%, lateral tunnel 100%, extracardiac conduit 98%, *P* value .21; left 98%, right 96%, biventricular 100%, indeterminate 100%, *P* value .91). White matter injury was evident in 86% of the cohort, with no differences observed between warfarin and aspirin groups (OR, 0.99; confidence interval [CI], 0.24-4.0; *P* value .99).

Variation in practice in terms of anticoagulation and fenestration was noted; however, those 2 factors did not seem to influence the incidence of clinically symptomatic or subclinical strokes (all stroke: fenestrated 44% vs nonfenestrated 35%, OR, 1.45, CI, 0.56-3.79, *P* value .45; clinical stroke: fenestrated 8% vs nonfenestrated 5%, OR, 1.69, CI, 0.36-7.97, *P* value .50).

Extracranial Thrombosis

Extracranial thrombosis was detected in 5% of participants who underwent MRI or BMD screening (n = 121). Pulmonary embolism and cardiac thrombosis were reported in 2% and 3% of participants, respectively. Thromboprophylaxis did not appear to be associated with extracranial thrombosis (Table E2).

Bleeding

To assess bleeding, we emailed the WA-BAT questionnaire to 490 registry participants, for whom 32 emails were deemed invalid. A total of 100 respondents completed the WA-BAT questionnaire (22% participation rate).

TABLE 3. Australia and New Zealand Fontan Registry participant characteristics

	Total (n = 490)
Male (%)	263 (54)
Age, median (IQR)	21.5 (16.9-27.6)
Age at Fontan, median (IQR)	4.7 (3.4-6.9)
Years post-Fontan, median (IQR)	16.2 (11.3-22.70)
Isomerism/heterotaxy (%)	37 (8)
Dominant ventricular morphology (%)*	
Left	322 (66)
Right	126 (26)
Biventricular	28 (6)
Indeterminate	14 (3)
Fontan type (%)† (n = 487)	
ECC	236 (49)
LT	150 (31)
AP	101 (21)
Fenestrated Fontan (%)† (n = 485)	153 (32)
Clinical stroke (%) n = 437	39 (9)

IQR, Interquartile range; *ECC*, extracardiac conduit; *LT*, lateral tunnel; *AP*, atriopulmonary connection. *Missing 1. †Missing 2.

Analysis of the WA-BAT demonstrated differences between the warfarin and aspirin groups in terms of the cessation of anticoagulation, epistaxis, and oral contraceptive use (Table E3). More participants on warfarin stopped their anticoagulant during the previous 5-year period (56% vs 21%; *P* value .001) and stopped anticoagulation before undergoing a medical procedure (49% vs 9%; $P < .0001$). Participants taking warfarin also experienced more episodes of epistaxis compared with participants on aspirin (47% vs 24%; *P* value .023). Additionally, there was an increased number of patients receiving warfarin and taking the combined oral contraceptive pill (*P* value .01).

The rates of minor bleeding were comparable between patients receiving warfarin and aspirin. No patient with either treatment had a change of thromboprophylaxis type as a result of bleeding or thrombosis. Furthermore, self-estimated menstrual bleeding volumes were similar between women on both therapies. Iron-deficiency anemia was reported in approximately one-quarter of all respondents, regardless of thromboprophylaxis type.

Bone Mineral Density

A total of 120 participants underwent a DXA scan (Table 5). Overall, participants had a lower mean BMD than the age-matched reference population (z score <0), regardless of the type of thromboprophylaxis (Table 2). Participants receiving warfarin had reduced BMD compared with their aspirin counterparts at all measured sites, with BMD in the left and right femoral neck sites being statistically significantly lower. Rates of clinically significant reduced BMD (as determined by a z score of <−2) were detected most often at the lumbar spine site (17%). No differences in clinically significant reduced BMD were observed between the warfarin and aspirin groups at any of the measured sites.

