

Pros and Cons

Is Warfarin mandatory

for a patient with fenestrated Fontan operation?

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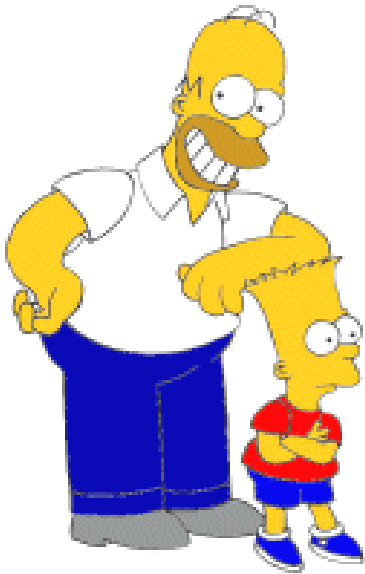
Information

5

3

extracardiac Fontan operation
fenestration (+)

(SaO₂) 88%

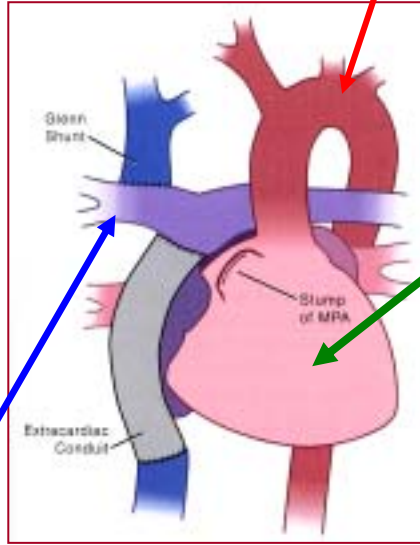


patent extracardiac Fontan pathway
no visible thrombus
still patent fenestration
(mean Doppler Pr Gr of 5mmHg)
good ventricular dimension and function
(according to visual inspection)
no atrioventricular and aortic regurgitation



