A report on prophylactic anticoagulation after Fontan procedure for Universitätsklinikum Schleswig-Holstein/Campus Kiel

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LIST OF ABBREVIATIONS

AE	Adverse event
ASA	Acetylsalicylic acid
AT	Antiplatelet therapy
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CVA	Cerebrovascular accidents
d	Day
DARE	Database of Abstracts of Reviews of Effects
DOAC	Direct oral anticoagulants
DVT	Deep venous thrombosis
FAQ	Frequently asked questions
GIN	Guidelines International Network
HRQoL	Health-related quality of life
HR	Hazard ratio
HTA	Health technology assessment
INR	International normalised ratio
IU	International unit
IVC	Inferior vena cava
kg	Kilogram
KSR	Kleijnen Systematic Reviews
mg	Milligram
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence (UK)
NOAC	Non-vitamin K antagonists oral anticoagulants
NR	Not reported
OR	Odds ratio
PA/AT	Prophylactic anticoagulation/antiplatelet therapy
PA-VKA	Prophylactic anticoagulation Vitamin K antagonist
PCPC	Partial cavo-pulmonary connection
PE	Pulmonary embolism
PICOS	Population, intervention, comparator(s), outcome(s), and study design
RCT	Randomised controlled trial
SCPC	Superior cavopulmonary shunt
SDM	Shared decision making
TE	Thromboembolic events
TEC	Thrombotic and embolic complications
TIA	Transient ischaemic attack
UK	United Kingdom
VKA	Vitamin K antagonists
yrs	Years

1. PROJECT OBJECTIVES

1.1 GLOBAL AIM

A key aim of the research project "Making SDM a reality" is to create interactive websites to inform patients as part of shared decision making (SDM).

1.2 SPECIFIC OBJECTIVES

To describe the interventions available to patients after a Fontan procedure. The goal of the Fontan procedure is to reroute venous blood into the pulmonary arterial circulation.[1]

To present evidence on the effectiveness and efficacy of prophylactic anticoagulation, including vitamin K antagonist and non-vitamin K antagonist oral anticoagulants, antiplatelet therapy, including acetylsalicylic acid, or no prophylactic anticoagulation/antiplatelet therapy.

2. METHODS

2.1 INCLUSION CRITERIA

The specific objectives underpinning the literature searches for this topic were developed in conjunction with clinical departments at Universitätsklinikum Schleswig-Holstein/Campus Kiel. No needs assessment was provided at the start of this review. Inclusion and exclusion criteria for this review are set out in Table 1, using the population, intervention, comparator(s), outcome(s), and study design (PICOS) format.

Table 1: Prophylactic anticoagulation after Fontan procedure: PICOS

Item	Included	Excluded
Populations	• All post Fontan procedure patients	• History of thrombosis • Absolute/established indication for anticoagulation (e.g. specific risk factors)
Interventions	• Prophylactic anticoagulation: Vitamin K antagonists (VKA, e.g. Marcumar), • Prophylactic anticoagulation: Non-vitamin K antagonists oral anticoagulants (NOACs) – sometimes referred to as Direct Oral Anticoagulants (DOACs) • Antiplatelet therapy: Acetylsalicylic acid (ASA) • No prophylactic anticoagulation/ antiplatelet therapy (PA/AT)	
Comparators	• Any of the above	
Outcomes	• Frequency of dosing; frequency/route of administration (e.g. oral anticoagulation is lifelong, regular clotting tests for VKAs) • Prolong life/ mortality/life expectancy • Symptom improvement (e.g. thromboembolism rate, deep venous thrombosis, etc.) • HRQoL • Time to return to usual activity • Hospitalisation • Feelings/satisfaction • Risks/side effects/long-term negative side effects	
Study designs	• Systematic reviews • Guidelines • Other Shared Decision Making	Pre January 2015 except primary studies

Item	Included	Excluded
	(SDM) tools • Large single studies (where evidence gaps exist from other studies)	
Subgroup	None specified	
ASA = acetylsalicylic acid; HRQoL = health-related quality of life; PICOS = population, intervention, comparator(s), outcome(s), and study design; DOAC = Direct Oral anticoagulants; NOAC = non-vitamin K antagonist oral anticoagulants; SDM = shared decision making; VKA = vitamin K antagonist		

2.2 FREQUENTLY ASKED QUESTIONS

The following research questions were identified as frequently asked questions (FAQs):

1. What does the treatment involve?
2. Will the treatment prolong life?
3. Will it help symptoms, thromboembolism rate, occurrence/freedom of thromboembolic events (deep venous thrombosis (DVT), pulmonary embolism (PE))?
4. How will treatment impact quality of life (HRQoL)?
5. Will it impact risk of having to go into the hospital?
6. What are the risks/side effects?
7. Are long-term negative effects of treatment to be expected (including impact on everyday life, participation in contact sports, pauses/changes to therapeutic management)?

2.3 LITERATURE SEARCHES

Literature searches were carried out to identify relevant systematic reviews and evidence-based guidelines regarding Fontan-type surgery. To inform FAQs, a second targeted database search on Fontan procedure/univentricular heart and shared decision making was also undertaken.

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range for systematic reviews and guidelines to 2015-2020. Targeted searches on SDM and Fontan procedure were also limited to the last five years as current and up-to-date evidence in this area was considered to be most relevant. Searches were not limited by language or publication status.

2.4 SEARCH SOURCES

2.4.1 Systematic reviews and guidelines

The following systematic review specific databases were searched from 2015 to present:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2020/12/Iss12

- Database of Abstracts of Reviews of Effects (DARE) (www.crd.york.ac.uk): up to 2015/03
- Health Technology Assessment (HTA) database (www.crd.york.ac.uk): up to 2018/03
- INAHTA (https://database.inahta.org/): up to 2020/11/12
- KSR Evidence (KSR): up to 2020/11/12
- Epistemonikos (www.epistemonikos.org): up to 2020/11/12

The following guidelines resources were searched from 2015 to present:

- Guidelines International Network (G-I-N) (www.g-i-n.net): up to 2020/11/11
- NHS Evidence (www.evidence.nhs.uk): up to 2020/11/12
- ECRI Guidelines Trust (https://guidelines.ecri.org/): up to 2020/11/12
- NICE (www.nice.org.uk): up to 2020/11/12
- TRIP Database (https://www.tripdatabase.com/): up to 2020/11/12

Full details of all search strategies are presented in Appendix 1.

2.4.2 Targeted searches

To identify questions relevant to shared decision making, targeted searches were undertaken in the following databases from 2015 to present:

- EMBASE (Ovid): 1974-2020/12/07
- MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946- 2020/12/08
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to 2020/12/Iss12

Full details of all search strategies are presented in Appendix 1.

2.4.3 Handling of citations

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling.

2.4.4 Supplementary searches

Reference lists of all included studies were checked for relevant studies. In addition, internet searches were performed to add qualitative patient-related information to inform the more narrative FAQs.

2.5 Study Selection, Quality Assessment And Data Extraction

Two reviewers independently screened the title and abstract of each record identified by the searches and determined the potential relevance of each record. For potentially relevant

records, the full paper was obtained, independently checked, and inclusion criteria applied. Disagreements were resolved through discussion.