Height for age, fracture rates, vitamin D, and dietary calcium levels were comparable between the groups; however, those in the aspirin group were younger (median, 19 vs 24 years; *P* value .004); 45% of male and 41% of female patients had experienced bone fracture over their lifetime. None of the fractures reported were deemed low-impact fractures. In general, bone age matched chronological age

TABLE 4. Magnetic resonance imaging study participant characteristics based on thromboprophylaxis type

	Total (n = 84)	Warfarin (n = 46)	Aspirin (n = 38)	*P* value
Male (%)	49 (58)	27 (59)	22 (58)	.94
Age, median (IQR)	20.7 (15.9-27.4)	22.6 (17.4-28.7)	17.9 (14.9-24.9)	.03
Age at Fontan, median (IQR)	4.7 (3.5-6.9)	4.8 (3.5-7.9)	4.6 (3.4-6.2)	.32
Years post-Fontan, median (IQR)	15.7 (10.5-22.5)	16.5 (10.6-22.8)	13.2 (10.3-19.3)	.21
Isomerism/heterotaxy (%)*	9 (11)	5 (11)	4 (10)	.36
Dominant ventricular morphology (%)†				.47
Left	48 (57)	27 (59)	21 (55)	
Right	25 (30)	14 (30)	11 (29)	
Biventricular	5 (6)	3 (7)	2 (5)	
Indeterminate	5 (6)	1 (2)	4 (11)	
Fontan type*				.135
ECC	53 (63)	25 (54)	28 (74)	
LT	20 (24)	13 (28)	7 (18)	
AP	9 (11)	7 (15)	2 (5)	
Fenestrated Fontan (%)*	25 (30)	21 (47)	4 (11)	<.001

IQR, Interquartile range; *ECC*, extracardiac conduit; *LT*, lateral tunnel; *AP*, atriopulmonary connection. *Missing 2. †Missing 1.

TABLE 5. Bone mineral density study participant characteristics based by thromboprophylaxis type

	Total (n = 120)	Warfarin (n = 67)	Aspirin (n = 53)	*P* value
Male (%)	68 (57)	39 (58)	29 (55)	.7
Age, median (IQR)	20.8 (15.5-28.1)	24.0 (17.0-29.2)	18.6 (14.9-24.3)	.004
Age at Fontan, median (IQR)	4.8 (3.6-6.6)	4.8 (3.8-7.3)	4.7 (3.5-6.0)	.24
Years post-Fontan, median (IQR)	15.8 (10.5-22.3)	17.1 (11.5-23)	14.4 (9.5-18.9)	.4
Isomerism/heterotaxy (%)	11 (9)	7 (10)	4 (8)	.16
Dominant ventricular morphology (%)*				.15
Left	71 (59)	40 (61)	31 (59)	
Right	33 (28)	20 (30)	13 (25)	
Biventricular	8 (7)	5 (8)	3 (6)	
Indeterminate	7 (6)	1 (2)	6 (11)	
Fontan type (%)†				.047
ECC	78 (66)	38 (58)	40 (77)	
LT	28 (24)	18 (27)	10 (19)	
AP	12 (10)	10 (15)	2 (4)	
Fenestrated Fontan (%)†	36 (31)	32 (49)	4 (8)	<.001

IQR, Interquartile range; *ECC*, extracardiac conduit; *LT*, lateral tunnel; *AP*, atriopulmonary connection. *Missing n = 1. †Missing n = 2.

in both groups, with a mean difference between age and bone age of 0.87 years (standard deviation, 0.82).

Quality of Life

A total of 90 participants completed the PedsQL assessment. There was no difference between the warfarin and aspirin groups for overall health-related QoL, as well as for each of the assessed dimensions (Table 6). A post hoc analysis of participants undergoing warfarin home-INR monitoring demonstrated a positive impact on QoL (Table 6), with the home INR group scoring a mean of 10 points higher (mean 70.5) compared with the warfarinized, nonhome INR group (mean 60.4; *P* value .05).

DISCUSSION

The first Fontan procedure was performed more than 50 years ago.[17] An estimated 70,000 patients are alive today post-Fontan, with this population expected to double within 2 decades.[18,19] Thromboprophylaxis reduces the incidence of thrombosis; however, the wide practice variation evident in our data suggests that uncertainty still exists with regard to the best thromboprophylactic strategy for these patients. A single randomized controlled trial demonstrated no difference between the 2 strategies, aspirin and warfarin, as did a retrospective analysis of data from our own registry.[20] Nevertheless, recent clinical guidelines do not definitively recommend aspirin in preference to warfarin in low-risk patients.[19] In this regard, our study adds to current evidence with regard to the potential consequences of these 2 therapies.

