

Table 2. Characteristics of included studies – Fontan-circulatie

Study	Participants	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Studies with follow-up ≤ 1 year						
Ankola, 2021	<p><u>N at baseline</u></p> <ul style="list-style-type: none"> Aspirin: 103 Warfarin: 52 Enoxaparin: 13 <p><u>Age¹</u> (median (IQR)) 3.3 (2.8-3.9) years</p> <p><u>Sex²</u> 39% female</p>	<ul style="list-style-type: none"> Aspirin Warfarin Enoxaparin 	30 days	<ul style="list-style-type: none"> Thrombotic complications (defined by echocardiographic or ultrasonographic detection of intracardiac thrombi, comprised of thrombi in central veins, Fontan baffle, pulmonary arteries, atria and ventricles; or deep venous thrombi, such as those occurring proximal to the central veins, or the occurrence of embolic stroke) 	<p><u>Funding</u> No external funding</p> <p><u>Conflicts of interest</u> None</p>	Some concerns (for all outcome measures)
McCrinkle, 2021	<p><u>N at baseline</u></p> <ul style="list-style-type: none"> Rivaroxaban: 66 Aspirin: 34 <p><u>Age (mean, SD)</u></p> <ul style="list-style-type: none"> Rivaroxaban: 4.1 (1.7) years Aspirin: 4.2 (1.8) years 	<ul style="list-style-type: none"> Rivaroxaban (10 mg/day) Aspirin (5 mg/day) 	12 months	<ul style="list-style-type: none"> Thrombotic complications (any thrombotic event (venous or arterial), defined as the appearance of a new thrombotic burden within the cardiovascular system noted on either routine surveillance or clinically indicated imaging, or the occurrence of a clinical event known to be strongly associated with thrombus (e.g. stroke or pulmonary embolism))⁴ Haemorrhage (<i>major bleeding events</i>, as defined by the International Society on Thrombosis and Hemostasis, <i>clinically relevant nonmajor bleeding</i>, and <i>trivial (minimal) bleeding events</i>) Ischemic stroke Adverse events 	<p><u>Funding</u> Bayer AG and Janssen Research & Development, LLC</p> <p><u>Conflicts of interest</u> Several, please refer to the disclosures in the article</p>	Some concerns (for all outcome measures)

Study	Participants	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
	<u>Sex</u> <ul style="list-style-type: none"> Rivaroxaban: 45% female Aspirin: 32% female 					
Studies with follow-up > 1 year						
Egbe, 2017	<u>N at baseline</u> ³ 387 <u>Age (mean, SD)</u> ¹ 28 (7) years <u>Sex</u> ² 48% female	<ul style="list-style-type: none"> Warfarin Aspirin 	8 (2) years	<ul style="list-style-type: none"> Thrombotic complications (thrombotic and embolic complications were classified into 2 groups: systemic TEC defined as intracardiac thrombus, ischemic stroke, or systemic arterial embolus, and nonsystemic TEC defined as Fontan conduit/right atrial thrombus or pulmonary embolus. 	<u>Funding</u> None <u>Conflicts of interest</u> None	Some concerns (for all outcome measures)
Kawamatsu, 2021	<u>N at baseline</u> <ul style="list-style-type: none"> DOACs: 36 Antiplatelet: 43 VKA: 41 Combination of an antiplatelet and anticoagulant: 14 	<ul style="list-style-type: none"> DOACs (dabigatran (300 mg/day or 220 mg/day), rivaroxaban (15 mg/day or 10 mg/day), apixaban (10 mg/day), or edoxaban (60 mg/day or 30 mg/day)): 36 Antiplatelet: 43 VKA: 41 Combination of an antiplatelet and anticoagulant: 14 	95 ± 64 months	<ul style="list-style-type: none"> Thrombotic complications (thrombotic events, defined as any symptomatic arterial thromboembolism including cerebral infarction, peripheral arterial embolism, and thrombotic pulmonary embolism; and any obvious thrombus formation in the cardiac chambers or Fontan route) Haemorrhage (<i>major bleeding</i>, defined using the International Society on Thrombosis and Haemostasis criteria: significant bleeding necessitating hospitalization, interventions, ≥ 2 	<u>Funding</u> Not reported <u>Conflicts of interest</u> None	Some concerns (for all outcome measures)

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	<p><u>Age (mean, SD)</u></p> <ul style="list-style-type: none"> • DOACs: 30 (8) • Antiplatelet: 26 (6) • VKA: 27 (8) • Combination of an antiplatelet and anticoagulant: 28 (7) <p><u>Sex</u></p> <ul style="list-style-type: none"> • DOACs: 44% female • Antiplatelet: 65% female • VKA: 39% female • Combination of an antiplatelet and anticoagulant: 71% female 			<p>units of packed cells, or a hemoglobin drop >2.0 g/dl; or bleeding that was fatal or occurred at intracranial, intraspinal, in traocular, pericardial, intra-articular, and intramuscular sites with compartment syndrome.</p> <p><i>Minor bleeding</i>, defined as any bleeding that could not be classified as major bleeding)</p>		
Al-Jazairi, 2019	<p><u>N at baseline</u></p> <ul style="list-style-type: none"> • Aspirin: 36 • Warfarin: 366 <p><u>Age (median (IQR))¹</u></p> <p>3.0 (2.0) years</p>	<ul style="list-style-type: none"> • Aspirin • Warfarin 	13.6 years (IQR = 8.7)	<ul style="list-style-type: none"> • Thrombotic complications (defined as (first) late thromboembolic complications (TECs), occurring at least 1 year following the Fontan procedure) • Haemorrhage (defined as late <i>major</i>, clinically relevant <i>nonmajor</i>, and <i>minor bleeding</i>, occurring 1 year after the Fontan procedure) 	<p><u>Funding</u></p> <p>None</p> <p><u>Conflicts of interest</u></p> <p>None</p>	Some concerns (for all outcome measures)

