European Journal of Cardio-Thoracic Surgery Advance Access published May 26, 2016

European Journal of Cardio-Thoracic Surgery (2016) 1–8
doi:10.1093/ejcts/ezw159

ORIGINAL ARTICLE

Cite this article as: 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; doi:10.1093/ejcts/ezw159.

CONGENITAL

No difference between aspirin and warfarin after extracardiac Fontan in a propensity score analysis of 475 patients

Ajay J. Iyengar[a,b,c], David S. Winlaw[d,e], John C. Galati[b,f], Gavin R. Wheaton[g], Thomas L. Gentles[h], Leeanne E. Grigg[i], Robert N. Justo[j], Dorothy J. Radford[k], Chantal Attard[l], Robert G. Weintraub[b,c,m], Andrew Bullock[n], Gary S. Sholler[d,e], David S. Celermajer[e,o] and Yves d'Udekem[a,b,c,*] on behalf of the Australia and New Zealand Fontan Registry

[a] Department of Cardiac Surgery, Royal Children's Hospital, Melbourne, Australia
[b] Murdoch Childrens Research Institute, Melbourne, Australia
[c] Department of Paediatrics, Faculty of Medicine, The University of Melbourne, Melbourne, Australia
[d] Heart Centre for Children, The Children's Hospital at Westmead, Sydney, Australia
[e] The University of Sydney, Sydney, Australia
[f] Department of Mathematics and Statistics, La Trobe University, Melbourne, Australia
[g] Department of Cardiology, Women's and Children's Hospital, Adelaide, Australia
[h] Green Lane Paediatric and Congenital Cardiac Service, Starship Children's Hospital, Auckland, New Zealand
[i] Department of Cardiology, The Royal Melbourne Hospital, Melbourne, Australia
[j] Paediatric Cardiology, Queensland Paediatric Cardiac Service, Lady Cilento Children's Hospital, Brisbane, Australia
[k] Adult Congenital Heart Unit, The Prince Charles Hospital, Brisbane, Australia
[l] Department of Haematology, Royal Children's Hospital, Melbourne, Australia
[m] Department of Cardiology, Royal Children's Hospital, Melbourne, Australia
[n] Children's Cardiac Centre, Princess Margaret Hospital for Children, Perth, Australia
[o] Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia

* Corresponding author. Department of Cardiac Surgery, Royal Children's Hospital, Flemington Rd, Parkville, VIC 3052, Australia. Tel: +61-3-93455200; fax: +61-3-93456001; e-mail: yves.dudekem@rch.org.au (Y. d'Udekem).

Received 4 November 2015; received in revised form 23 March 2016; accepted 9 April 2016

Abstract

OBJECTIVES: The most effective method of long-term thromboprophylaxis after the Fontan procedure is not clear. We compared the rates of thromboembolic events between patients receiving aspirin and warfarin after an extracardiac conduit Fontan procedure in a bi-national registry.

METHODS: All patients who underwent an extracardiac conduit Fontan procedure from 1997 to 2010 in Australia and New Zealand were identified. Medication status and routine follow-up and echocardiographic data were obtained from all patients. Survival analysis with propensity score matching and adjustment was performed to determine the treatment effect of warfarin compared with that of aspirin beyond the first year of follow-up, after which time patients had settled on their long-term thromboprophylaxis strategy.

RESULTS: Of 570 eligible patients, the data of 475 patients who were regularly followed up without mechanical valve replacement were available for analysis. Long-term thromboprophylaxis consisted of warfarin in 301 patients (63%), aspirin in 157 (33%) and none in 17 (4%). The 10-year rate of freedom from all thromboembolic events was 91% [95% confidence interval (CI) 88–94%]. Thromboembolic events beyond the first year of follow-up occurred in 18 patients (6 on aspirin and 12 on warfarin). After (i) propensity score adjustment and (ii) matching yielding 164 pairs, the hazard rates of thromboembolic events beyond the first year were not statistically different between the warfarin and aspirin groups [(i) hazard ratio (HR) 2.3, 95% CI 0.7–7.4, $P = 0.2$ and (ii) HR 1.5, 95% CI 0.5–4.7, $P = 0.5$, respectively].

CONCLUSIONS: No difference in the hazard rates of late thromboembolic events was observed between aspirin and warfarin beyond the first year after the extracardiac conduit Fontan procedure.

Keywords: Fontan procedure • Thromboprophylaxis • Warfarin • Aspirin • Congenital heart disease

INTRODUCTION

The Fontan circulation is an ideal environment for thrombosis. While some form of thromboprophylaxis is deemed necessary to prevent the occurrence of thromboembolic events [1], no consensus yet exists on the optimal medication. The evidence to support either aspirin or warfarin is lacking [2].

The Australia and New Zealand Fontan Registry was created with the aim of using retrospective follow-up data from multiple centres to create a dataset that could answer research questions

based on varying treatment practices in the region [3]. In Australia and New Zealand, since 1997, all centres have adopted the extracardiac conduit as the exclusive mode of Fontan completion. While creating the registry, we registered the variation in thromboprophylaxis practice between centres. We hypothesized that, after propensity score matching in this contemporary cohort of patients operated with a standard technique, no difference would be observed between patients treated with warfarin and aspirin.