Cerebrovascular Injury

The clinically reported symptomatic stroke rate for our cohort was 6% post-Fontan and is comparable with

TABLE 6. Comparison of quality of life outcomes by thromboprophylaxis type and type of international normalized ratio monitoring

PedsQL dimensions	Warfarin (n = 59) mean (SD)	Aspirin (n = 31) mean (SD)	*P* value
Total Scale Score	63.5 (18.5)	65.8 (16.7)	.564
Physical Functioning	60.7 (24.6)	65.7 (19.9)	.327
Emotional Functioning	61.6 (19.7)	61.1 (20.0)	.913
Social Functioning	70.9 (17.5)	69.7 (20.0)	.764
School \ Work Functioning	62.3 (23.2)	66.1 (21.9)	.453
PedsQL dimensions	**Home INR monitoring (n = 18) mean (SD)**	**Non-home INR monitoring (n = 41) mean (SD)**	***P* value**
Total Scale Score	70.5 (21.0)	60.4 (16.7)	.054
Physical Functioning	71.5 (24.0)	56.0 (23.6)	.025
Emotional Functioning	68.6 (23.6)	58.5 (17.3)	.071
Social Functioning	75.6 (18.1)	68.9 (17.0)	.178

PedsQL, Pediatric quality of life inventory; *SD*, standard deviation; *INR*, International normalized ratio.

previously published rates of 3% to 19%.[21] However, a strikingly large proportion of asymptomatic cerebral infarction was revealed on MRI of the brain, with 39% of our cohort showing radiologic evidence of stroke. A significant finding of our study was the absence of difference in rates of cerebral infarction in patients taking aspirin compared with those taking warfarin. Given the heterogeneity of our participants and the cross-sectional nature of the study, equivalence of warfarin and aspirin as primary thromboprophylaxis cannot be equivocally determined. However, given that we observed high rates of cerebral infarction across our cohort, regardless of thromboprophylaxis type, obvious differences in benefit were not observed between treatment groups. Although similar findings have been observed previously, those studies only reported clinically diagnosed stroke and did not screen patients for asymptomatic stroke.[20,22]

Some physicians may believe that particular patients may benefit from warfarin because they are more susceptible to thromboembolism. As an example, one could postulate that the shunting related to the fenestration may put their patients at a higher risk of stroke. Our cohort was remarkably uniform in the incidence of stroke. The variation of practice by region allowed us to compare the outcomes of patients with and without fenestration for both warfarin and aspirin, and we could not demonstrate any differences in the brain MRI of these patients after more than 5 years of consecutive treatment. However, whether larger numbers would show a difference remains to be seen.

We also observed no statistically significant differences in stroke rate based on Fontan type or dominant ventricular morphology. However, given the relatively small numbers per Fontan type and morphological subgroup, the lack of difference does not exclude a potential effect.

In the early stages of life, patients undergoing surgery for congenital heart defects experience brain injuries at a significant rate. Beca and colleagues[11] quoted a rate of white matter injury as high as 44% in infants postcardiac surgery. Cordina and colleagues[23] reported that adults with chronic cyanotic heart disease were likely to have stroke on cerebral imaging.

This study shows extremely high rates of white matter injury. Because of the cross-sectional design of our study, at which stage of life or which surgical stage these events occurred, remains to be determined. The need for further study in this sphere has recently been emphasized in a scientific Statement from the American Heart Association.[19] Furthermore, the clinical and neurologic implications of cerebrovascular injury observed post-Fontan warrant investigation using thorough neurocognitive testing techniques.

Extracranial Thrombosis

Our reported rate of extracranial thrombosis of 5% is comparable to the rate of clinically detected thrombosis of 6% from the randomized trial by Monagle and colleagues.[21] Monagle and colleagues' study found that screening using transesophageal echocardiography detected a higher rate of cardiac thrombosis than was routinely clinically detected. Furthermore, a retrospective study in a US Fontan cohort also found that up to 43% of thromboses detected were asymptomatic.[1] We similarly expect that specifically screening our population with sensitive imaging would increase the rate of thrombosis detected by including more asymptomatic cases. The clinical significance of asymptomatic thrombosis is yet to be determined. However, given the risk of Fontan failure or embolization to the brain and the high rate of stroke we detected in our cohort, the rate and clinical significance of asymptomatic thrombosis warrant further investigation.