2.6 DATA SYNTHESIS

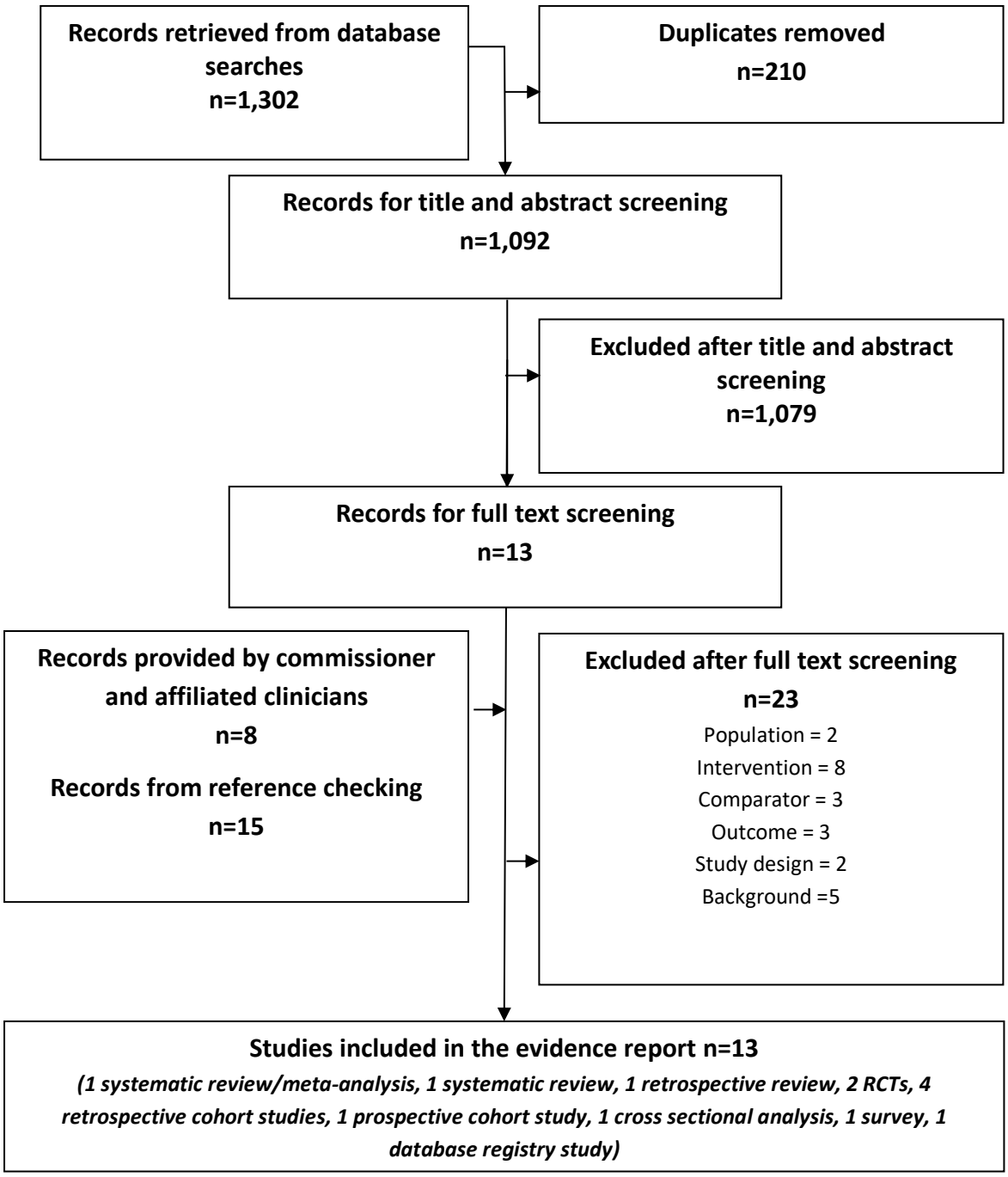
Data from each study was extracted by one reviewer and checked by another. Any disagreements were resolved through consensus. Where necessary, primary studies reported in systematic reviews were checked to determine if they reported any additional evidence for outcomes that were not reported in secondary sources (i.e. evidence gaps).

3. RESULTS

3.1 LITERATURE SEARCHES AND INCLUSION ASSESSMENT

A total of 1,302 records were retrieved from literature searches. After de-duplication, 1,092 titles and abstracts were screened by two reviewers. Thirteen full papers were identified as potentially relevant along with an additional 15 identified through reference checking, two records were supplied by the commissioner and six records were supplied by affiliated clinicians. After further review, 23 records were excluded. A total of thirteen studies were identified. Two systematic reviews, including one with a meta-analysis were identified through data base searching. Further reference checking also led to identification of two randomised controlled trials (RCT), four retrospective cohort studies, one retrospective review, one prospective cohort study, one cross sectional study, one database registry study, and one survey. A summary of the study selection process according to a modified PRISMA flow chart is reported in Figure 1.

Figure 1: PRISMA flow diagram for prophylactic anticoagulation after Fontan procedure



3.2 OVERVIEW OF INCLUDED STUDIES

Nine frequently asked questions (FAQs see section 2.2) were compiled, and inclusion/exclusion criteria were developed through consultations with the commissioner, and scoping the available evidence, to develop a comprehensive body of evidence to answer the FAQs. One systematic review/meta-analysis, two systematic reviews, one retrospective review, two RCTs, three retrospective cohort studies, one, prospective cohort study, one survey, one database registry study, and one cross sectional analysis and their associated interventions are summarised in Table 2. Details regarding the excluded studies are provided in Table 3.

Alsaied 2015

Alsaied 2015[2] is a systematic review/meta-analysis of published studies that evaluated the role of using thromboembolism prophylaxis in Fontan patients. Studies were included in the review if a direct comparison between different thromboembolism prophylaxis interventions or thromboembolism prophylaxis and no prophylaxis was made.[2]

Stalikas 2020

Stalikas 2020[3] is a systemic review investigating the safety and efficacy of non-vitamin K oral anticoagulants (NOAC) among adult patients. Inclusion criteria were defined as adult patients with congenital heart disease of any severity who received NOAC for either atrial arrhythmias, primary thromboprophylaxis or secondary thromboprophylaxis.[3] Only two of the four studies included in this review included adults with a Fontan circulation. One was a single centre retrospective chart review of 21 patients (Georgekutty 2018[4]) and one was Yang 2020[5] which was an international prospective study including 74 patients who had a Fontan circulation.

Monagle 2011

Monagle 2011[6] is a multicentre, international, randomised controlled trial. Patients were randomised to either the ASA group or the warfarin group upon completion of the Fontan procedure.[6] The patients who were randomised to the warfarin group received 10 to 20 U/kg/d of heparin initially before starting with a loading dose of 0.1 mg/kg of warfarin.[6]

McCrindle 2013

McCrindle 2013 [7] is a multicentre, randomised controlled trial of acetylsalicyclic acid versus warfarin for thromboprophylaxis after the Fontan procedure was performed. This RCT is a secondary analysis of the Monagle 2011[6] trial and was conducted in 111 patients. [7]

Table 2: Included studies

Main paper	Source Type	VKA	NOAC	AT	No PA/AT	FAQs						
						1	2	3	4	5	6	7
Alsaied 2015[2]	Systematic review / meta-analysis	Yes	No	Yes	Yes			✓				
Stalikas 2020[3]	Systematic review	No	Yes	No	No			✓			✓	
Monagle 2011[6]	RCT	Yes	No	Yes	No	✓		✓	✓		✓	
McCrindle 2013 [7]		Yes	No	Yes	No			✓				
Potter 2013[1]	Retrospective cohort studies	Yes	No	Yes	Yes	✓						
Seipelt 2002[8]		Yes	No	Yes	Yes	✓	✓				✓	
Mahnke 2005[9]		Yes	No	Yes	Yes			✓				
Kawamatsu 2021 [10]		Yes	Yes	Yes	Yes			✓			✓	
Manlhiot 2012[11]	Cross sectional analysis	Yes	No	Yes	Yes	✓	✓					
du Plessis 2018[12]	Survey	Yes	No	Yes	No				✓			
Yang 2019 [13]	Prospective cohort study	No	Yes	No	No			✓			✓	
Egbe 2016 [14]	Retrospective review	Yes	No	Yes	No		✓	✓		✓	✓	
Khairy 2008[15]	Database registry study	Yes	No	Yes	No		✓					

AT = antiplatelet therapy; FAQ = frequently asked question; NA = not applicable; NOAC = non-vitamin K antagonist oral anticoagulant; PA/AT = prophylactic anticoagulation/ antiplatelet therapy; VKA = vitamin K antagonist

FAQs:

1 What does the treatment involve?

2 Will the treatment prolong life?

3 Will it help symptoms, thromboembolism rate, occurrence/freedom of thromboembolic events (deep venous thrombosis (DVT), pulmonary embolism (PE))?

4 How will treatment impact quality of life (HRQoL)?

5 Will it impact risk of having to go into the hospital?

6 What are the risks/side effects?

7 Are long-term negative effects of treatment to be expected (including impact on everyday life, participation in contact sports, pauses/changes to therapeutic management)?