METHODS

The design and administration of the Australia and New Zealand Fontan Registry have been previously described [3]. Since 1997, the extracardiac conduit became the predominant technique of Fontan procedure performed in both countries, and from 2006 has been the sole Fontan technique used. The analysis of early and late outcomes of the whole cohort of 570 extracardiac Fontan patients has recently been published [4]. From this dataset, a total of 30 patients were excluded who died prior to discharge (7 patients), were referred from outside Australia or New Zealand (17) or had mechanical prosthetic valves (6). We attempted to obtain the discharge summary, yearly clinical summary and echocardiogram or magnetic resonance imaging report for the remaining eligible local patients. All transthoracic echocardiograms were acquired by cardiologists with post-fellowship training in paediatric or grown-up congenital cardiology, or by sonographers with dedicated training in congenital imaging. These images were then reviewed and reported by the treating cardiologist. The frequency of imaging was generally yearly, but was determined by the treating cardiologists according to institutional preference and clinical need. Anticoagulation status and occurrence of thromboembolism were determined from the clinical summary and imaging reports. Patients who were transplanted or died during the first year after their Fontan (3 patients), those who were lost to follow-up for any period of more than 5 years (51) and those with <1 year of follow-up available (12) were excluded from the analysis, leaving a cohort of 475 patients (88%) with sufficient complete follow-up.

Pre- and perioperative variables were obtained from the registry database. The study conformed to the 'STROBE STATEMENT: Guidelines for reporting observational studies' [1, 5] and to the standards set by the Declaration of Helsinki. Ethical review board approvals were granted from each participating institution.

Thromboprophylaxis status

Thromboprophylaxis regime varied according to institutional preference. Institutions with a preference for long-term anticoagulation with aspirin routinely administered warfarin for 3–6 months before transitioning to low-dose aspirin (5 mg/kg/day, equating in practice to doses between 50 and 150 mg). For this reason, we limited the analysis to the risk of thromboembolic events beyond the first year, once all patients had settled on their long-term thromboprophylaxis strategy.

Of 475 patients included in the study, 410 (86%) were initially anticoagulated with warfarin. Those who were destined to receive lifelong low-dose aspirin (157 patients, 33%) were transitioned during the first year of follow-up. Patients were determined to be in a treatment group (aspirin or warfarin) based on the medication they had settled on at their 1-year post-Fontan follow-up visit. Participants who crossed from one anticoagulant treatment to another beyond the first year had their follow-up terminated for the analysis at the time of crossover (20 patients). Those who were on aspirin plus warfarin (1 patient) were assigned to the warfarin group.

End-points

The primary end-point was time to first thromboembolic event, which was defined as any thrombus evident on imaging (including thrombus within the Fontan circuit, deep venous thrombosis and pulmonary embolism) or any clinical event associated with thrombotic embolism [stroke, transient ischaemic attack (TIA), pulmonary embolism and end-organ infarction]. Stroke and TIA were defined as neurological deficit lasting ≥72 and <72 h, respectively. All pulmonary embolic events were confirmed by echocardiography, computed tomography or ventilation–perfusion scan.

Bleeding was defined as Bleeding Academic Research Consortium (BARC) Types 2 (overt haemorrhage that is actionable) to 5 (fatal bleeding) [2, 6]. Minor bleeding events (BARC Types 0 and 1) were excluded.

The timing of events was divided into: (i) pre-Fontan, (ii) early postoperative occurring prior to hospital discharge, (iii) during the first year after Fontan and (iv) events beyond the first year.

A composite end-point of time to first bleeding or thromboembolic event is also reported.

Statistical analysis

All analyses were performed in Stata 13 (StataCorp LP, College Station, TX, USA). Analysis of the association between anticoagulant regimen and time to first thromboembolic event was performed using Cox proportional hazards regression. Kaplan–Meier survival curves were generated for each end-point. Smoothed hazard functions were generated using a Gaussian kernel density estimate and visual adjustment of the Silverman kernel width to mitigate over-smoothing. No patient suffered recurrent thromboembolic events, so repeated events analysis was not performed.