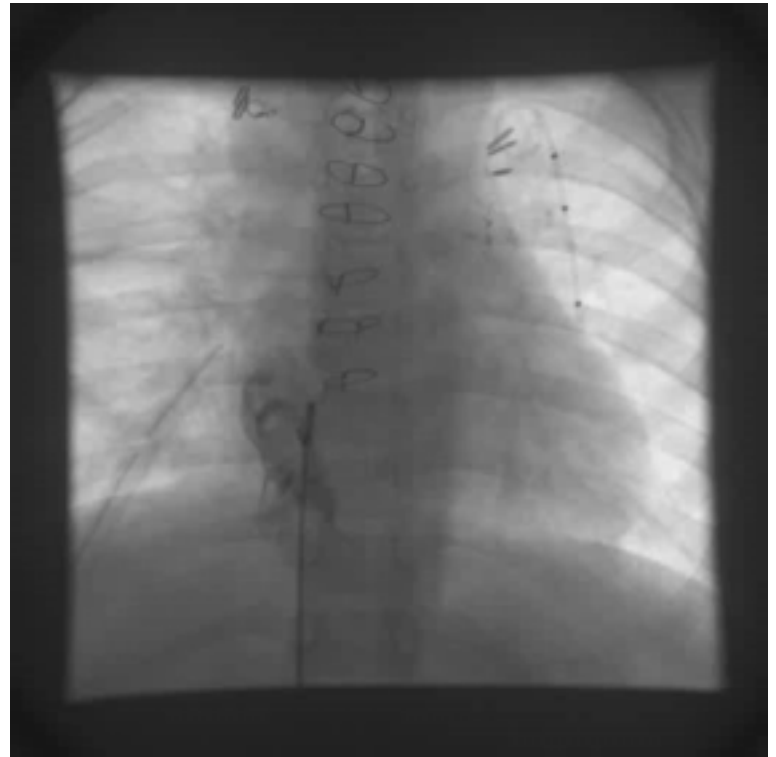


Systemic vascular resistance



Ventricular function

Pulmonary vascular resistance



Risk factors for Fontan Op. ; Proposed Incremental Risk Scale

Risk Factor	No Incremental Risk	Moderate Increase in Risk	High Risk
Age	<2 yr*	<1.5 yr	<1 yr
Mean PA pressure	<15 mm Hg	≥15 < 18 mm Hg	≥18 mm Hg
McGoon index†	>2.4	>1.8 < 2.4	<1.8
Pulmonary vascular resistance (PVR)	<2 Wood units	>2 < 3 Wood units	>3 Wood units
Transpulmonary gradient	<6 mm Hg	>6 < 12 mm Hg	>12 mm Hg
Ventricular end-diastolic pressure (VEDP)	<10 mm Hg	>10 < 14 mm Hg	>14 mm Hg
Ejection fraction	>60	45–60	<45
AV valve insufficiency	None or mild	Moderate	Severe
Heterotaxia	No heterotaxia	Polysplenia	Asplenia
History of PA banding	No PA banding	Yes	PA band associated with branch PA stenosis
Mayo Clinic index‡	<2	2–4	>4
Nakata index§	>250	250–200	<200
PA stenosis	None	Mild to moderate	Severe
Restrictive BVF	No restriction	Mild (<30 mm Hg)	Moderate to severe (>30 mm Hg)
Left AV valve	Normal	Stenosis	Atresia valve

AV = atrioventricular; BVF = bulboventricular foramen; PA = pulmonary artery.

*According to institutional preferences, this age may be variable. At the Hospital de Niños of Buenos Aires, the cutoff age between low and moderate risk is considered 4 years.

†McGoon index: $RPA \text{ (mm)} + LPA \text{ (mm)} / \text{descending aorta at the diaphragm (mm)}$.

‡Mayo Clinic index: $PVR \text{ (Wood units)} + VEDP \text{ (mm Hg)} / Qp \text{ (L/min/m}^2\text{)} + Qs \text{ (L/min/m}^2\text{)}$.

§Nakata index: $RPA + LPA \text{ (mm}^2\text{/m}^2\text{)}$.

Updated Version of the Optimal Criteria for Fontan Op (Tchervenkov and Tsang, 1999)

1. Normal sinus rhythm
2. Normal caval and pulmonary venous connections
3. *Normal PVR, with a mean PAP < 15-20 mm Hg*
4. No significant PA branch stenosis that would preclude surgical repair
5. PA-Aorta ratio > 0.75
6. Normal ventricular function
7. No systemic AVVR
8. Normal diastolic ventricular function
9. Optimal minimal age: uncertain, probably 2-4 Y
10. Unobstructed systemic circulation (no aortic arch obstruction or SAS)

Assumptions from informed data

1. Preoperative risk factor ?
2. Current status of preoperative risk factor
3. To close or not

PVR/PAP

Good CO. good ventricular function, normal lung
Pressure gradient through fenestration =5mmHg
transpulmonary pressure gradient
Mixed venous saturation 68% (AV difference 20%)
Pulmonary vein saturation 95%
Hemoglobin 15mg/dL
LVEDP <10mmHg

- Mean PAP <15mmHg
- PVR 1-2 wood unit

Consider cardiac
cath and closure
of fenestration

PROBLEMs associated with fenestration Fontan operation

Problems associated with Fontan operation
ventricular function
arrhythmia
thromboembolism

Problems associated with fenestration
decreased oxygen saturation
increase cardiac output
paradoxical embolism

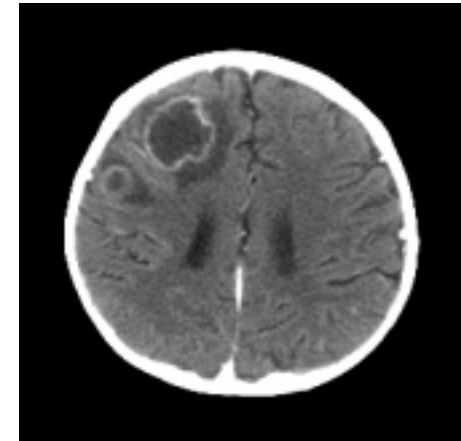
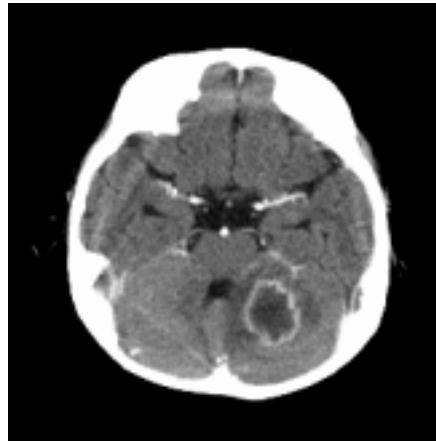