Potter 2013

Potter 2013[1] is a retrospective cohort study conducted on the New England registry of patients born in 1985 or earlier with Fontan surgery at Boston Children's Hospital. The purpose of this study was to assess and compare the effect of prophylactic aspirin and warfarin on thromboembolic events.[1]

Seipelt 2002

Seipelt 2002[8] is a retrospective cohort study conducted among patients who underwent a modified Fontan procedure (a significant alteration of surgical technique which includes a total cavopulmonary connection). Patients were divided into three groups which included patients who did not receive prophylaxis, patients treated with ASA at a dose of 2-3 mg/kg/d, and patients treated with warfarin therapy.[8]

Mahnke 2005

Mahnke 2005[9] is a retrospective cohort study of all patients who underwent Fontan palliation and were followed by the cardiology division at the Children's Hospital of Pittsburgh between 1976 and 2001. The type of anticoagulation utilised (if any) was at the discretion of the attending cardiologist. The study aim was to determine the risk of late clinical thromboembolic events, per patient year, for those on different anticoagulation therapies after Fontan procedure.[9]

Manlhiot 2012

Manlhiot 2012[11] is a cross sectional analysis in which the objective was to describe the incidence of thrombotic complications across three stages of ventricle palliation and the association between thromboprophylaxis use and thrombotic risk. The Fontan group was comprised of 162 patients.[11]

du Plessis 2018

du Plessis 2018 [12] is a study in which adults with a Fontan circulation in the Australian and New Zealand Fontan Registry were invited to complete a survey. 57 patients participated in the survey. [12]

Yang 2019

Yang 2019 [13] is a prospective cohort study in which the safety and efficacy of NOACs were investigated among patients who had a Fontan circulation. This study was conducted in 74 patients. [13]

Egbe 2016

Egbe 2016 is a retrospective review of adults with atrial arrhythmia after a Fontan procedure and had been evaluated at the Mayo Clinic between 1994-2014. [14] This study followed 278 patients.

Khairy 2008

Khairy 2008 [15] is a study conducted from a database registry of patients who had been born in 1985 or earlier with Fontan surgery who had been followed-up at Children's Hospital Boston. The study focused on 261 patients. [15]

Kawamatsu 2021

Kawamatsu 2021[10] is a retrospective cohort study in which the clinical records of adult patients with a Fontan circulation were reviewed and classified by used therapeutic agents used. This study identified 139 patients. [10]

Table 3: Excluded studies

Study	Main exclusion reason
Bouhout 2020[16]	Intervention- Did not include the specified intervention: • Prophylactic anticoagulation Vitamin K antagonist (PA-VKA) • Prophylactic anticoagulation non-Vitamin K antagonist • Antiplatelet therapy • No prophylactic anticoagulation or antiplatelet therapy
Ali 2019[17]	
Oldenburger 2016[18]	
Kouatli 1997[19]	
Kaulitz 2005[20]	
d'Udekem 2007[21]	
Haas 2000[22]	
van den Bosch 2004 [23]	
Garcia Ropero 2018[24]	Background
Kverneland 2018[25]	
Houeijeh 2020[26]	
Gnanappa 2017[27]	
Giglia 2013[28]	
Alsaied 2017[29]	Outcome- Did not address the FAQs.
Marshall 2020[30]	
Takawira 2008[31]	
Cheung 2005[32]	Comparator
Georgekutty 2018[4]	
Egbe 2017[33]	
Pujol 2020[34]	Population
Agarwal 2017[35]	
Chun 2004[36]	Study design
Jacobs 2002[37]	

3.3 FAQ1: What does the treatment involve?

The Fontan procedure is one of the most performed surgeries among congenital heart disease patients.[25] While the procedure has provided improved survival and quality of life among patients, the potential for major complications, such as thrombosis and thromboembolism remain.[2] Patients who received the Fontan procedure have been noted to experience decreased levels of circulating anticoagulants.[2] Strategies to address thrombosis and thromboembolism include embolectomy, thrombolytic treatment, or the use of anticoagulant therapies such as vitamin K anticoagulants, non-vitamin K anticoagulants, or antiplatelet therapy.[2, 3, 38] Anticoagulant and antiplatelet therapies can be taken as prophylaxis measure to prevent the occurrence of thrombosis or thromboembolism after the Fontan procedure.[2] Vitamin K anticoagulants, such as warfarin, and non-vitamin K anticoagulants, such as dabigatran, apixaban, or rivaroxaban, can be taken as an oral tablet.[3,

[38] The dose for each will be based on patient body weight.[38] Antiplatelet therapy, such as acetylsalicylic acid, can be consumed as an oral medication, with the dose per day determined by the patient's body weight.[6]

International Normalised Ratio (INR) monitoring and dose adjustments can be used to ensure the patient is receiving the drug within the therapeutic range.[6] This can be performed every 2-3 weeks for stable patients, while patients who experience dosing challenges may need INR monitoring more frequently. [6]

3.4 FAQ2: Will the treatment prolong life?

While no systematic reviews were identified that examined overall survival as a comparison of different therapies, Seipelt 2002[8] reported overall survival as 85% at year 1, 82% at 5 years and 79% at 10 years – however this was for a mix of patients on VKA, NOAC and no PT/AT. Similarly, Manlhiot 2012[11] did not report separate mortality results for patients treated with VKA or AT. However, thrombotic complications for VKA and AT were associated with increased mortality after initial palliation (HR 5.5, P < .001) and superior cavopulmonary shunt (SCPC) (HR 12.5, P < .001). According to Manlhiot 2012[11], thrombotic complications were reported as the primary cause of death in 21% of patients and the secondary cause of death in 24% of patients.[11] Egbe 2016 [14] observed that the occurrence of thrombotic and embolic complications (TEC) was associated with a higher risk of death. Of the 81 patients who experienced TEC, 72% received antiplatelet therapy, whereas 27% had received anticoagulation therapy. [14] Khairy 2008 [15] reported that over a median of 12.2 years 76 of 261 patients had died. The authors noted that the absence of warfarin or aspirin therapy was found to be an independent predictor of mortality from thromboembolism. [15]

3.5 FAQ3: Will it help symptoms, thromboembolism rate, freedom of DVT/PE?

Two systematic reviews, one retrospective review, one prospective cohort study, one retrospective cohort study, one cohort study, and two RCTs were identified to provide evidence regarding the experience or easing of symptoms following prophylaxis.

Alsaied 2015[2] noted the occurrence of thromboembolic events (TE). These events included PE, stroke, transient ischaemic attack (TIA), renal infarction, and chylothorax (innominate vein thrombus), but were not quantified.[2] Meta-analysis of 10 studies involving 1,200 patients with an average follow-up time of 7.1 years revealed a total incidence of thromboembolic events of 11.3%. Patients who received TE prophylaxis with either aspirin or warfarin had lower incidence of TE compared with no PA/AT (odds ratio (OR) 0.425, 95% confidence interval (CI) 0.194 to 0.929, P<0.01). Overall incidence of TE was 8.6% for AT (aspirin), 9% for VKA (warfarin) and 18.6% for no PA/AT. An OR of 0.363, 95% CI 0.177 to 0.744, P<0.01) was reported for AT versus no PA/AT and an OR of 0.327, 95% CI 0.168 to 0.634, P<0.01) for VKA versus no PA/AT. There was, however, no significant difference between warfarin and aspirin in TE incidence (OR 0.936, 95% CI 0.609 to 1.438, P=0.54, I2=0%) when all types of Fontan procedure were considered, regardless of the timing of the event after surgery. Separate analysis was undertaken on seven studies involving new generation Fontan (i.e., total

cavopulmonary connection). No significant difference in TE incidence between patients treated with warfarin versus aspirin (OR 0.813, 95% CI 0.471 to 1.401, P=0.34) was observed for this more contemporary form of Fontan, see Table 5. Additionally, there was no significant difference in incidence of early TE (within six months of the operation) or late TE (>6 months) between patients receiving warfarin and aspirin (OR 0.784, 95% CI 0.310 to 1.982, P=0.37) and (OR 0.776, 95% CI 0.249 to 2.42, P=0.3).

Monagle 2011[6] reported no significant difference between warfarin and ASA in terms of thrombosis experience, albeit that a numerical advantage was evident for those treated with ASA. However, when, in the same study, analysis was restricted to those with a clinical presentation (more serious thromboses) numerical advantage was not evident with proportions being virtually identical between groups. See Table 4.