To counteract potential bias caused by marked baseline heterogeneity in measured variables between the aspirin and warfarin groups (Table 1), a propensity score was calculated. Clinically relevant factors were selected *a priori*, and additional factors were included if univariable logistic regression demonstrated an association with treatment assignment [odds ratio (OR) >2.5 or <0.4 or a *P*-value <0.10]. The model was considered saturated if the area under the receiver operating characteristic (ROC) curve was greater than 0.8. The final model included the factors summarized in Supplementary Material. The final model did not include the centre as a random effect, as the residual bias was too large. Pre-Fontan saturation was also excluded from the propensity model due to missing data in 20 patients on aspirin. Propensity scores were (i) included in a multivariable model to counteract the effect of heterogeneity between groups and (ii) used to match patients who had close propensity scores [3, 7, 8]. We thus constructed two survival models for each end-point: (i) including the propensity score as a covariate for all individuals and (ii) restricting the analysis to propensity score-matched pairs. Matched pairs were created by performing 1 : 1 nearest-neighbour matching, and a clustered sandwich estimator of variance was used in the survival model to calculate confidence intervals. Residual bias for

Table 1: Patient characteristics according to the thromboprophylaxis group

	None (17 patients)	Aspirin (157 patients)	Warfarin (301 patients)
Male, *n* (%)	9 (53%)	85 (54%)	184 (61%)
Dextrocardia, *n* (%)	0 (0%)	17 (11%)	19 (6%)
Isomerism, *n* (%)	0 (0%)	13 (8%)	21 (7%)
Hypoplastic left heart syndrome, *n* (%)	3 (18%)	6 (4%)	62 (21%)
Ventricular morphology, *n* (%)			
Left	10 (59%)	90 (57%)	156 (52%)
Right	6 (35%)	53 (34%)	114 (38%)
Biventricular/indeterminate	1 (6%)	14 (9%)	31 (10%)
Pre-Fontan procedures			
Number of prior palliations, mean (SD)	2.2 (0.7)	2.2 (0.8)	2.5 (1.1)
Prior pulmonary artery banding, *n* (%)	5 (29%)	48 (31%)	67 (22%)
Pre-Fontan haemodynamics			
Oxygen saturation (%), mean (SD)[a]	75 (20)	84 (6)	81 (6)
Pulmonary artery pressure (mmHg), mean (SD)[b]	11.5 (2.4)	10.8 (2.7)	11.1 (2.6)
Aortopulmonary or veno-venous collaterals, *n* (%)	2 (12%)	19 (12%)	103 (34%)
Arterio-venous malformations, *n* (%)	1 (6%)	4 (3%)	24 (8%)
Fontan operative characteristics			
Concomitant procedure, *n* (%)	3 (18%)	15 (10%)	41 (14%)
Fenestration, *n* (%)	5 (29%)	17 (11%)	168 (56%)
Age at Fontan, median (IQR)	5.7 (5.1–7.0)	4.8 (3.9–5.8)	4.7 (3.8–5.8)
Associated interventions before or at time of Fontan			
Atrioventricular valve repair, *n* (%)	1 (6%)	5 (3%)	22 (7%)
Aortic arch intervention, *n* (%)	6 (35%)	40 (25%)	119 (40%)

SD: standard deviation; IQR: interquartile range.
[a]Missing in 28 patients.
[b]Missing in 56 patients.

a covariate in the propensity model was considered a greater than 5% standardized percentage bias in the matched cohort, which is defined as the percentage difference of the sample means in the treated and non-treated subsamples as a percentage of the square root of the average of their sample variances [3, 9]. The overall bias of the model was assessed by determining the median standardized bias. This was calculated by deriving the standardized biases for each covariate in the propensity model, and finding the median value. A model was considered to have an acceptable level of overall bias if the median bias after matching was <5%.

The end-points analysed were (i) time to first thromboembolic event and (ii) a composite of time to first bleeding or thromboembolic event. Time was measured starting from Fontan completion with entry to the survival model at the first-year follow-up visit.

Post hoc sensitivity analysis was performed using the '*stpower*' command in Stata 13, to calculate the minimum effect size or hazard ratio that could be detected based on the number of matched pairs obtained and the number of events actually observed.

RESULTS

The whole cohort consisted of 570 patients with an extracardiac conduit. After excluding the 7 early deaths, 17 patients referred from overseas and 6 patients with mechanical valve prostheses, there were 540 patients remaining. Follow-up that was complete was available in 475 patients (88%), comprising follow-up of 3479 patient-years and a median duration of 7 years (interquartile range 4.7–9.7).

The characteristics of the whole cohort of 475 patients with complete follow-up are presented in Tables 1 and 2 and characteristics included in the propensity score model of the matched cohort are presented in Table 3.

Thromboprophylaxis regimen

At the time of discharge from hospital, 410 patients (86%) were receiving warfarin, 52 (1%) aspirin, 3 (1%) both aspirin and warfarin, and 10 (2%) no thromboprophylaxis. By the time of the clinic visit beyond 1 year after the Fontan procedure, patients had settled on their long-term thromboprophylaxis strategy, which consisted of warfarin in 300 patients (63%), aspirin in 157 (33%) and aspirin with warfarin in 1 patient. The remaining 17 patients (4%) received no thromboprophylaxis during the period of follow-up analysed.

There were 20 patients (4%) who crossed between groups after the first year of follow-up. Seven patients who were on aspirin switched to warfarin: 5 patients after a developing a thromboembolic event, 1 an arrhythmia and 1 protein-losing enteropathy. Eight patients ceased warfarin therapy, due to patient preference in 5 patients, medical comorbidity in 1, bleeding in 1 and poor compliance in 1. One patient who suffered a thromboembolic event switched from warfarin alone to warfarin plus aspirin. One who was on warfarin plus aspirin transitioned to aspirin alone after an episode of haemoptysis. One who was not on any therapy commenced on aspirin after occurrence of atrial arrhythmia. The final patient was non-compliant with aspirin, and it was thus ceased.