Nightmare
case 1

3 years old male presenting with abdominal pain and low cardiac output
10 days after fenestration Fontan operation
on warfarin (low INR)

REDO fenestration Extracardiac Fontan
d/t thrombus in Fontan pathway

Left arm weakness developed after 7days
Fever (+) headache (+)



Multiple brain abscess (Aspergillus(+)) treated with amphotericin B

Nightmare
case 2



10 years old male presenting with aphasia and hemiparesis
Fontan operation seven years ago
no medication, follow-up loss for several years
sick sinus syndrome on EKG



Permanent pacemaker and anticoagulation with warfarin

Predisposing risk factors of thrombosis after Fontan

Slow and nonpulsatile flow through the caval veins

Poorly contracting, enlarged, and thickened atrium

with or without arrhythmias

Small transpulmonary gradient that decreases flow within the tunnel

Low cardiac output with or without atrioventricular valve regurgitation

Obstructed conduit or a complex

Thromboembolism after Fontan operation

The frequency of thromboembolic events in patients with Fontan physiology : as high as 20% to 33%
by Rosenthal et al. 1995, Jahangiri et al. 1994, Balling, 2000 , etc

Prevalence of “Silent” Pulmonary Emboli in Adults After the Fontan Operation ; 5 of 30(17%)
Pulmonary emboli were not present in any patients (30%) taking warfarin
by Chetan Varma, et al. 2003

The incidence of venous thrombosis despite prophylactic oral warfarin,
: 7.4%. *by Jonas 1995*

Studies that had thromboembolic events as the primary outcome measure

<i>Author et al.</i>	<i>Patients in series (survivors)</i>	<i>No. (%) of thromboses</i>	<i>Stroke or arterial emboli: N (%)</i>
Rosenthal ⁶	70	11 (16)	3 (4)
Jahangiri ⁷	64 (57)	8 (14)	3 (5)
du Plessis ¹⁹	645	NA	17 (3)
Day ²⁰	68	NA	6 (9)
Matthews ²¹	25 (16)	NA	3 (19)
Fletcher ²²	64	6 (9)	NA
Dobell ²³	128	4 (3)	NA
Danielson ²⁴	449	18 (4)	NA
Kaulitz ²⁵	72	5 (6)	NA

NA, Not assessed.

Studies in which thromboembolic events were not the primary outcome measure, but that gave some details of thromboembolic events

<i>Author et al.</i>	<i>Patients in series (N)</i>	<i>No. (%) of thromboses</i>	<i>Stroke or arterial emboli: N (%)</i>
Driscoll ¹	352	3 (1)	4 (1)
Fontan ²⁶	100	3 (3)	NA
Prenger ³	22	2 (7)	NA
Laks ²⁷	45	1 (2)	NA
Annechino ²⁸	38	1 (3)	NA
Myers ²⁹	34	1 (3)	NA
Mair ³⁰	65	1 (2)	NA
Cromme-Dijkhuis ³¹	37	2 (5)	NA
Cromme-Dijkhuis ⁴⁵	66	3 (5)	NA

NA, Not assessed.

INTRACARDIAC THROMBUS FORMATION AFTER THE FONTAN OPERATION

Gunter Balling, et al. *J Thorac Cardiovasc Surg* 2000;119:745-52

Echocardiographic findings

	<i>No thrombus</i>	<i>Thrombus formation</i>	<i>P values</i>
No. of patients (n = 52)	35	17	
Spontaneous contrast	23	11	.99
SV function (normal/fair/reduced/poor)	17/6/6/6	9/3/4/1	.7
AV valve regurgitation (no/mild/moderate/severe)	7/23/4/0	5/12/0/1	.4

SV, Single ventricle; AV, atrioventricular.