Bleeding

In this era of introduction of new antithrombotic agents, the characterization of the bleeding complications of a target population such as the one living with a Fontan circulation gives insights of the results of conventional practice. Overall, there were high rates of heavy menstrual bleeding, bruising, and bleeding from minor wounds and after tooth removal across the cohort. Despite these incidences of bleeding, thromboprophylaxis was only stopped because of bleeding in 1 individual. Patients receiving warfarin experienced more epistaxis and ceased anticoagulation more commonly before a medical procedure than those receiving aspirin.

There were minimal differences in bleeding rates between warfarin and aspirin groups. The lack of difference in perceived menstrual bleed volumes between the groups was unexpected. We hypothesized that an increase in the rate of menorrhagia would be expected in the warfarin group. The lack of difference may be because therapy, such as the contraceptive pill, is used as treatment for menorrhagia and thus likely prescribed to women receiving warfarin who have experienced excessive menstrual bleeding. This is highly plausible because the women receiving warfarin reported higher levels of oral contraceptive use.

Our study demonstrated that microhemorrhages on brain MRI are ubiquitous in the Fontan population. The majority of patients receiving warfarin and all patients receiving aspirin had evidence of microhemorrhage. The pervasive nature of these events suggests their cause is due to events common to both thromboprophylaxis groups such as chronic venous hypertension, surgical variables, or cardiopulmonary bypass, for which 300-500 IU/kg continuous infusions of heparin are routinely administered. Only 1 participant had evidence of macrohemorrhage. Although this participant was receiving warfarin, it is unclear whether thromboprophylaxis choice was a contributing factor to the hemorrhagic event. Whether an increased sample size

would reveal an increased risk of macrohemorrhage supports the need for further research in this population.

Bone Mineral Density

Our Fontan cohort had reduced BMD compared with the healthy reference population. Previous studies have also observed a reduction in BMD in both children and adults with Fontan circulation compared with the healthy reference population.[24,25]

The results of our study demonstrate that participants receiving warfarin have further decreased levels of BMD compared with those receiving aspirin. Despite this difference, there were no differences in clinically significant BMD reduction. Previous studies have similarly observed an association of warfarin with reduced BMD; however, these studies were limited by small numbers.[24,26] Whether reduced BMD associated with warfarin is a direct drug effect or reflects differences in patient selection or surgical management requires further investigation.

Fracture rates were equivalent in the warfarin and aspirin groups (45% and 39%, respectively). Lyons and colleagues[27] reported on a South Wales population, where by 15 years, 64% of boys and 39% of girls can expect to have fractured a bone. Male participants in our cohort were older (median, 20.8 years) and had a lower incidence of fracture (45%) than in the Lyons study population. We speculate that the physical restriction placed on Fontan patients, either because of their condition or prescribed for bleeding risk, has subsequently reduced the opportunity for fractures to occur throughout childhood.

The importance of peak bone mass and its corresponding relationship to osteoporosis risk and fracture rate have been well defined.[28] The lower BMD observed in our cohort may well reflect higher risk of osteoporosis and its attendant morbidity as this population ages, which supports the focus on bone health outcomes in this group. The findings of our study also justify the recommendation of regular BMD screening in the Fontan population, and particularly those receiving warfarin.

Quality of Life

QoL has increasingly been identified as an important clinical outcome measure of thromboprophylaxis management in children.[29] We hypothesized that participants receiving warfarin would have poorer health-related QoL than those receiving aspirin because of the required INR monitoring and restrictions on physical activity. No statistical difference in QoL was observed between participants when using the PedsQL. These results may indicate that health-related QoL is more influenced by the patient's underlying health condition rather than thromboprophylaxis. This statement is supported by a study from Uzark and colleagues[30] that demonstrated a significant decrease in QoL scores in Fontan patients compared with controls, using the PedsQL tool. Another study by the same group also noted that QoL worsened with disease severity in children with congenital heart disease, further supporting the notion that QoL is influenced by underlying medical condition.[31] However, because neither study assessed a thromboprophylaxis regimen, there is a clear gap in knowledge in this area that requires further investigation.