In the overall cohort, treatment assignment analysis by univariable logistic regression revealed that the following factors were associated with long-term warfarin anticoagulation: fenestration

Table 2: Patient characteristics according to thromboembolic events

	None (444 patients)	During first year (16 patients)	Beyond first year (18 patients)
Male, *n* (%)	262 (59%)	13 (81%)	7 (39%)
Dextrocardia, *n* (%)	38 (9%)	0 (0%)	0 (0%)
Isomerism, *n* (%)	32 (7%)	1 (6%)	1 (6%)
Hypoplastic left heart syndrome, *n* (%)	63 (14%)	4 (25%)	3 (17%)
Ventricular morphology, *n* (%)			
Left	245 (55%)	6 (38%)	10 (56%)
Right	159 (35%)	6 (58%)	6 (33%)
Biventricular/indeterminate	40 (9%)	4 (25%)	2 (11%)
Pre-Fontan procedures			
Number of prior palliations, mean (SD)	2.4 (1.0)	2.3 (0.7)	2.3 (1.1)
Prior pulmonary artery banding, *n* (%)	112 (25%)	3 (19%)	7 (39%)
Pre-Fontan haemodynamics			
Oxygen saturation (%), mean (SD)[a]	82 (7)	81 (6)	80 (4)
Pulmonary artery pressure (mmHg), mean (SD)[b]	11.0 (2.6)	11.2 (2.1)	11.5 (2.6)
Aortopulmonary or veno-venous collaterals, *n* (%)	116 (26%)	4 (25%)	2 (11%)
Arterio-venous malformations, *n* (%)	27 (6%)	1 (6%)	0 (0%)
Fontan operative characteristics			
Concomitant procedure, *n* (%)	58 (13%)	2 (13%)	1 (6%)
Fenestration, *n* (%)	172 (39%)	8 (50%)	5 (28%)
Age at Fontan, median (IQR)	4.8 (3.9–5.8)	4.4 (3.5–5.6)	5.2 (4.4–6.2)
Associated interventions before or at time of Fontan			
Atrioventricular valve repair, *n* (%)	28 (6%)	0 (0%)	1 (6%)
Aortic arch intervention, *n* (%)	153 (35%)	4 (25%)	8 (44%)
Pre-Fontan thromboembolic event, *n* (%)	6 (1%)	2 (13%)	0 (0%)
Warfarin at time of event, *n* (%)	272 (61%)	14 (88%)	12 (67%)

SD: standard deviation; IQR: interquartile range.
[a]Missing in 28 patients.
[b]Missing in 56 patients.

Table 3: Characteristics of patients in the propensity score-matched cohort according to the thromboprophylaxis group

	Aspirin (164 patients)	Warfarin (164 patients)	Residual bias (%)	*t*-Test *P*-value
Male, *n* (%)	91 (55%)	93 (57%)	3	
Dextrocardia, *n* (%)	19 (12%)	15 (9%)	9	
Systemic right ventricle, *n* (%)	55 (34%)	40 (24%)	19	
Hypoplastic left heart syndrome, *n* (%)	6 (4%)	4 (2%)	4	
Common atrioventricular valve, *n* (%)	22 (13%)	20 (12%)	4	
Isomerism, *n* (%)	14 (9%)	15 (9%)	2	
Pre-Fontan procedures, mean (SD)	2.2 (0.8)	2.3 (0.9)	4	
Prior pulmonary artery banding, *n* (%)	52 (32%)	42 (26%)	14	
Pre-Fontan haemodynamics				
Aortopulmonary or veno-venous collaterals, *n* (%)	20 (12%)	47 (29%)	23	<0.001
Arterio-venous malformations, *n* (%)	4 (2%)	11 (7%)	24	
Fontan operative characteristics				
Fenestration, *n* (%)	17 (11%)	41 (25%)	35	<0.001
Age at Fontan, median (IQR)	4.9 (3.9–5.9)	4.7 (4.0–5.7)	3	
Associated interventions before or at time of Fontan				
Atrioventricular valve repair, *n* (%)	8 (5%)	8 (5%)	0	
Aortic arch intervention, *n* (%)	41 (25%)	38 (23%)	4	
Thromboembolic risk factors				
Pre-Fontan thromboembolism	4 (3%)	2 (1%)	9	
Early postoperative thromboembolism	1 (1%)	1 (1%)	0	
Events during the first year of follow-up	2 (1%)	3 (2%)	4	

SD: standard deviation; IQR: interquartile range.
Only *P*-values for factors with residual bias have been presented.