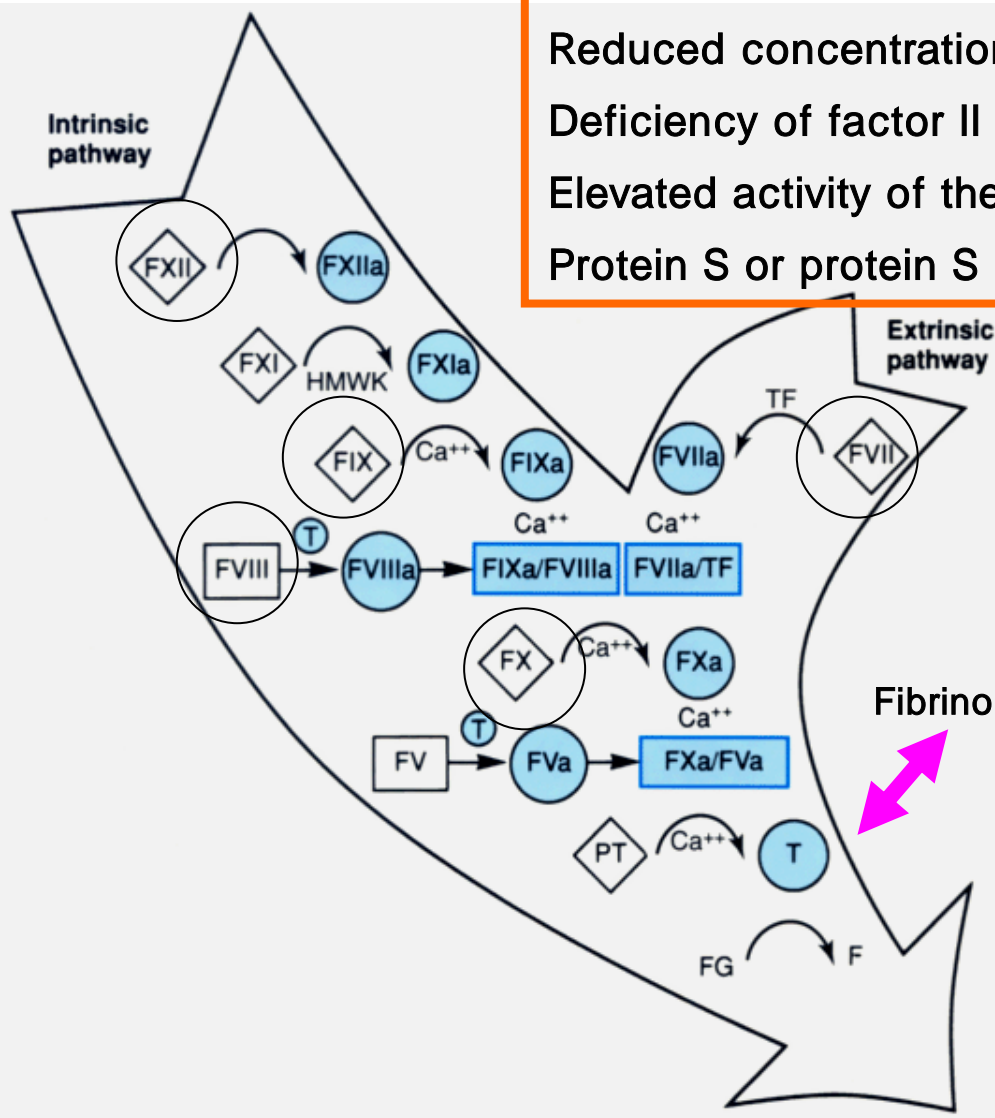
Reports with TEE to assess occurrence rate of intracardiac thrombi in patients after Fontan operations

<i>Authors</i>	<i>No. of patients</i>	<i>No. of patients with thrombus</i>	<i>95% CI</i>
Stümper and colleagues, 1991 ¹⁶	18	3 (17%)	3.6–41.4
Fyfe and colleagues, 1991 ¹⁷	30	6 (20%)	7.7–38.6
Feltes and colleagues 1994, ¹⁸	9	4 (44%)	13.7–78.8
Shirai and colleagues, 1998 ¹⁹	16	3 (19%)	4.1–45.7
Presented study	52	17 (33%)	20.3–41.1

CI, Confidence interval.

Coagulation abnormality after fontan operation

Reduced concentration of antithrombin III,
Deficiency of factor II and factor X, VII, IX, plasminogen
Elevated activity of the von Willebrand factor
Protein S or protein S deficiency



Fibrinolytic system – protein C, S antithrombin III

Mean Factor Levels Between Control Subjects and Patients Immediately Before the Fontan Operation^a