McCrindle 2013 [14] presented a secondary analysis of the study by Monagle 2011 [6]. The trial was able to note that the risk of thrombosis decreased with appropriately controlled warfarin or ASA therapy. [7] According to McCrindle 2013 [7], of the patients who had been assigned to warfarin, 66% were noted to have controlled INR (>30% of INR values within the target), whereas 33% of patients had uncontrolled INR. This trial also noted that patients who received warfarin and achieved target INR levels >30% of the time, or ASA, had a 3.5-fold decrease in risk in thrombosis when compared to patients who did not meet INR levels. [7]

Mahnke 2005[9] undertook a retrospective cohort study of all patients who underwent Fontan palliation and were followed by the cardiology division at the Children's Hospital of Pittsburgh between 1976 and 2001. This long follow-up was intended to inform incidence of late cerebrovascular accidents (CVA) following the Fontan procedure. The overall conclusion was that late CVA was not related to anticoagulation strategy or time from Fontan procedure but was associated with a residual right-to-left shunt and lateral tunnel-type Fontan palliation.[9] Estimates of CVA incidence are set out in Table 4.

Stalikas 2020[3] observed the occurrence of thromboembolism among patients. The types of thromboembolism events included DVT, PE, intracardiac thrombus, and ischaemic stroke. These events were each experienced by a total of four patients.[3]

Egbe 2016 [14] observed TEC, major bleeding and minor bleeding. Of the entire cohort of 278 patients, 81 experienced a TEC. [14] The types of TEC included a Fontan conduit/right atrial thrombus, pulmonary embolus, intracardiac thrombus, ischaemic stroke, and systemic arterial embolus. [14] 16 patients were identified as having had more than one TEC. [14]

Yang 2019 [13] completed a prospective cohort study to explore the occurrence of thromboembolic events among patients with a Fontan circulation. A total of three thromboembolic events had been identified during follow-up. [13]

Kawamatsu 2021 [10] undertook a retrospective cohort study examining the clinical records of 139 adult patients who had a Fontan circulation between 2015 and 2018. During this period, 10 thrombotic, events had occurred. [10] In this study, thrombotic events included any symptomatic arterial thromboembolism including cerebral infarction, peripheral arterial

embolism, thrombotic pulmonary embolism and any obvious thrombus formation in the cardiac chambers or Fontan route. Asymptomatic DVT below the knee were not included. [10]

Table 4: Incidence of thrombosis and thromboembolic events

Source	Ref in Source document	Median follow-up time (months)	Intervention	Dose	N	No events (% of N)	Measure of effect
Thromboembolic events							
Alsaied 2015 [2]	Meta-analysis 10 studies	85	VKA	Warfarin - mixed	536	48 (9%)	OR 0.327 (95% CI 0.168 to 0.634, P<0.01) versus No PT/AT; OR 0.936 (95% CI 0.609 to 1.438, P=0.54) v AT
			AT	Aspirin - mixed	465	40 (8.6%)	OR 0.363 (95% CI 0.177 to 0.744, P<0.01) versus No PT/AT; OR 0.936 (95% CI 0.609 to 1.438, P=0.54) v VKA
			No PT/AT	NA	199	37 (18.6%)	OR 0.327, 95% CI 0.168 to 0.634, P<0.01) versus VKA; OR 0.363 (95% CI 0.177 to 0.744, P<0.01) v AT
	Meta-analysis 7 studies	NR	VKA with new Fontan	Warfarin - mixed	363	36 (10.1%)	OR 0.813 (95% CI 0.471 to 1.401, P=0.34 versus AT
			AT with new Fontan	Aspirin - mixed	399	42 (10.5%)	OR 0.813 (95% CI 0.471 to 1.401, P=0.34 versus VKA)
			No PT/AT with new Fontan	NA	128	22 (17.2%)	NR
Egbe 2016 [14]	NA	10 years	VKA	Warfarin NR	278	81 (29.1%)	NR
			AT	Aspirin NR			
			No PA/AT	No treatment			
Stalikas 2020 [3]	Georgekutty 2018	26.3 patient years	NOAC	Dabigatran 110 mg b.i.d.	551	1 (0.18%)	3.13% (95% CI: 1.18–8.03)
	Yang 2020	613 patient years		Dabigatran NR		1 (0.18%)	
				Abixaban NR		2 (.36%)	
				Rivaroxaban NR		1 (0.18%)	

Source	Ref in Source document	Median follow-up time (months)	Intervention	Dose	N	No events (% of N)	Measure of effect
Yang 2019 [13]	NA	1.4 ±0.9 years (mean)	NOAC	Anabaptist NR	74	3 (4.05%)	Annual incidence 2.9% (95% CI 0.7& to 7.6%)
				Dabigatran NR			
				Edoxaban NR			
				Rivaroxaban NR			
Thrombosis							
Monagle 2011[6]	NA	24	VKA	Warfarin Loading dose = 0.1 mg/kg Titrated to INR of 2.0-3.0	54	13 (24%)	HR 1.35 (95% CI 0.62 to 3.00) based on Kaplan- Meier estimate
			AT	ASA 5 mg/kg/d	57	8 (14%)	
Kawamatsu 2021[10]	NA	1114 patient years	VKA	NR	41	5 (12.2%)	
			DOAC	Dabigatran, Rivaroxaban, Apixaban, or Edoxaban NR	36	0	
			AT	NR	43	3 (7%)	
			No PA/AT	NA	5	2 (40%)	
Thrombosis associated with a clinical presentation							
Monagle 2011[6]	NA	24	VKA	Warfarin Loading dose = 0.1mg/kg Titrated to INR of 2.0-3.0	54	3 (6%)	P=0.8
			AT	ASA 5 mg/kg/d	57	4 (8%)	
McCrindle 2013 [7]	NA	30	VKA	Controlled Warfarin 0.1mg/kg	25	3 (12% overall sample n=86)	Univariable HR (95% CI) 0.34 (0.10–1.13) P=0.08
			AT	Aspirin 5 mg/kg/d		12 (48% overall sample n=86)	Univariable HR 0.74 (0.33–1.09 P=0.45

Source	Ref in Source document	Median follow-up time (months)	Intervention	Dose	N	No events (% of N)	Measure of effect
			VKA	Uncontrolled warfarin NR		7 (28% overall sample n=86)	Univariable HR 3.70 (2.81–4.58) P=0.004
Estimated incidence of Late Cerebrovascular Accidents							
Mahnke 2005[9]	NA	42	VKA	Warfarin NR	28	0	Estimate per 100 patient-years = 0
		97	AT	Aspirin NR	98	2	Estimate per 100 patient-years = 0.25
		85	No PA/AT	NA	23	1	Estimate per 100 patient-years = 0.61

* It is presumed that 10 patients experienced 13 events

ASA = acetylsalicylic acid; AT = antiplatelet therapy; b.i.d = twice a day; DOAC = direct oral anticoagulants; HR = hazard ratio; INR = international normalised ratio; NA = not applicable; NOAC = non-vitamin K antagonist oral anticoagulant; OR = odds ratio; PA/AT = prophylactic anticoagulation/ antiplatelet therapy; VKA = vitamin K antagonist

3.6 FAQ4: How will treatment impact quality of life (HRQoL)?

No systematic reviews were identified that described the impact treatment would have on quality of life. One RCT[6] discussed the potential impact treatment would have on quality of life. Monagle 2011 noted that warfarin therapy can impose a burden on children due to the need for regular blood tests and potential lifestyle restrictions to reduce the occurrence of trauma-induced bleeding. [6] Such limitations could include reduced participation in sports.[6] One study addressed patient concerns regarding the impact of living with a Fontan circulation including the influence of anti-coagulation treatment on quality of life. In this survey-based study conducted by du Plessis [12], an identified concern of participants was related to pregnancy and the ability to conceive. du Plessis [12] also noted that given these concerns, some participants stated that they have explored or were willing to explore other options including surrogacy or adoption.