[OR 10.4, 95% confidence interval (CI) 6.0–18], lower pre-Fontan saturation (OR 0.90 for every 1% increase, 95% CI 0.86–0.93), hypoplastic left heart syndrome (HLHS) (OR 6.5, 95% CI 2.6–16), pre-Fontan collaterals (OR 2.9, 95% CI 1.7–5.1), prior or concomitant aortic arch intervention (OR 1.9, 95% CI 1.3–3.0), number of prior procedures (OR 1.3 for each additional procedure, 95% CI 1.1–1.6) and absence of a prior pulmonary artery band (OR 0.7, 95% CI 0.4–1.0). Additionally, there were trends towards associations for pre-Fontan arterio-venous malformations (OR 2.6, 95% CI 0.9–7.5), absence of dextrocardia (OR 0.6, 95% CI 0.3–1.1), prior or concomitant valve repair (OR 2.0, 95% CI 0.9–4.5), early postoperative thromboembolic event (OR 4.3, 95% CI 0.5–34) and thromboembolic event during the first year of follow-up (OR 3.8, 95% CI 0.8–17).

Thromboembolic events

Thromboembolic events were noted prior to Fontan completion in 8 patients (1.5%), in the early postoperative period in 9 (1.7%), during the first year in 7 (1.3%) and during late follow-up after the first postoperative year in 18 (3.5%). Pre-Fontan events consisted of embolic stroke in 5 patients, pulmonary embolism in 2 and central vein thrombosis in 1. Early postoperative events consisted of embolic stroke in 3 patients, watershed infarcts in 3, conduit thrombosis in 2 and renal embolism in 1. The Fontan circuit was fenestrated in 7 of the 9 patients who suffered early postoperative events, and all 4 early systemic embolic infarcts occurred in patients with a fenestrated Fontan circuit. Events occurring after hospital discharge but during the first year of follow-up consisted of conduit thrombus in 5 patients and symptomatic pulmonary embolism in 2. All conduit thrombi were asymptomatic and were detected on routine screening echocardiography. Six of the 7 patients who experienced events during the first year were on warfarin at the time, and as a result, 2 of these patients received combined anticoagulation and antiplatelet therapy for a period of 3–6 months with eventual thrombus resolution.

Thromboembolic events beyond the first year of follow-up consisted of stroke in 3, TIA in 2, conduit thrombus in 10 and pulmonary embolism in 3. Nine out of 10 conduit thrombi were detected on routine screening echocardiography and caused no symptoms, whereas the remaining patient was being investigated for exertional breathlessness by transoesophageal echocardiography. At the time of their event, 12 patients (67%) were taking warfarin and 6 (33%) were taking aspirin. Out of the 5 patients who suffered a stroke or TIA, the Fontan circuit was fenestrated in 1, whereas in the other 4 it was not fenestrated; 3 were on warfarin and 2 on aspirin at the time of their event. No patient suffered recurrent events.

Of the 18 patients who suffered a thromboembolic event while on warfarin, 8 (44%) had an international normalized ratio (INR) of <2 at the time of or immediately prior to the event. Among patients who had reintervention, there were 19 reoperations and 38 catheter-based interventions. Of the 19 patients who were reoperated, 2 suffered thromboembolic events: one a TIA while on aspirin and the other a conduit thrombosis while on warfarin. No patients who had a catheter-based intervention suffered an event.

Bleeding events

Bleeding that satisfied the study definition of BARC Types 2–5 occurred in 12 patients (3%). These consisted of post-traumatic intracranial haemorrhage in 3, spontaneous intracerebral haemorrhage in 1, major epistaxis in 1, haemoptysis in 1, gastrointestinal bleeding in 3, severe menorrhagia with iron deficiency anaemia in 1, vaginal haemorrhage in 1 and superficial post-traumatic haemorrhage in 1. Eleven of the bleeding events were associated with warfarin (91%), and 4 (36%) occurred while the INR was greater than 3.

Survival analysis

The rate of freedom from all thromboembolic events was 99% (95% CI 98–100%) at 30 days, 97% (96–99%) at 1 year, 94% (91–96%) at 5 years and 91% (88–94%) at 10 and 12 years (Fig. 1). The 12-year rate of freedom from bleeding events was 91% (95% CI 83–95%). The 12-year rate of freedom from thromboembolism or bleeding was 84% (77–90%). The unadjusted rates of thromboembolic events occurring beyond the first year after the Fontan were 0.54 (95% CI 0.24–1.2) per 100 patient-years for aspirin and 0.57 (95% CI 0.32–1.0) for warfarin. The 12-year rates of freedom from the composite end-point for the aspirin and warfarin groups were 93% (95% CI 86–97%) and 79% (95% CI 68–87%),