Variable	Controls (n = 37)	Pre-Fontan (n = 38)	p Value ^b	No. (%) Pre-Fontan Patients Below Normal Range
Fibrinogen (mg/L)	271 ± 76	263 ± 97	0.74	0 (0)
Factor II (%)	95 ± 11	76 ± 11	<0.001	28 (74)
Factor V (%)	113 ± 18	78 ± 18	<0.001	28 (74)
Factor VII (%)	88 ± 18	49 ± 15	<0.001	17 (45)
Factor VIII (%)	90 ± 24	75 ± 23	<0.01	1 (3)
Factor IX (%)	72 ± 13	63 ± 20	0.03	9 (24)
Factor X (%)	94 ± 11	79 ± 15	<0.001	13 (34)
Antithrombin III (%)	105 ± 16	81 ± 15	<0.001	16 (42)
Plasminogen (%)	100 ± 14	89 ± 21	<0.01	1 (3)
Protein C (%)	102 ± 20	66 ± 16	<0.001	21 (55)
Protein S (%)	89 ± 14	79 ± 22	0.03	10 (29)

^a Data presented as mean ± SD, n = 37 for controls except fibrinogen (n = 24), n = 38 for pre-Fontan patients except protein S (n = 35). ^bBased on two-sample Student *t* tests.

Kirsten et.al. Ann Thorac Surg 2002;73:1770-7)

Comparison Between Pre- and Postoperative Factor Levels^a

Variable	Preoperative (mean ± SD)	Postoperative (mean ± SD)	p Value ^b
Fibrinogen (mg/L)	263 ± 97	299 ± 117	0.11
Factor II (%)	76 ± 11	56 ± 16	<0.001
Factor V (%)	78 ± 18	67 ± 27	<0.01
Factor VII (%)	49 ± 15	25 ± 9	<0.001
Factor VIII (%)	75 ± 23	122 ± 42	<0.001
Factor IX (%)	63 ± 20	68 ± 22	0.24
Factor X (%)	79 ± 15	53 ± 16	<0.001
Antithrombin III (%)	81 ± 15	58 ± 18	<0.001
Plasminogen (%)	89 ± 21	54 ± 24	<0.001
Protein C (%)	65 ± 14	47 ± 18	<0.001
Protein S (%)	78 ± 21	43 ± 21	<0.001

^a Comparisons were based on 37 patients with both pre- and post-Fontan measurements, except protein S (n = 34). ^b Based on paired t tests.

Kirsten, et.al. *Ann Thorac Surg* 2002;73:1770–7)

Profile of coagulation factors and protein levels for group 1 patients (n = 14) measured both before and after the Fontan operation

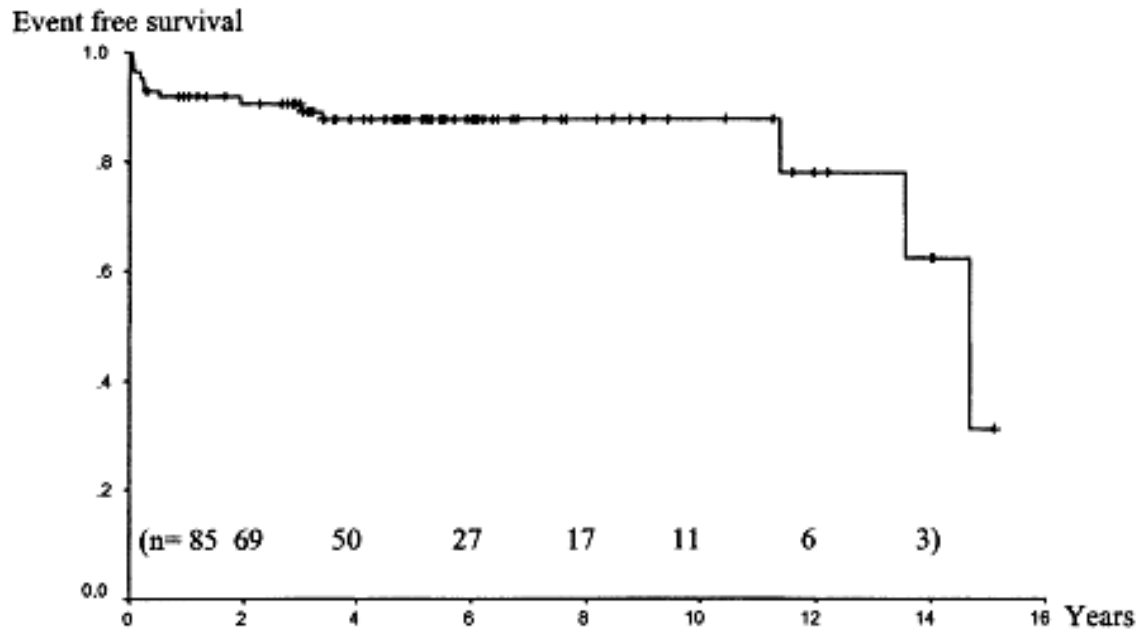
	Before Fontan (mean ± SD)	After Fontan (mean ± SD)	P value
Factor V (%)	97.6 ± 26.0	86.6 ± 27.8	.22
Factor VII (%)	57.7 ± 20.4	40.8 ± 19.5	.002
Factor VIII (%)	134.1 ± 40.8	210.3 ± 55.2	<.001
Factor X (%)	58.6 ± 13.3	72.6 ± 14.2	<.001
Antithrombin III (%)	92.0 ± 14.6	74.5 ± 14.1	<.001
F1+2 (nmol/L)	0.60 ± 0.24	1.54 ± 0.63	<.001
Protein C (%)	80.1 ± 9.8	65.6 ± 11.7	.004
Protein S (%)	58.2 ± 13.9	48.1 ± 19.1	.02