A post hoc analysis of patients receiving warfarin in home versus nonhome INR monitoring demonstrated reduced QoL in the nonhome INR group compared with the home INR group. The difference in score is also above the minimal clinically important difference of the PedsQL tool as described by Varni and colleagues.[16] A difference in score above the minimal clinically important difference is an indication that a change in a patient's management is beneficial in the absence of unacceptable side effects or excessive costs.[32] These results are in line with a study by Jones and colleagues,[33] who found an improvement in parent's perceived QoL of their children when they began home INR monitoring after a period of nonhome INR monitoring. We hypothesize that the increase in perceived QoL in the home INR group may be due to an increase in the patient's sense of control over his/her health. Furthermore, because home INR monitoring is conducted under the guidance of a comprehensive anticoagulation clinic, the clinical support received from the clinic staff may also improve QoL perception.

Study Limitations

Our study had a number of limitations mainly due to the cross-sectional design of the study and the challenges of recruiting participants to a time-intensive study. As mentioned previously, we could not demonstrate any differences in the brain MRI of these patients after more than 5 years of consecutive treatment. However, given the relatively small number of participants per treatment group, it is possible that our study was underpowered to detect subtle differences.

The participation rate for our study varied from 17% to 25% for the various study arms. This participation rate was in the expected range based on our experience with Fontan cohorts. Factors that may have affected the participation rate included the requirement for participants to travel to the study sites, the length of time required for MRI/DXA investigations, and the potential for unease when undergoing tests (lying still for long periods, confinement of MRI). Despite the fallout of potential participants, our study cohort appears to be representative of the ANZ Fontan Registry participants who were eligible for our study (Tables 3-5).

Furthermore, because of the differences in participation requirements such as in-person versus virtual participation for MRI/DXA assessments compared with the online bleeding/QOL assessments, these study arms

represent sub-cohorts, although with some overlap (12% of online participants also underwent MRI/DXA). Although individual participation varied between the study arms, this does not change the overall findings of our study; however, these differences should be considered when determining the clinical implications of our findings.

An important limitation in comparing warfarin with aspirin outcomes is the geographical distribution of patients receiving each treatment; 91% of the warfarin group came from region 1 or 2, and 71% of the aspirin group came from region 3. The possibility that differences in other aspects of care (surgical, supportive) requires further examination. Furthermore, in patients receiving warfarin who are from regions with a known preference for aspirin, it is not known if warfarin selection was based on the presence of perceived additional thrombosis risk such as reduced cardiac or lung function. Further investigation focusing on the impact of these factors on thrombosis risk is warranted.

CONCLUSIONS

Our study found that cerebrovascular injury is a frequent occurrence in the ANZ Fontan population regardless of thromboprophylaxis type. Furthermore, we report lower BMD and higher bleeding rates associated with warfarin therapy.

Given the high rates of clinically asymptomatic stroke and ubiquitous findings of microhemorrhages and white matter injury, a study with serial MRI may be useful to determine when these changes occur and what factors are associated with their occurrence. Early detection of cerebrovascular injury may assist with the identification of children at higher risk of neurodevelopmental problems and allow early implementation of interventions to reduce the long-term burden of disease. The timing of MRI may be appropriate in the postoperative period, when risk of thromboembolic events and cerebral injury is known to be high.

Given that low BMD is clinically important and potentially treatable, an emphasis should be placed on bone health. The importance of vitamin D sufficiency, adequate calcium intake, and appropriate weight-bearing exercise should be communicated to patients. Furthermore, when long-term warfarin therapy has occurred, BMD screening is recommended.

Our results suggest that aspirin should be offered as primary long-term thromboprophylaxis after Fontan surgery; however, consideration must be given to important clinical features such as cardiac function and lung function, neither of which was investigated in this study. Where warfarin use is determined to be appropriate, a comprehensive home INR monitoring service should be offered when possible. A shift from warfarin to aspirin therapy post-Fontan would have a cost benefit to the patient and the healthcare system.[34]

Conflict of Interest Statement

Y.d'U. receives consultant fees from Actelion and Merck Sharp & Dohme Corp. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

The authors thank the ANZ Fontan Registry team and Karin Du Plessis and Charlotte Verrall for assistance with participant recruitment.