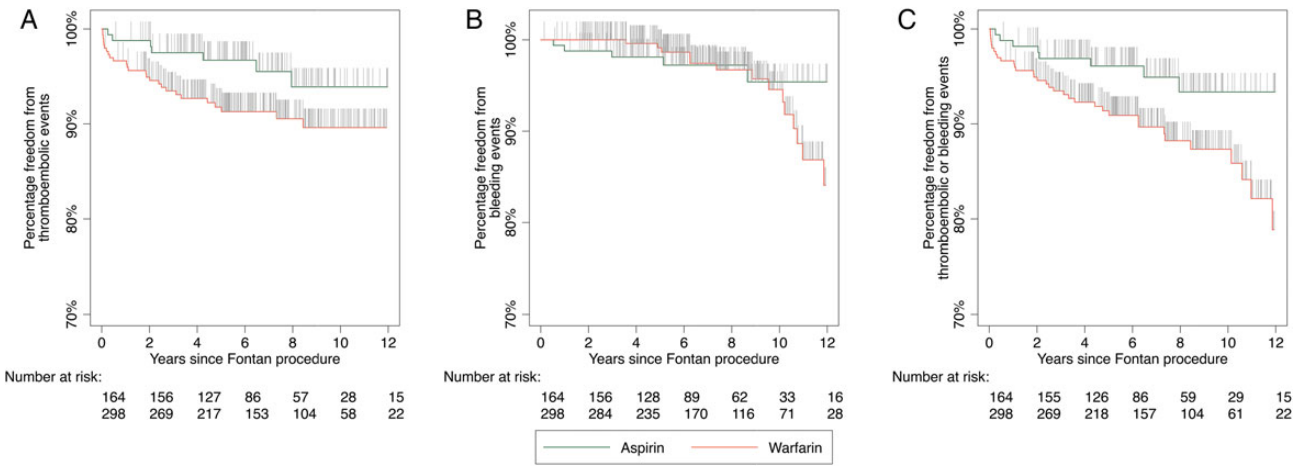

Figure 1: Freedom from (**A**) thromboembolic events, (**B**) bleeding events and (**C**) a composite of both events; aspirin (green) versus warfarin (red).

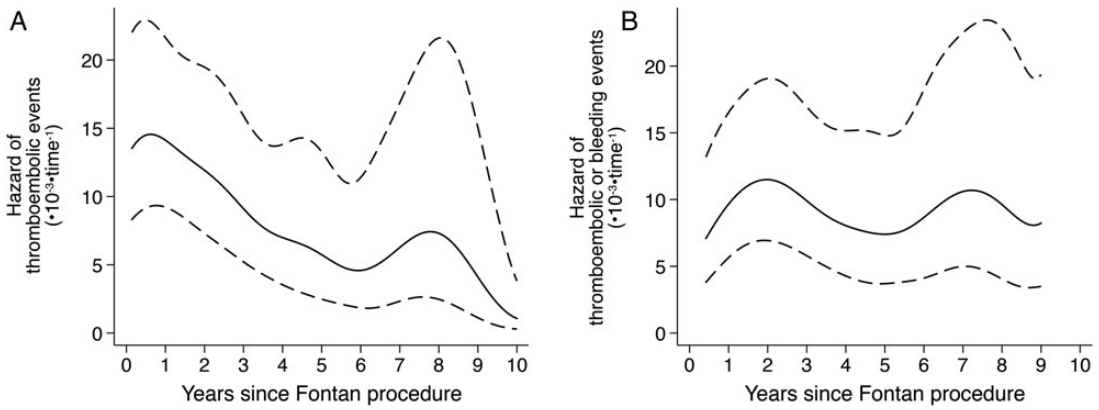

Figure 2: Smoothed hazard function for (**A**) thromboembolic events, demonstrating an early high-risk phase followed by a progressive decline in risk as previously shown by others [1], and (**B**) thromboembolic or bleeding events. Dotted lines represent 95% confidence intervals.

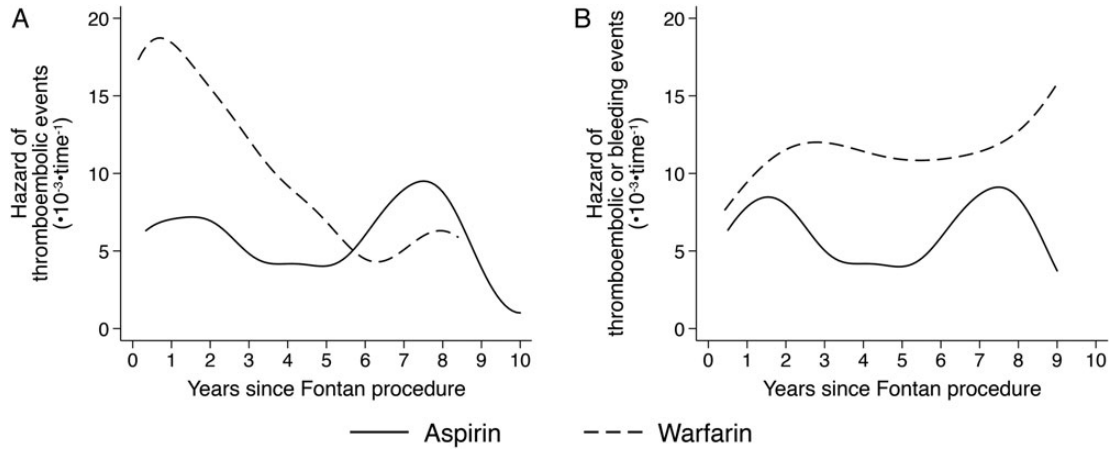

Figure 3: Smoothed hazard functions by the thromboprophylaxis group for (**A**) thromboembolic events and (**B**) thromboembolic or bleeding events.