3.7 FAQ5: Will it impact risk of having to go into the hospital?

One retrospective review [14] was identified to provide evidence regarding the possibility of returning to the hospital due to TEC. Egbe 2016 [14] reported that of 81 patients who experienced TEC this was comprised of a total of 97 TEC events. Of those who experienced TEC, 38 events (39%) required hospitalisation. The key reasons for hospitalisation included anticoagulation and imaging evaluation.[14] Egbe 2016[14] noted that anticoagulation appeared to be associated with a lower risk of hospitalisation.

Table 5: Re-hospitalisation events

Source	Ref in source document	Follow-up time	Intervention	Dose	N	N Long-term negative effects (% of N)
Egbe 2016 [14]	NA	10 years	VKA	Warfarin NR	97	38 hospitalisation events (39%)
			AT	Aspirin NR		

AT = antiplatelet therapy; d = day; INR = international normalised ratio; kg = kilogram; mg = milligram; NA = not applicable; NOAC = non-vitamin K antagonist oral anticoagulant; NR = not reported; PA/AT= prophylactic anticoagulation/ antiplatelet therapy; VKA = vitamin K antagonist

3.8 FAQ6: WHAT ARE THE RISKS/SIDE EFFECTS?

Data were compiled from one systematic review, one RCT, one retrospective review, one prospective cohort study, and two retrospective cohort studies regarding the experience of potential risks and side effects from the use of prophylaxis treatments after a Fontan procedure. However, the identified studies only report patients who received either VKA, NOAC, or no intervention. The most frequently reported risks included major bleeding and asymptomatic thrombus formation. Major bleeding appeared to be affiliated with every intervention of interest. However, VKA and AT appeared to be more often related to minor bleeding events. Details from studies which reported patients who received only one type of thromboprophylaxis of interest are set out in Table 6.

Stalikas 2020[3] reported three Fontan patients who had experienced major bleeding. The three patients (4.1%) all received a NOAC in either the form of apixaban or rivaroxaban. [3] However, in the reference in the source document, Yang 2020, the number of patients who received each NOAC was not described.[3] The major bleeds were identified as gastrointestinal and menorrhagia.

In one RCT, Monagle 2011[6], identified two Fontan patients who experienced major bleeding during the 24-month follow-up period. One patient was in the group of 54 patients who received warfarin, while the other patient was in the group of 57 patients who received ASA who died before receiving the assigned drug.[6] Additional minor bleeding events were identified in locations including the nose, oral, gastrointestinal, genitourinary, skin, and other.[6] See Table 6.

Seipelt 2002[8], a retrospective cohort study, reported no major bleeding events. However, in one Fontan patient (1%), an asymptomatic thrombus in the right atrium was identified.[8] The patient did not receive anticoagulation prophylaxis and was later treated with heparin and warfarin.[8]

Egbe 2016[14] reported the occurrence of major and minor bleeding events. In this review, major bleeding was defined as intracranial bleeding, pericardial, or pleural hematoma requiring drainage or any bleeding requiring a transfusion. [14] Minor bleeding was defined as cutaneous bleeding, epistaxis, gastrointestinal bleeding, or any bleeding event that did not meet the criteria for major bleeding. [14] Egbe 2016 [14] reported 6 major bleeding events and 15 minor bleeding events. Due to the occurrence of major bleeding anticoagulation and/or antiplatelet therapy was discontinued. [14]

Yang 2019 [13] reported major bleeding and minor bleeding events. In this study major bleeding was defined as significant bleeding necessitating hospitalisation/ interventions of ≥2 units of packed cells and / or with a haemoglobin drop >1.24 mmol/L (20g/L) and/or bleeding that was fatal or occurred in a critical location such as the intracranial, intraspinal, intraocular, pericardial, intra-articular, or intramuscular with compartment syndrome. [13] Minor bleeding was defined as bleeding that could not be classified as major bleeding. [13] Yang 2019 [13] reported three occurrences of major bleeding, two which were classified as menorrhagia and

one that was classified as major gastrointestinal bleeding. Minor bleeding was reported 15 times. [13]

Kawamatsu 2021 [10], a retrospective cohort study, reported a total of 18 major bleeding events. This study defined major bleeding as a significant bleeding which necessitated hospitalisation, interventions, ≥ 2 units of packed cells, or a haemoglobin drop >2.0g/dl or bleeding that was fatal or occurred at intracranial, intraspinal, intraocular, pericardial, intra-articular, and intramuscular sites with compartment syndrome. [10] The types of major bleeding included menorrhagia, gastrointestinal bleeding, intra-cranial bleeding or other unspecified major bleeding event. [10]

Table 6: Risks/side effects

Source	Ref in source document	Follow-up time	Intervention	Dose	N	Number with event (% of N)
Major bleeding						
Alsaied 2015 [2]	D'Udekem 2007	12 years	VKA	Warfarin NR	215	2(0.93%)
			AT	Aspirin NR		
			No PA/AT	No treatment		
Stalikas 2020[3]	Yang 2020	613 (patient-years)	NOAC	Apixaban NR	74	3 (4.1%)
			NOAC	Rivaroxaban NR		
Monagle 2011[6]	NA	24 months	AT	ASA 5 mg/kg/d	57	1 (2%)
			VKA	Warfarin Loading dose = 0.1mg/kg Titrated to INR of 2.0-3.0	54	1 (2%)
Manlhiot 2012 [11]	NA	2.3 years	VKA	Warfarin Loading dose = 0.1mg/kg Titrated to 2.0-3.0	162	1 (.61%)
			AT	Enoxaparin 1.5 mg/ kg/d (age 2 months) or 1.0 mg/kg/d (noninfants)		
			No PA/AT	No treatment		
Egbe 2016[14]	NA	10 years	VKA	Warfarin NR	278	6 (2.15%)
			AT	Aspirin NR		
			No PA/AT	No treatment		
Yang 2019 [13]	NA	1.4 ±0.9 years	NOAC	Anabaptist NR	74	3 (4.05%)
				Dabigatran NR		
				Edoxaban NR		
				Rivaroxaban NR		
Kawamatsu 2021[10]	NA	1114 patient years	VKA	NR	41	6 (14.6%)
			DOAC	Dabigatran, Rivaroxaban, Apixaban, or Edoxaban NR	36	1 (2.8%)

Source	Ref in source document	Follow-up time	Intervention	Dose	N	Number with event (% of N)
			AT	NR	43	3 (7%)
			No PA/AT	NA	5	0
Asymptomatic thrombus formation						
Seipelt 2002[8]	NA	NR	No PA/AT	NA	101	1 (.99%)
Nose bleed						
Monagle 2011[6]	NA	24 months	AT	ASA 5 mg/kg/d	57	8 (14%)
			VKA	Warfarin Loading dose = 0.1mg/kg Titrated to INR of 2.0-3.0	54	12 (26%)
Oral bleed						
Monagle 2011[6]	NA	24 months	AT	ASA 5 mg/kg/d	57	1 (2%)
			VKA	Warfarin Loading dose = 0.1mg/kg Titrated to INR of 2.0-3.0	54	5 (9%)
Gastrointestinal bleed						
Monagle 2011[6]	NA	24 months	AT	ASA 5 mg/kg/d	57	3 (5%)
			VKA	Warfarin Loading dose = 0.1mg/kg Titrated to INR of 2.0-3.0	54	4 (7%)
Kawamatsu 2021[10]	NA	1114 patient years	VKA	NR	41	2 (4.9%)
			DOAC	Dabigatran, Rivaroxaban, Apixaban, or Edoxaban NR	36	0
			AT	NR	43	0
			No PA/AT	NA	5	0

Source	Ref in source document	Follow-up time	Intervention	Dose	N	Number with event (% of N)
Skin bleed						
Monagle 2011[6]	NA	24 months	AT	ASA 5 mg/kg/d	57	2 (4%)
			VKA	Warfarin Loading dose = 0.1mg/kg Titrated to INR of 2.0-3.0	54	4 (8%)
Menorrhagia						
Kawamatsu 2021[10]	NA	1114 patient years	VKA	NR	41	2 (4.9%)
			DOAC	Dabigatran, Rivaroxaban, Apixaban, or Edoxaban NR	36	1 (2.8%)
			AT	NR	43	2(4.6%)
			No PA/AT	NA	5	0
Intra-cranial bleeding						
Kawamatsu 2021[10]	NA	1114 patient years	VKA	NR	41	1 (2.4%)
			DOAC	Dabigatran, Rivaroxaban, Apixaban, or Edoxaban NR	36	0
			AT	NR	43	0
			No PA/AT	NA	5	0
Other bleed						
Monagle 2011[6]	NA	24 months	AT	ASA 5 mg/kg/d	57	4 (7%)
			VKA	Warfarin Loading dose = 0.1mg/kg Titrated to INR of 2.0-3.0	54	9 (17%)
Kawamatsu 2021[10]	NA	1114 patient years	VKA	NR	41	1 (2.4%)
			DOAC	Dabigatran, Rivaroxaban, Apixaban, or Edoxaban NR	36	0
			AT	NR	43	1 (2.3%)