References

1. Rosenthal DN, Friedman AH, Kleinman CS, Kopf GS, Rosenfeld LE, Hellenbrand WE. Thromboembolic complications after Fontan operations. *Circulation*. 1995;92(9 Suppl):II287-93.
2. Jahangiri M, Ross DB, Redington AN, Lincoln C, Shinebourne EA. Thromboembolism after the Fontan procedure and its modifications. *Ann Thorac Surg*. 1994;58:1409-13.
3. Shirai LK, Rosenthal DN, Reitz BA, Robbins RC, Dubin AM. Arrhythmias and thromboembolic complications after the extracardiac Fontan operation. *J Thorac Cardiovasc Surg*. 1998;115:499-505.
4. Kaulitz R, Luhmer I, Bergmann F, Rodeck B, Hausdorf G. Sequelae after modified Fontan operation: postoperative haemodynamic data and organ function. *Heart*. 1997;78:154-9.
5. Day RW, Boyer RS, Tait VF, Ruttenberg HD. Factors associated with stroke following the Fontan procedure. *Pediatr Cardiol*. 1995;16:270-5.
6. du Plessis AJ, Chang AC, Wessel DL, Lock JE, Wernovsky G, Newburger JW, et al. Cerebrovascular accidents following the Fontan operation. *Pediatr Neurol*. 1995;12:230-6.
7. Mathews K, Bale JF Jr, Clark EB, Marvin WJ Jr, Doty DB. Cerebral infarction complicating Fontan surgery for cyanotic congenital heart disease. *Pediatr Cardiol*. 1986;7:161-6.
8. Giglia TM, Massicotte MP, Tweddell JS, Barst RJ, Bauman M, Erickson CC, et al. Prevention and treatment of thrombosis in pediatric and congenital heart disease. *Circulation*. 2013;128:2622-703.
9. Tomkiewicz-Pajak L, Hoffman P, Trojnarska O, Lipczynska M, Podolec P, Undas A. Abnormalities in blood coagulation, fibrinolysis, and platelet activation in adult patients after the Fontan procedure. *J Thorac Cardiovasc Surg*. 2014;147:1284-90.
10. Iyengar AJ, Winlaw DS, Galati JC, Gentles TL, Weintraub RG, Justo RN, et al. The Australia and New Zealand Fontan registry: description and initial results from the first population-based Fontan registry. *Intern Med J*. 2014;44:148-55.
11. Beca J, Gunn JK, Coleman L, Hope A, Reed PW, Hunt RW, et al. New white matter brain injury after infant heart surgery is associated with diagnostic group and the use of circulatory arrest. *Circulation*. 2013;127:971-9.
12. Flegal K, Cole T. Construction of LMS parameters for the centers for disease control and prevention 2000 growth charts. *Natl Health Stat Report*. 2013;63:1-3.
13. Rasmussen AR, Wohlfahrt-Veje C, Tefre de Renzy-Martin K, Hagen CP, Tinggaard J, Mouritsen A, et al. Validity of self-assessment of pubertal maturation. *Pediatrics*. 2015;135:86-93.
14. Clover E, Miller M, Bannerman E, Magarey A. Relative validation of a short food frequency questionnaire to assess calcium intake in older adults. *Aust N Z J Public Health*. 2007;31:450-8.
15. Attard C, Huang J, Newall F, Monagle P, d'Udekem Y, Ignjatovic V. Development and validation of the warfarin-aspirin bleeding assessment tool (WABAT) in children. *J Pediatr Hematol Oncol*. 2020;42:e513-4.
16. Varni JW, Burwinkle TM, Seid M. The PedsQL™ as a pediatric patient-reported outcome: reliability and validity of the PedsQL™ Measurement Model in 25,000 children. *Expert Rev Pharmacoecon Outcomes Res*. 2005;5:705-19.
17. Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax*. 1971;26:240-8.
18. Schilling C, Dalziel K, Nunn R, Du Plessis K, Shi WY, Celermajer D, et al. The Fontan epidemic: population projections from the Australia and New Zealand Fontan registry. *Int J Cardiol*. 2016;219:14-9.