F1+2, Prothrombin fragment.

Jahangiri, et al. *J Thorac Cardiovasc Surg* 2000;120:778-82)

Thromboembolic Complications After Fontan Procedures: Comparison of Different Therapeutic Approaches

Seipelt RG, et al. *Ann Thorac Surg* 2002;74:556–62



Freedom from thromboembolism in 85 patients with modified Fontan operation. Data in parentheses indicate numbers of patients at risk.

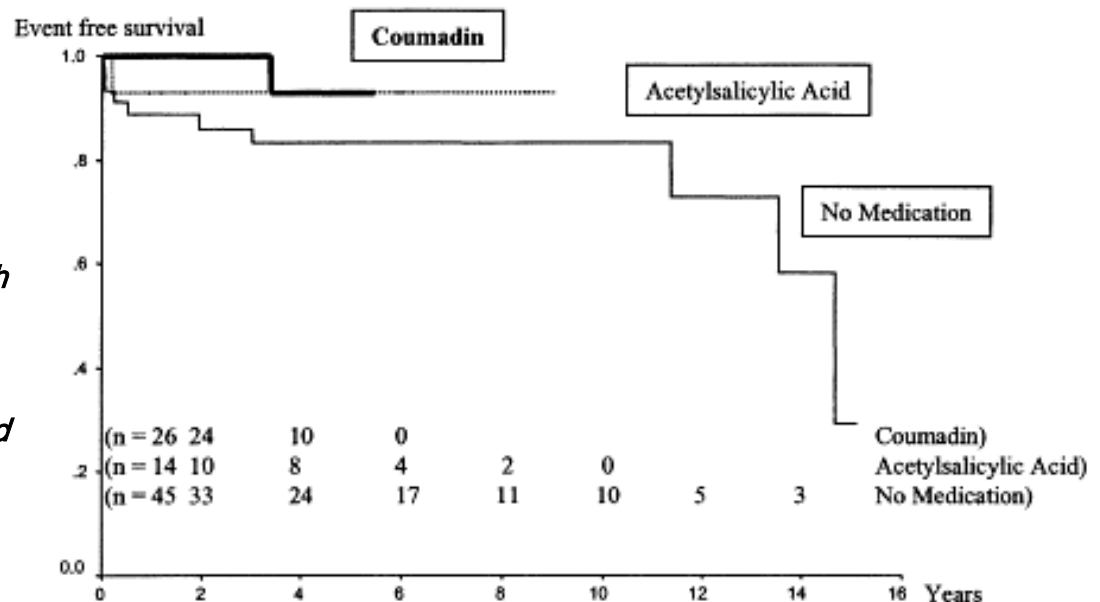
Comparison of the Initial Anticoagulant Regimen With Regard to Thromboembolic Events and Possible Risk Factors

	Group I (n = 45)	Group II (n = 14)	Group III (n = 26)	p Value
Thromboembolic events ^a	10 (22%)	1 (7%)	1 (4%)	0.072
Mean follow-up (y) ^b	5.3 ± 4.5	4.4 ± 2.8	3.6 ± 1.3	0.134
Type of operation				0.001
TCPC	21	6	26	
Modified Fontan	24	8	0	
Atrial arrhythmias	13 (28%)	2 (14%)	3 (12%)	0.272
Impaired LV function	2 (4%)	1 (7%)	1 (4%)	0.916
Age at operation (y)	8.8 ± 9.4	5.8 ± 7.4	5.9 ± 7.1	0.287

^a The number of thromboembolic events of group I to III do not match with the total number because of exclusion of one thromboembolic event occurring 2 months after withdrawal of Coumadin. $p = 0.036$ between group I and group III. ^b $p = 0.018$ between group I and group III.

group I without medication (n 45),
group II with acetylsalicylic acid (n 14)
group III with Coumadin (n 26).