Table 4: Results of Cox regression analysis with propensity score adjustment and matching

	HR	95% CI	*P*-value
Thromboembolic events occurring beyond Year 1			
Unadjusted (*n* = 451)	1.3	0.5–3.7	0.6
Propensity score adjusted (*n* = 451)	2.3	0.7–7.4	0.2
Propensity-matched cohort (*n* = 328)	1.5	0.5–4.7	0.5
Thromboembolic or bleeding events occurring beyond Year 1			
Unadjusted (*n* = 450)	1.8	0.6–4.8	0.3
Propensity score adjusted (*n* = 450)	2.2	0.7–6.9	0.2
Propensity-matched cohort (*n* = 328)	1.7	0.6–5.2	0.4

Hazard ratios are of the warfarin group compared with the aspirin group.
HR: hazard ratio; CI: confidence interval.

respectively. There was a time-related decline in the overall hazard function for thromboembolic events (Figs 2 and 3).

The results of the propensity score-derived models are presented in Table 4. The model was saturated with an area under the ROC curve of 0.84. The mean propensity scores for patients in the warfarin and aspirin groups were 0.77 (95% CI 0.74–0.79) and 0.44 (95% CI 0.41–0.48, $P < 0.001$), respectively. The median standardized biases before and after matching were 18 and 4%, respectively.

After matching on the propensity score, 164 pairs of patients (328 patients in total) in the warfarin and aspirin groups were identified. The variables included in the propensity score model are presented in Supplementary Material and, after the matching process, there was residual bias between the aspirin and warfarin groups, respectively, in the following characteristics: the proportion of patients with arterio-venous or veno-venous collaterals (12 vs 29%, $P < 0.001$) and the proportion with a fenestrated Fontan (11 vs 25%, $P < 0.001$).

The Cox regression results for the propensity score-based analyses (Table 4) illustrate higher point estimates for the risk of late thromboembolic events in patients treated with warfarin compared with those treated with aspirin [hazard ratio (HR) 2.3, 95% CI 0.7–7.4, $P = 0.2$ after propensity score adjustment, and HR 1.5, 95% CI 0.5–4.7, $P = 0.5$ in the matched cohort]; however, the confidence limits are wide. The results of the analysis of the composite outcome (thromboembolism or bleeding) were similar.

Sensitivity analysis

Post hoc sensitivity analysis was performed to determine the minimum effect size that could be detected with the sample obtained in the propensity-matched cohort. This showed that, with 164 patients in each group and 18 events in total, a minimum hazard ratio of 3.8 could be detected with an 80% power and a significance level of 0.05.

DISCUSSION

The absence of thromboprophylaxis is associated with thromboembolic events after the Fontan procedure [4, 10], and anticoagulation or antiplatelet therapy has been widely recommended [11]. There is no consensus on the optimal method of thromboprophylactic therapy after Fontan surgery. Whether a patient receives aspirin or warfarin remains institutionally based in Australia and New Zealand. The extracardiac technique has been uniformly adopted in this region since 1997 [4]. Because of the standardization of our Fontan technique and the concomitant variation in thromboprophylaxis practice in our region, we had a unique opportunity to review the rates of thromboembolic events in patients with a single contemporary technique with two different thromboprophylaxis approaches. The recruitment of patients to prior randomized controlled trials has proved difficult and could not establish differences in long-term events [12].

The primary outcome in this study was any thromboembolic event occurring beyond the first year of follow-up, and our results suggest that there was no difference between warfarin and aspirin upon the rates of thromboembolic or bleeding events. In fact, point estimates demonstrated a slightly higher risk of thromboembolic events in the warfarin group; however, the study was underpowered to detect a clinically meaningful difference, as only differences above HR 3.8 could be detected. A lack of superiority of warfarin has been previously suggested, but the impact of warfarin on long-term outcomes had remained unclear [2, 13]. The routine administration of warfarin after Fontan surgery should thus be put into question [14]. The burden of warfarin anticoagulation compared with aspirin administration is undeniable. There is a growing concern that the long-term use of warfarin is associated with low bone mineral density and increased fracture risk [15, 16]. It has been previously demonstrated that close to half of the INR measurements of patients on warfarin after Fontan surgery are outside target values [1]. While it is uncertain whether our findings will change clinical practice, they should at the minimum reassure those willing to consider the use of long-term aspirin beyond the first year for the sake of patient convenience, and those interested in initiating randomized trials of these two treatments.

Limitations

This study is limited by its retrospective nature because only events that became clinically relevant were reported and asymptomatic thrombi may not always have been detected. Nevertheless, the rate of thromboembolism in this series is similar to other contemporary epidemiological studies [17]. Individual patients' longitudinal INR measurements were not collected, so the adequacy of anticoagulation in those receiving warfarin could not be assured.