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	<u>Sex²</u> 58% male					
Iyengar, 2016	<u>N at baseline</u> <ul style="list-style-type: none"> Aspirin: 157 Warfarin: 301 <u>Age (median (IQR))</u> <ul style="list-style-type: none"> Aspirin: 4.8 (3.9-5.8) years Warfarin: 4.7 (3.8-5.8) years <u>Sex</u> <ul style="list-style-type: none"> Aspirin: 46% female Warfarin: 39% female 	<ul style="list-style-type: none"> Aspirin Warfarin 	7 years (4.7-9.7)	<ul style="list-style-type: none"> Thrombotic complications (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. 	<u>Funding</u> Several sources, please refer to article <u>Conflicts of interest</u> 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).	Some concerns (for all outcome measures)
Pessotti, 2014	<u>N at baseline</u> <ul style="list-style-type: none"> Aspirin: 15 Warfarin: 15 <u>Age (mean, SD)</u>	<ul style="list-style-type: none"> Aspirin: 10 mg/kg/ day (maximum dose of 100 mg/day) Warfarin: initial dose of 0.1 mg/kg/day 	2 years	<ul style="list-style-type: none"> Thrombotic complications Mortality 	<u>Funding</u> None <u>Conflicts of interest</u>	Some concerns (for all outcome measures)

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	<ul style="list-style-type: none"> Aspirin: 4.8 (3.3) years Warfarin: 5.8 (3.8) years <p><u>Sex</u></p> <ul style="list-style-type: none"> Aspirin: 53% female Warfarin: 33% female 				Not reported	
Seipelt, 2002	<p><u>N at baseline</u></p> <ul style="list-style-type: none"> Aspirin: 14 Warfarin: 26 <p><u>Age (mean, SD)¹</u></p> <p>7.3 (8.1) years</p> <p><u>Sex</u></p> <p>46% female</p>	<ul style="list-style-type: none"> Aspirin: 2 to 3 mg/kg/d Warfarin: target internationalized normalized ratio between 2.2 and 2.7 	5.7 ± 3.5 years	<ul style="list-style-type: none"> Thrombotic complications (thromboembolic events or thrombus formation) 	<p><u>Funding</u></p> <p>Not reported</p> <p><u>Conflicts of interest</u></p> <p>Not reported</p>	Some concerns (for all outcome measures)
McCrinkle, 2013	<p><u>N at baseline</u></p> <ul style="list-style-type: none"> Aspirin: 57 Warfarin: 54 	<ul style="list-style-type: none"> Aspirin (5 mg/kg/day) Warfarin (0.1 mg/kg titration to achieve an international normalized 	2.5 years	<ul style="list-style-type: none"> Thrombotic complications (thrombotic events (venous or arterial, 	<p><u>Funding</u></p> <p>Research grant from the Heart and Stroke Foundation of Ontario</p>	Some concerns (for all outcome measures)

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	<p><u>Age (mean, SD)</u>¹ 4.8 (2.8) years</p> <p><u>Sex</u>² 36% female</p>	ratio (INR) of 2 to 3 with heparin lead-in)		<p>defined as the appearance of a space- occupying lesion</p> <p>on ultrasound within the cardiovascular system (mild laminar thickening of the internal surface of the Fontan pathway was not included) or the occurrence of a clinical event known to be strongly associated with thrombus (stroke, pulmonary embolism)</p> <ul style="list-style-type: none"> • Hemorrhage⁵ (<i>major bleeding and minor bleeding</i>) • Mortality⁵ 	<p>(grant-in-aid NA-3565), National Heart Foundation of Australia project grant, the Henderson Research Centre, Hamilton, and the CIBC World Markets Children's Miracle Foundation</p> <p><u>Conflicts of interest</u></p> <p>Mr. Roberts is a statistical consultant for Coaxia Inc. and Bayer Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose</p>	
Potter, 2013	<p><u>N at baseline</u></p> <ul style="list-style-type: none"> • Aspirin: 51 • Warfarin: 54 <p><u>Age (median (IQR))</u></p> <ul style="list-style-type: none"> • Aspirin: 6.8 (4.5, 15.9) years 	<ul style="list-style-type: none"> • Aspirin • Warfarin 	14.5 years (IQR 8.7–18.4 years)	<ul style="list-style-type: none"> • Thrombotic complications (occurrence of a fatal or non-fatal thromboembolic event, whether within the systemic or pulmonary circulation) 	<p><u>Funding</u></p> <p>Not reported</p> <p><u>Conflicts of interest</u></p> <p>Dr. Khairy has received research support for an</p>	Some concerns (for all outcome measures)

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	<ul style="list-style-type: none"> Warfarin: 11.3 (8.0, 17.6) years <p><u>Sex</u></p> <ul style="list-style-type: none"> Aspirin: 49% female Warfarin: 48% female 				investigator initiated grant from Boehringer Ingelheim.	

*For further details, see risk of bias table in the appendix

¹Only overall age was reported

²Only overall sex was reported

³Only overall sample size was reported

⁴Ischemic stroke is described as a separate outcome in this summary of the literature

⁵Derived from Monagle, 2011 (original article)