Kaplan-Meier plot for the three initial prophylactic approaches (n 85): patients with Coumadin therapy, with acetylsalicylic acid, and without anticoagulant prophylaxis. Data in parentheses indicate numbers of patients at risk. Log-rank test between Coumadin and no medication: $p = 0.031$ after 3 years and $p = 0.12$ after 5 years. Log-rank test between Coumadin and acetylsalicylic acid: $p = 0.17$ after 3 years and $p = 0.67$ after 5 years.



Increased platelet reactivity and significant changes in coagulation markers after cavopulmonary connection (*Heart* 2001;85:61–6)

Platelet markers

	<i>TCPC (n=10)</i>	<i>BDG (n=8)</i>	<i>All patients (n=18)</i>	<i>Controls (n=33)</i>
Collagen agg (%PPP)	72 (61–79)*	78 (54–89)	73 (61–84)†	61 (47–69)
ADP agg (%PPP)	68 (53–74)	76 (51–88)	69 (53–77)*	56 (40–66)
Platelets × 10 ⁹ /litre	220 (165–255)	204 (190–233)*	207 (182–253)†	256 (218–299)
TxB ₂ (ng/ml)	265 (149–487)	418 (197–604)	295 (197–562)	303 (233–376)

Data are given as median (interquartile range).

*p < 0.05; †p < 0.01 *v* controls.

ADP agg, ADP induced platelet aggregation; BDG, bidirectional Glenn anastomosis; collagen agg, collagen induced platelet aggregation; %PPP, percentage of platelet poor plasma; TCPC, total cavopulmonary anastomosis; TxB₂, thromboxane B₂.

Coagulation markers

	<i>TCPC (n=8)</i>	<i>BDG (n=8)</i>	<i>All patients (n=16)</i>	<i>Controls (n=33)</i>
Prot C:c (U/ml)	0.8 (0.6–0.8)*	0.7 (0.6–1.0)	0.8 (0.6–0.8)†	1.0 (0.8–1.1)
Prot S Ag (U/ml)	0.8 (0.7–0.9)	0.7 (0.6–0.8)*	0.8 (0.6–0.8)†	0.9 (0.8–0.9)
AT-III (U/ml)	0.9 (0.8–0.9)*	0.8 (0.7–0.8)*	0.8 (0.8–0.9)†	1.0 (0.9–1.0)
F ₁₊₂ (nmol/l)	0.7 (0.5–0.8)*	0.8 (0.5–1.1)*	0.7 (0.5–0.9)†	1.3 (1.1–1.8)
II, VII, X (rel U)	0.6 (0.4–0.7)*	0.6 (0.5–0.7)*	0.6 (0.5–0.7)†	0.8 (0.8–0.9)
FVII:c (U/ml)	0.7 (0.5–0.9)*	0.7 (0.6–0.8)*	0.7 (0.6–0.9)†	1.0 (0.8–1.1)

Data are given as median (interquartile range).

*p < 0.05; †p < 0.01 *v* controls.

AT-III, antithrombin III; BDG, bidirectional Glenn anastomosis; F₁₊₂, prothrombin fragment 1 +2; FVII:c, factor VII clot activity; Prot C:c, protein C clot activity; Prot S Ag, protein S antigen; TCPC, total cavopulmonary anastomosis; II, VII, X, coagulation factor II, VII, X activity.

How does one decide on the most appropriate therapy?

Anticoagulation

Many reports
about
thromboembolism

Prophylaxis for thromboembolism

Non-randomized
study needed

Serious bleeding in at least 0.5% per patient
year

Streif W, et al. Analysis of warfarin therapy
in pediatric patients: a prospective cohort study of 319
patients. Blood 1999;94:3007-14.