Because the majority of our patients were transitioned during the first year to aspirin from an initial treatment with warfarin, our study does not provide the appropriate design to analyse the difference between anticoagulation regimens in this high-risk period.

Propensity score matching attempts to account for covariates that predict receiving treatment, by selecting matched pairs from each group with similar probabilities of treatment assignment. Treatment with warfarin was associated with a number of unfavourable characteristics (HLHS, pre-Fontan collaterals and fenestration). Thus, the proportion of patients in the matched cohort with these characteristics is much smaller (Tables 1 versus 3) than in the overall cohort. Additionally, residual bias in the proportion of patients with fenestration and pre-Fontan collaterals remained even after propensity score matching. These factors limit the generalizability of the findings in the analysis for patients with certain adverse features such as HLHS, fenestration and pre-Fontan collaterals.

Owing to the small number of thromboembolic events, a propensity score-matched cohort that included the centre could not be analysed and a centre effect cannot be ruled out. Finally, sensitivity analysis showed that only large effect sizes could be detected with the sample size and the number of events observed in this cohort. Smaller differences as have been observed may or may not be due to random variation and remaining selection bias. Further data are required to conclusively rule out smaller differences.

Conclusion

In this bi-national, multicentric, propensity score-matched study of thromboprophylaxis beyond 1 year after the extracardiac Fontan procedure, no differences were found in the rates of thromboembolism between patients taking aspirin and warfarin.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

ACKNOWLEDGEMENTS

The authors thank our research assistants, Karin du Plessis, Janina Chapman, Ingrid King, Charlotte Verrall, Megan Upjohn and Lisa Cowcher, for their invaluable assistance in the creation and maintenance of the Registry and Belinda Bortone for administrative

support. The authors acknowledge the support provided to the Murdoch Childrens Research Institute by the Victorian Government's Operational Infrastructure Support Program.

Funding

Ajay J. Iyengara has received postgraduate awards from the Royal Australasian College of Surgeons (Catherine Marie Enright Kelly and Eric Bishop Scholarships) and the National Health and Medical Research Council (NHMRC) and The National Heart Foundation of Australia (1038802). Yves d'Udekem is a Career Development Fellow of The National Heart Foundation of Australia (CR 10M 5339). This research project was supported by the Victorian Government's Operational Infrastructure Support Program. The Australia and New Zealand Fontan Registry is funded by grants from the NHMRC (project grants 1012241, 1047923 and 1065794) HeartKids and the ANZ Bank Trustees.

Conflict of interest: Yves d'Udekem is a consultant for the companies MSD and Actelion. Yves d'Udekem is an National Health and Medical Research Council (NHMRC) Clinician Practitioner Fellow (1082186).

REFERENCES

[1] 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.

[2] Marrone C, Galasso G, Piccolo R, de Leva F, Paladini R, Piscione F *et al*. Antiplatelet versus anticoagulation therapy after extracardiac conduit Fontan: a systematic review and meta-analysis. Pediatr Cardiol 2011;32:32–9.

[3] 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.

[4] Iyengar AJ, Winlaw DS, Galati JC, Wheaton GR, Gentles TL, Grigg LE *et al*. The extracardiac conduit Fontan procedure in Australia and New Zealand: hypoplastic left heart syndrome predicts worse early and late outcomes. Eur J Cardiothorac Surg 2014;46:465–73.

[5] Elm von E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–9.

[6] Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J *et al*. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–47.

[7] D'Agostino RB. Propensity scores in cardiovascular research. Circulation 2007;115:2340–3.

[8] Blackstone EH. Comparing apples and oranges. J Thorac Cardiovasc Surg 2002;123:8–15.

[9] Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Stat 1985;39:33–8.

[10] Monagle P, Karl TR. Thromboembolic problems after the Fontan operation. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2002;5: 36–47.

[11] Wilson DG, Wisheart JD, Stuart AG. Systemic thromboembolism leading to myocardial infarction and stroke after fenestrated total cavopulmonary connection. Br Heart J 1995;73:483–5.

[12] 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.

[13] Jacobs ML. The Fontan operation, thromboembolism, and anticoagulation: a reappraisal of the single bullet theory. J Thorac Cardiovasc Surg 2005;129:491–5.

[14] Moffett BS, Kim S, Bomgaars LR. Readmissions for warfarin-related bleeding in pediatric patients after hospital discharge. Pediatr Blood Cancer 2013;60:1503–6.

[15] Avgeri M, Papadopoulou A, Platokouki H, Douros K, Rammos S, Nicolaidou P *et al*. Assessment of bone mineral density and markers of bone turnover in children under long-term oral anticoagulant therapy. J Pediatr Hematol Oncol 2008;30:592–7.

[16] 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.

[17] Idorn L, Jensen AS, Juul K, Reimers JI, Johansson PI, Sørensen KE *et al*. Thromboembolic complications in Fontan patients: population-based prevalence and exploration of the etiology. Pediatr Cardiol 2013;34: 262–72.