19. Rychik J, Atz AM, Celermajer DS, Deal BJ, Gatzoulis MA, Gewillig MH, et al. Evaluation and management of the child and adult with Fontan circulation: a scientific statement from the American Heart Association. *Circulation*. 2019;140:e234-84.
20. Iyengar AJ, Winlaw DS, Galati JC, Wheaton GR, Gentles TL, Grigg LE, et al. No difference between aspirin and warfarin after extracardiac Fontan in a propensity score analysis of 475 patients. *Eur J Cardiothorac Surg*. 2016;50:980-7.
21. Monagle P, Cochrane A, Roberts R, Manlhiot C, Weintraub R, Szechtman B, et al. A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children. *J Am Coll Cardiol*. 2011;58:645-51.
22. McCrindle BW, Manlhiot C, Cochrane A, Roberts R, Hughes M, Szechtman B, et al. Factors associated with thrombotic complications after the Fontan procedure: a secondary analysis of a multicenter, randomized trial of primary thromboprophylaxis for 2 years after the Fontan procedure. *J Am Coll Cardiol*. 2013;61:346-53.
23. Cordina R, Grieve S, Barnett M, Lagopoulos J, Malitz N, Celermajer DS. Brain volumetric, regional cortical thickness and radiographic findings in adults with cyanotic congenital heart disease. *Neuroimage Clin*. 2014;4:319-25.
24. Bendaly EA, DiMeglio LA, Fadel WF, Hurwitz RA. Bone density in children with single ventricle physiology. *Pediatr Cardiol*. 2015;36:779-85.
25. D'Ambrosio P, Tran D, Verrall CE, Attard C, Singh MF, Ayer J, et al. Prevalence and risk factors for low bone density in adults with a Fontan circulation. *Congenit Heart Dis*. 2019;14:987-95.
26. Barnes C, Newall F, Ignjatovic V, Wong P, Cameron F, Jones G, et al. Reduced bone density in children on long-term warfarin. *Pediatr Res*. 2005;57:578-81.
27. Lyons RA, Delahunty AM, Kraus D, Heaven M, McCabe M, Allen H, et al. Children's fractures: a population based study. *Inj Prev*. 1999;5:129-32.
28. Flynn J, Foley S, Jones G. Can BMD assessed by DXA at age 8 predict fracture risk in boys and girls during puberty?: an eight-year prospective study. *J Bone Miner Res*. 2007;22:1463-7.
29. Jones S, Newall F, Manias E, Monagle P. Assessing outcome measures of oral anticoagulation management in children. *Thromb Res*. 2011;127:75-80.
30. Uzark K, Zak V, Shrader P, McCrindle BW, Radojewski E, Varni JW, et al. Assessment of quality of life in young patients with single ventricle after the Fontan operation. *J Pediatr*. 2016;170:166-72.e1.
31. Uzark K, Jones K, Slusher J, Limbers CA, Burwinkle TM, Varni JW. Quality of life in children with heart disease as perceived by children and parents. *Pediatrics*. 2008;121:e1060-7.
32. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials*. 1989;10:407-15.
33. Jones S, Monagle P, Manias E, Bruce AA, Newall F. Quality of life assessment in children commencing home INR self-testing. *Thromb Res*. 2013;132:37-43.
34. Schilling C, Dalziel K, Iyengar AJ, d'Udekem Y. The cost differential between warfarin versus aspirin treatment after a Fontan procedure. *Heart Lung Circ*. 2017;26:e44-7.