Bleeding

Tracheal calcification

Hair loss

Reduced bone density

Compliance

Cost

Clinical recommendations and treatment guidelines should be based on the best available evidence

What is the most appropriate therapy of oral anticoagulation for a child with the high risk of thromboembolism ?

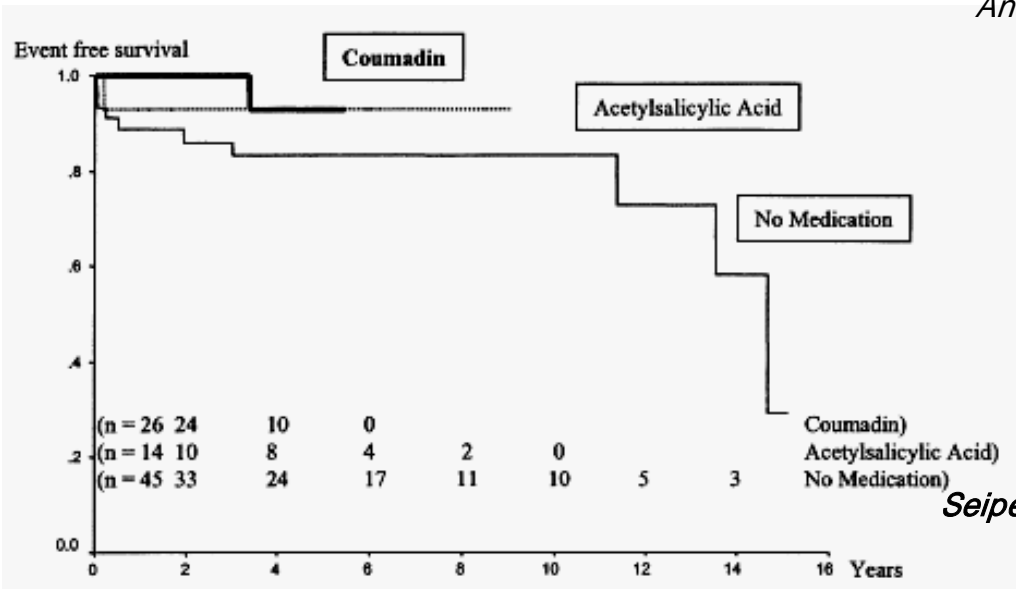
Risk-Benefit Assessment of Oral Anticoagulant Therapy in Patients With Coronary Artery Disease: Meta-Analysis of 44 Trials Involving 24 115 Patients*

Anticoagulation Intensity	No. of Trials (No. of Patients)	Ischemic Events Odds Ratio (95% CI)	P	Major Bleeding Odds Ratio	P
High vs control	16 (n=10 056)	0.57 (0.51–0.63)	0.0001	39	0.00001
Moderate vs control	4 (n=1365)	0.85 (0.80–1.34)	>0.10	35	0.00001
Moderate to high vs ASA	7 (n=3457)	0.88 (0.63–1.24)	>0.10	14	0.00001
Moderate + ASA vs ASA	3 (n=480)	0.44 (0.23–0.83)	0.01	16	>0.01
Low + ASA vs ASA	3 (n=8435)	0.91 (0.79–1.06)	>0.01	5	0.05

*Constellation of death, myocardial infarction, or stroke events per 1000 patients.

Adapted from Anand and Yusuf, 1999.²²⁵

Anand SS, Yusuf S. *JAMA*. 1999;282:2058–2067.



Seipelt RG, et al. *Ann Thorac Surg* 2002;74:556–62

Recommendation

1) The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

Primary prophylaxis for Fontan surgery in children

For children after Fontan surgery, we suggest therapy with **aspirin (5 mg/kg/d)** or **therapeutic heparin followed by VKAs to achieve a target INR of 2.5 (INR range, 2 to 3)**

Remark: The optimal duration of therapy is unknown. Whether patients with fenestrations require more intensive therapy until fenestration closure is unknown.

2) My recommendation

- 1) Therapeutic heparin followed by warfarin to achieve a target INR of 2.5 (INR range, 2 to 3) or
- 2) Warfarin to achieve a target INR of 2.0 (INR range, 1.5 to 2.5) plus low dose aspirin (5mg/kg/day)

Remark:

The optimal duration of therapy ; VKAs at least for one year, or more

Until the fenestration is closed

Restrict competitive strenuous exercise

Helmet and other safety guards

Self monitoring of INR available in the near future