Source	Ref in source document	Follow-up time	Intervention	Dose	N	Number with event (% of N)
			No PA/AT	NA	5	0
Any minor bleed						
Monagle 2011		24 months	AT	ASA 5 mg/kg/d	57	8 (14%)
			VKA	Warfarin Loading dose = 0.1mg/kg Titrated to INR of 2.0-3.0	54	18 (33%) *
Egbe 2016[14]	NA	10 years	VKA	Warfarin NR	278	15 (5.4%)
			AT	Aspirin NR		
			No PA/AT	No treatment		
Yang 2019 [13]	NA	1.4±0.9 years	NOAC	Anabaptist NR	74	15 (20.2%)
				Dabigatran NR		
				Edoxaban NR		
				Rivaroxaban NR		

*P=0.03

ASA = acetylsalicylic acid; AT = antiplatelet therapy; DOAC = direct oral anticoagulants; NOAC = non-vitamin K antagonist oral anticoagulant; PA/AT = prophylactic anticoagulation/ antiplatelet therapy

3.9 FAQ7: ARE LONG-TERM NEGATIVE EFFECTS OF TREATMENT EXPECTED?

No comparative evidence was found.

4. DISCUSSION

4.1 SUMMARY OF MAIN FINDINGS

There is a paucity of meaningful data regarding the interventions available to patients after a Fontan procedure and the effectiveness and efficacy of prophylactic anticoagulation. However, this review presents limited evidence regarding vitamin K antagonists (VKA), non-vitamin K antagonist oral anticoagulants (NOAC), antiplatelet therapy (AT), as well as treatment without prophylactic anticoagulation or antiplatelet therapy (PA/AT) after a Fontan procedure.

The key findings of this review are summarised in Table 7. The results should be interpreted with caution due to the limitation of the evidence. The limitations of this review were largely attributed to a low number of study participants, paucity of information in regard of NOACs and under-reporting of follow-up times in primary studies.

The Fontan procedure is able to improve survival among patients.[2] Upon completion of the procedure, prophylactic anticoagulation treatment may be necessary in order to prevent serious complications. However, the choice of which type of treatment to utilise is less clear due to the limited available evidence.

The use of AT was found to be related to higher mortality and a higher incidence of thrombosis when compared to VKA. However, VKA was reported to be related to more needs for rehospitalisation when compared to AT. The reasons for rehospitalisation included revision surgery, conversion surgery, or transplantation. VKA was also reported to be related to major bleeding more often when compared to other treatments.

The evidence was limited, especially for children after a Fontan procedure using NOACs as an intervention. Major bleeding was reported in the literature for three patients who received NOAC.

In rare circumstances, such as those experienced by a single participant, patients who received no prophylactic anticoagulation or antiplatelet therapy experienced atrial flutter, mobile right atrial thrombosis, and asymptomatic thrombosis formation.

4.2 ONGOING AND FUTURE STUDIES

A German guideline on the univentricular heart during childhood and adolescence was published in August 2013.[39] According to the relevant website[40], the guideline has been valid for five years, i.e. until August 2018, and is currently undergoing revision. However, no timeline has been provided for this update. The document includes one statement regarding partial cavopulmonary connection (PCPC), indicating that due to the paucity of data regarding antithrombotic therapy following PCPC, a decision about antithrombotic treatment should be made on a case-by-case basis.[40]

Three interventional prospective randomized controlled trials in Fontan paediatric patients are nearing completion in mid-2020. The first is examining rivaroxaban versus aspirin in 112 patients (NCT02846532)[41]; the second is studying 200 patients, to compare 3-arms: apixaban,

VKA, and low-molecular-weight heparin (NCT02981472)[42]; while the third (SAXOPHONE) describes the use of apixaban in children and infants. [43]

4.3 Comparison With Other Reviews

Two systematic reviews were found relating to this topic.

The most informative study is a review and meta-analysis by Alsaied 2015[2], which identified 10 studies involving 1,200 patients with an average follow-up time of 7.1 years. This study shows a significantly lower incidence of TE after Fontan procedure if either aspirin or warfarin is used irrespective of the type of Fontan procedure. Meta-analysis also suggests no significant difference in incidence of early or late TE in patients receiving aspirin compared with warfarin. This review includes all the primary studies we identified but focuses only on TEs.[2]

Stalikas 2020[3] is a systemic review investigating the safety and efficacy of non-vitamin-K oral anticoagulants among adult patients. Inclusion criteria were defined as adult patients with congenital heart disease of any severity who received NOAC for either atrial arrhythmias, primary thromboprophylaxis or secondary thromboprophylaxis. Only two studies provided information in relation to NOAC use following Fontan procedure. These were Yang 2020 which reported data from a patient registry and Georgekutty 2018 which reported retrospective data on patients who were treated with warfarin before NOAC initiation. Authors concluded that NOACs are both safe and effective in treating adults with coronary heart disease but acknowledged that there was only weak evidence in regard of patients with a Fontan circulation.[3]

4.4 Strength, Limitations And Uncertainties

We are confident all systematic reviews and primary studies which met the specified inclusion criteria have been identified. We identified three systematic reviews, one including a meta-analysis, one RCT, three retrospective cohort studies, and one cross-sectional analysis. However, multiple gaps in the evidence have been observed, including when recovery can be expected to begin, the length of the treatment effect, and the impact on health-related quality of life.

4.5 Recommendations For Further Research

Further studies are needed with larger populations to address concerns regarding the use of different types of prophylactic anticoagulation treatments after the Fontan procedure. The German guideline, upon completion of revision, might be able to provide updated guidance on this matter.[39]

Table 7: Summary of evidence:

Outcome	Source	VKA	NOAC	AT	No PT/AT	Certainty – quality of evidence	Assessment for use in DA
FAQ2: Will the treatment prolong life?							
All-cause mortality	No evidence					NA	●
FAQ3: Will the treatment help with symptoms?							
Thromboembolic events	Alsaied 2015[2]; Yang 2019 [13]; Egbe 2016 [14]; Stalikas 2020 [3]	OR 0.327 (95% CI 0.168 to 0.634, p<0.01) v No PT/AT; OR 0.936 (95% CI 0.609 to 1.438, p=0.54) v AT Incidence of TE=9%	No evidence	OR 0.363 (95% CI 0.177 to 0.744, P<0.01) v No PT/AT; OR 0.936 (95% CI 0.609 to 1.438, P=0.54) v VKA Incidence of TE= 8.6%	OR 0.327, 95% CI 0.168 to 0.634, P<0.01) v VKA; OR 0.363 (95% CI 0.177 to 0.744, P<0.01) v AT Incidence of TE= 18.6%	Moderate	⇗ Significant difference between VKA v No AT/PT and ASA v No AT/PT
Thrombosis	Monagle 2011[6]; Kawamatsu 2021 [10]	24% HR 1.35 (95% CI 0.62 to 3.00) v AT. HR 2.70 (95% CI 0.73 to 12.5, p=0.138) v AT; HR 0.35 (95% CI 0.06-2.66, p=0.27) v No PT/AT	No evidence	14% HR 1.35 (95% CI 0.62 to 3.00) v VKA. HR 2.70 (95% CI 0.73 to 12.5, p=0.0138) v VKA; HR 0.14 (95% CI 0.02 to 1.13, p=0.063) v No PT/AT	HR 0.35 (95% CI 0.06-2.66, p=0.27) v VKA; HR 0.14 (95% CI 0.02 to 1.13, p=0.063) v AT	Low	⇔ No significant difference between AT, VKA, and No AT/PT
Thrombosis associated with a clinical presentation	Monagle 2011[6]; McCrindle 2013 [7]	6% No significant difference compared to AT	No evidence	4% No significant difference compared to VKA	No evidence	Low	⇔ No significant difference