Key Words: aspirin, bone density, Fontan, single ventricle, stroke, warfarin

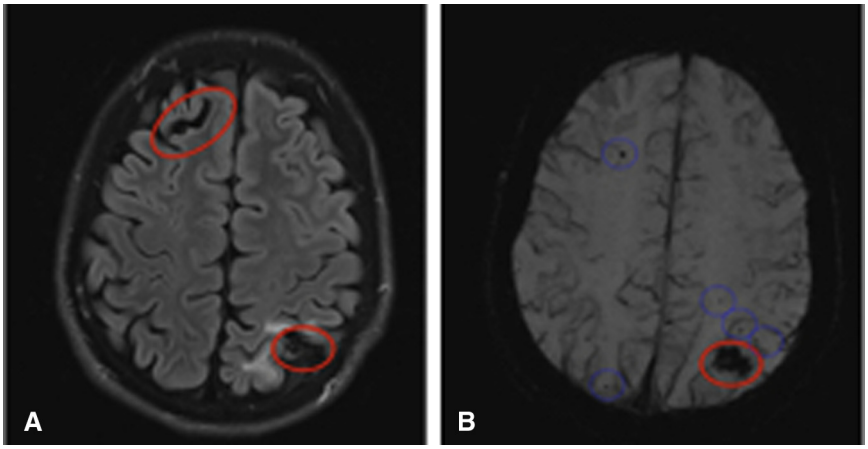

FIGURE E1. Spectrum of brain injury post-Fontan: example of the extent and spectrum of brain injury as observed in 1 participant who had undergone Fontan surgery. A, Axial fluid-attenuated inversion recovery sequence: frontal infarct; parietal cortical and subcortical infarct. B, Susceptibility-weighted imaging sequence: hemorrhagic transformation; microhemorrhages.

TABLE E1. Thromboprophylaxis and fenestration by Fontan surgery location for magnetic resonance imaging and bone mineral density participants

	Region 1	Region 2	Region 3	Region 4	Total	*P* value
Thromboprophylaxis						<.0001
Warfarin (%)	47 (90)	14 (64)	7 (17)	2 (40)	70	
Aspirin (%)	5 (10)	8 (36)	35 (83)	3 (60)	51	
Fenestration						<.0001
No (%)	28 (54)	13 (59)	39 (93)	2 (40)	82	
Yes (%)	24 (46)	9 (41)	3 (7)	3 (60)	36	

TABLE E2. Extracranial thrombosis by thromboprophylaxis type for magnetic resonance imaging and bone mineral density participants

	Total (n = 121)	Warfarin (n = 67w)	Aspirin (n = 54)	*P* value*	OR (95% CI)
Pulmonary embolism (%)	2 (2)	1 (2)	1 (2)	.872	0.79 (0.05-13.0)
Cardiac thrombosis	4 (3)	3 (5)	1 (2)	.422	2.46 (0.25-24.3)

OR, Odds ratio; *CI*, confidence interval. *Chi-square *P* value of difference.

TABLE E3. Warfarin and Aspirin Bleeding assessment tool measures by thromboprophylaxis type

Question	Warfarin (n = 66)	Aspirin (n = 34)	*P* value
Stopped using anticoagulant for a period within the last 5 y	37 (56.1%)	7 (20.6%)	.001
Stopped anticoagulant as a result of bleeding	2 (3.0%)	1 (2.9%)	.980
Stopped anticoagulant due to procedure	32 (48.5%)	3 (8.8%)	<.0001
Stopped anticoagulant due to other reasons	5 (7.6%)	3 (8.8%)	.828
Changed anticoagulation due to doctor's recommendation	8 (12.1%)	3 (8.8%)	.618
Changed anticoagulation due to bleeding	1 (1.5%)	0 (0%)	.471
Changed anticoagulation due to blood clot	3 (4.6%)	0 (0%)	.207
Experienced nosebleeds	31 (47.0%)	8 (23.5%)	.023
Experienced bruising at time of questionnaire completion	38 (57.6%)	22 (64.7%)	.491
Experienced bleeding from minor wounds	49 (74.2%)	23 (67.7%)	.487
Experienced bleeding after blood tests	(n = 33) 32 (48.5%) 18 (54.6%)		.570
Experienced bleeding in mouth	22 (33.3%)	8 (23.5%)	.311
Experienced bleeding after tooth removal	(n = 31) 18 (58.1%)	(n = 13) 9 (69.2%)	.488
Experienced gastrointestinal bleeding	7 (10.6%)	1 (2.94%)	.181
Female-specific questions			
Taking combined oral contraceptive pill	(n = 40) 18 (45%)	(n = 23) 3 (13.0%)	.010
Experience flooding (blood running around pad or tampon)	(n = 32) 18 (56.3%)	(n = 20) 13 (65%)	.532
Experience clots (visible on pad or tampon)	(n = 32) 23 (71.8%)	(n = 20) 17 (85%)	.274
Diagnosed with iron-deficiency anemia	(n = 32) 9 (28.1%)	(n = 20) 5 (25.5%)	.805
Experienced pregnancy	(n = 40) 6 (15%)	(n = 23) 4 (17.4%)	.803