Outcome	Source	VKA	NOAC	AT	No PT/AT	Certainty – quality of evidence	Assessment for use in DA
		(p=0.8); (HR: 3.53, 95% CI: 1.35 to 9.20, p < 0.01) vs AT		(p=0.8)			between AT and VKA
Estimated incidence of Late Cerebrovascular Accidents	Mahnke 2005[9]	0 per 100 patient years (estimate) No significant difference compared to AT or No AT/PT	No evidence	0.25 per 100 patient years (estimate) No significant difference compared to VKA or No AT/PT	0.61 per 100 patient years (estimate) No significant difference compared to VKA or AT	Low	⇔ No significant difference between AT, VKA, and No AT/PT
FAQ4: How will treatment impact quality of life?							
NA	No quantitative evidence					NA	●
FAQ5: Will treatment impact risk of having to go to hospital?							
Hospitalisation-related events	Egbe 2016 [14]	Limited available evidence	No evidence	Limited available evidence	No evidence	NA	⇔ No significant difference between AT and VKA
FAQ6: What are the risks / side effects?							
Major Bleeding	Alsaied 2015 [2]; Stalikas 2020 [3]; Monagle 2011[6]; Manlhiot 2012 [11]; Egbe 2016 [14]; Yang 2019 [13]; Kawamatsu 2021 [10]	HR 0.26 (95% CI 0.01 to 1.62, p=0.162) v NOAC; HR 2.27 (95% CI 0.58 to 11.1, p=0.241) v AT; HR 0.35 (95% CI 0.06	HR 0.26 (95% CI 0.01 to 1.62, p=0.162) v VKA; HR 1.03 (95% CI 0.04 to 13.8,	HR 1.03 (95% CI 0.04 to 13.8, p=0.985) v NOAC; HR 2.27 (95% CI 0.58 to 11.1, p=0.241) v VKA;	HR 0.35 (95% CI 0.06 to 2.66, p=0.275) v VKA	Low	⇔ No significant difference between AT, NOAC, VKA and no PT/AT

Outcome	Source	VKA	NOAC	AT	No PT/AT	Certainty – quality of evidence	Assessment for use in DA
		to 2.66, p=0.275) v No PT/AT	p=0.985) v AT;				
Asymptomatic Thrombus formation	Seipelt 2002 [8]	No evidence	No evidence	No evidence	Limited available evidence	Low	●
FAQ7: Are long-term negative effects of treatment to be expected?							
NA	No evidence					NA	●
AE = adverse events; AT = antiplatelet therapy; HR = hazard ratio; NA = not applicable; NOAC = non-Vitamin K antagonist oral anticoagulants; OR = odds ratio; PA/AT = prophylactic anticoagulation/ antiplatelet therapy; VKA = vitamin K antagonist							

Type of Arrow	Assessment for use in decision aid
⇧	**"Proof or strong indication of effect"** **Difference in favour of group A versus B based on high to moderate quality data*** **The effect estimate ideally should be significant, but may sometimes be only borderline significant but from several studies indicating a trend (that according to KSR should be mentioned)**
⇗	**"Indication or hint of effect"** **Difference in favour of group A versus B based on low quality data that appears reportable in the DA (e.g., large effect on survival based on registry data, consistently very convincing effects from observational studies supported by one small RCT with same direction of effect)**
⇔	**"No Proof/Indication of effect or a hint of effect that is too weak to report"** **No difference shown among groups based on moderate to high quality data** **or difference shown but does not seem reliable enough to be reported based on low or very low-quality data**
●	**No data to report: no difference shown from low/very low-quality studies or no studies**

*The term "Data Quality" includes assessment of evidence (level of evidence, risk of bias assessment) as well as transferability of study results to our target population. This should be either taken from original reviews/meta-analyses or provided by KSR for studies where no external evidence assessment exists.
In this review the quality of evidence was judged to be low where findings were generated from single RCTs. If all three RCTs reported the same finding then the certainty of evidence was judged to be moderate/low. An assessment of medium/ high reflects findings from all RCTs as well as the systematic review. An assessment of Strong is based on evidence from systematic review of RCTs with homogeneity. The highest level of evidence is reported for each outcome.

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APPENDIX 1: SEARCH STRATEGIES

SR/Guidelines searches

Database	Dates	Results
CDSR & CDSR Protocols	2015 – 2020/12/Iss12	45
DARE	2015 – 2015/03	0
HTA	2015 – 2018/03	2
INAHTA	2015 –2020/11/12	1
KSR Evidence	2015 –2020/11/12	105
Epistemonikos	2015- 2020/11/12	65
NHS Evidence	2015-2020/11/12	162
NICE	up to 2020/11/11	17
GIN	up to 2020/11/11	6
ECRI	up to 2020/11/12	9
TRIP	up to 2020/11/12	95
Total		**507**

SDM database searches

Database	Dates	Results
Embase	2015-2020/12/07	365
MEDLINE & PreMedline	2015-2020/12/08	344
CENTRAL	2015-2020/12/Iss12	86
Total		**795**

SR/Guidelines searches

Cochrane Database of Systematic Reviews (CDSR)(Wiley): up to 2020/12/Iss12
Searched: 9.12.20

#1 MeSH descriptor: [Fontan Procedure] explode all trees 59
#2 (Fontan* or "hemi-fontan") 1177
#3 (norwood) NEAR/3 (anastomosis or conduit* or circuit* or connection* or circulation or operation* or procedure* or palliation or surger*) 95

#4 (bidirectional or bi-directional) NEAR/3 (cavopulmonary or glenn) NEAR/3 (shunt* or procedure*) 16
#5 ("cavopulmonary connection" or TCPC) 57
#6 #1 or #2 or #3 or #4 or #5 1291
#7 MeSH descriptor: [Univentricular Heart] explode all trees 2
#8 MeSH descriptor: [Heart Defects, Congenital] explode all trees 2206
#9 (single NEAR/2 ventricle*) 245
#10 (cor NEAR/2 (monoventriculare or triloculare biabriatum or triloculare biatriorum or triloculare biatriorum or triloculare biatrium)) 0
#11 ((univentricular or monoventricular) NEAR/3 heart*) 42
#12 #7 or #8 or #9 or #10 or #11 2365
#13 #6 or #12 3451
#14 #13 with Cochrane Library publication date Between Jan 2015 and Dec 2020 1497

CDSR retrieved 40 records
CDSR protocols retrieved 5 records

Database of Abstracts of Reviews of Effects (DARE) (CRD): up to 2015/03
Health Technology Assessment (HTA) database (CRD): up to 2018/03
http://www.crd.york.ac.uk/CRDWeb/
Searched: 12.11.20
(Note: both resources are now archive only and are no longer added to)
1 MeSH DESCRIPTOR Fontan Procedure EXPLODE ALL TREES 2
2 (Fontan* or "hemi-fontan" or norwood) 44
3 MeSH DESCRIPTOR Heart Defects, Congenital 79
4 (univentricular or monoventricular) 4
5 #1 OR #2 OR #3 OR #4126
6 (#5) FROM 2015 TO 2020 2

DARE retrieved 0 hits
HTA retrieved 2 hits

INAHTA up to 2020/11/12
https://database.inahta.org/
Searched: 12.11.20
(("Fontan Procedure"[mhe]) OR (Fontan* or "hemi fontan" or Norwood or univentricular or monoventricular)) FROM 2015 TO 2021

Search retrieved 1 record

KSR Evidence: up to 2015/11/12
Searched: 12.11.20
1 Fontan* or "hemi-fontan" or norwood in Title 30 results
2 Fontan* or "hemi-fontan" or norwood in Abstract 49 results
3 ((univentricular or monoventricular) AND heart*) in All text 10 results
4 (single AND ventricle*) in All text 59 results

5 #1 or #2 or #3 or #4 in All text 105 results

Epistemonikos (https://www.epistemonikos.org/): up to 2020/11/12
Searched: 12.11.20
(title:(Fontan* OR "hemi-fontan" OR norwood OR univentricular OR monoventricular) OR abstract:(Fontan* OR "hemi-fontan" OR norwood OR univentricular OR monoventricular)) [Filters: protocol=no, classification=systematic-review, cochrane=missing, min_year=2015, max_year=2021]

Search retrieved 65 records

NHS Evidence: up to 2020/11/12
https://www.evidence.nhs.uk/
Searched 12.11.20
Limited to Guidelines, HTAs & SRs (2015-2020/11/12)

Keywords	Hits
Fontan* or "hemi fontan" or Norwood or univentricular or monoventricular	162
TOTAL	**162**

National Institute for Health and Care Excellence (NICE): up to 2020/11/11
https://www.nice.org.uk/
Searched 11.11.20

Limited to Guidelines

Keywords	Hits
Fontan or hemi-fontan or norwood	2
univentricular or monoventricular	2
Heart Defects	15
Total	**19**
Total without duplicates	**17**

Guidelines International Network (GIN) Library (Internet): up to 2020/11/11
http://www.g-i-n.net
Searched: 11.11.20

Search terms	Results
Fontan	0
Fontans	0
hemi-fontan	0
norwood	0
univentricular	1
monoventricular	0
Heart defects	5
Heart defect	5
Total	**11**

Total without duplicates	**6**

ECRI Guidelines (Internet): up to 2020/11/12
Searched 12.11.20
https://guidelines.ecri.org/

Keywords	**Hits**
Fontan	0
Fontans	3
hemi-fontan	0
norwood	0
univentricular	0
monoventricular	0
Heart defects	9
Heart defect	9
Total	**18**
Total after duplicates removed	**9**

TRIP Database: up to 2020/11/12
https://www.tripdatabase.com/
Searched 12.11.20

Limited to Guidelines from 2015

Keywords	**Hits**
Fontan or fontans or hemi-fontan or norwood or univentricular or monoventricular	95
Total	**95**

SDM Searches

Embase(Ovid): 1974-2020/12/07
Searched 9.12.20
(FP or Univentricular Heart) AND SDM (2015-C)
1 Fontan procedure/ or (Fontan$ or hemi-fontan$).ti,ab,ot,hw. (14650)
2 (norwood adj3 (anastomosis or conduit$ or circuit$ or connection$ or circulation or operation$ or procedure$ or palliation or surger$)).ti,ab,ot,hw. (2712)
3 (bidirectional adj3 (cavopulmonary or glenn) adj3 (shunt$ or procedure$)).ti,ab,ot,hw. (771)
4 ("cavopulmonary connection" or TCPC).ti,ab,ot. (1640)
5 or/1-4 (17562)
6 heart single ventricle/ or congenital heart malformation/ (35962)
7 (single adj2 ventricle$).ti,ab,ot,hw. (8120)
8 (cor adj2 (monoventriculare or triloculare biabriatum or triloculare biatriorum or triloculare biatriorum or triloculare biatrium)).ti,ab,ot,hw. (1)
9 ((univentricular or monoventricular) adj3 heart$).ti,ab,ot,hw. (1447)
10 or/6-9 (38062)

11 5 or 10 (50905)
12 *decision making/ or *patient decision making/ or *shared decision making/ (66933)
13 exp *decision support system/ (12577)
14 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (53368)
15 (decision$ adj2 aid$).ti,ab. (9010)
16 ((decision$ or choice$) adj3 (making$ or support$ or behaviour$ or behavior$)).ti,ab. (238949)
17 ((patient$ or consumer$) adj2 (involve$ or involving or participat$)).ti,ab. (99750)
18 ((patient-centred or patient centred or patient-centered or patient centered) adj2 care).ti,ab. (9242)
19 (person centred or person centered).ti,ab. (6838)
20 sdm.ti,ab. (3569)
21 or/12-20 (414647)
22 11 and 21 (629)
23 limit 22 to yr="2015 -Current" (365)

MEDLINE(Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946-2020/12/08
Searched 9.12.20
1 Fontan procedure/ or (Fontan$ or hemi-fontan$).ti,ab,ot,hw. (8818)
2 (norwood adj3 (anastomosis or conduit$ or circuit$ or connection$ or circulation or operation$ or procedure$ or palliation or surger$)).ti,ab,ot,hw. (1398)
3 (bidirectional adj3 (cavopulmonary or glenn) adj3 (shunt$ or procedure$)).ti,ab,ot,hw. (570)
4 ("cavopulmonary connection" or TCPC).ti,ab,ot. (1098)
5 or/1-4 (10437)
6 Univentricular Heart/ or Heart Defects, Congenital/ (53882)
7 (single adj2 ventricle$).ti,ab,ot,hw. (3641)
8 (cor adj2 (monoventriculare or triloculare biabriatum or triloculare biatriorum or triloculare biatriorum or triloculare biatrium)).ti,ab,ot,hw. (4)
9 ((univentricular or monoventricular) adj3 heart$).ti,ab,ot,hw. (1017)
10 or/6-9 (56075)
11 5 or 10 (62243)
12 exp Decision Making/ (205859)
13 exp decision support techniques/ (78165)
14 exp Decision Theory/ (12238)
15 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (38806)
16 (decision$ adj2 aid$).ti,ab. (6121)
17 ((decision$ or choice$) adj3 (making$ or support$ or behaviour$ or behavior$)).ti,ab. (175599)
18 ((patient$ or consumer$) adj2 (involve$ or involving or participat$)).ti,ab. (63556)
19 ((patient-centred or patient centred or patient-centered or patient centered) adj2 care).ti,ab. (6706)
20 (person centred or person centered).ti,ab. (5597)
21 sdm.ti,ab. (2761)
22 exp Informed Consent/ (41404)

23 (informed adj3 (consent* or agree* or assent*)).ti,ab. (39357)
24 or/12-23 (561675)
25 11 and 24 (866)
26 limit 25 to yr="2015 -Current" (344)

Cochrane Central Register of Controlled Trials (CENTRAL): up to 2020/12/Iss12
Searched: 9.12.20
#1 MeSH descriptor: [Fontan Procedure] explode all trees 59
#2 (Fontan* or "hemi-fontan") 1177
#3 (norwood) NEAR/3 (anastomosis or conduit* or circuit* or connection* or circulation or operation* or procedure* or palliation or surger*) 95
#4 (bidirectional or bi-directional) NEAR/3 (cavopulmonary or glenn) NEAR/3 (shunt* or procedure*) 16
#5 ("cavopulmonary connection" or TCPC) 57
#6 #1 or #2 or #3 or #4 or #5 1291
#7 MeSH descriptor: [Univentricular Heart] explode all trees 2
#8 MeSH descriptor: [Heart Defects, Congenital] explode all trees 2206
#9 (single NEAR/2 ventricle*) 245
#10 (cor NEAR/2 (monoventriculare or triloculare biabriatum or triloculare biatriorum or triloculare biatriorum or triloculare biatrium)) 0
#11 ((univentricular or monoventricular) NEAR/3 heart*) 42
#12 #7 or #8 or #9 or #10 or #11 2365
#13 #6 or #12 3451
#14 #13 with Cochrane Library publication date Between Jan 2015 and Dec 2020 1497
#15 MeSH descriptor: [Decision Making] explode all trees 3940
#16 MeSH descriptor: [Decision Support Techniques] explode all trees 2455
#17 MeSH descriptor: [Decision Theory] explode all trees 166
#18 ((share* or sharing* or inform*) NEAR/3 (decision* or deciding* or choice*)):ti,ab 4255
#19 (decision* NEAR/2 aid*):ti,ab 1631
#20 ((decision* or choice*) NEAR/3 (making* or support* or behaviour* or behavior*)):ti,ab 12489
#21 ((patient* or consumer*) NEAR/2 (involve* or involving or participat*)):ti,ab 15437
#22 ((patient-centred or patient centred or patient-centered or patient centered) NEAR/2 care):ti,ab 6236
#23 (person centred or person centered):ti,ab 1080
#24 sdm:ti,ab 401
#25 MeSH descriptor: [Informed Consent] explode all trees 725
#26 (informed NEAR/3 (consent* or agree* or assent*)):ti,ab 62609
#27 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 100550
#28 #14 and #27 90

CENTRAL retrieved 86