Which Fontan Patient Needs Anticoagulation

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Risk Stratified Approach
The Fontan Thrombophilia – Fact Check

Thrombosis prevalence - how hard are you looking?
50 Year old TA + NGA
1/5 missed on Transthoracic Echo
52 consecutive patients with Fontan procedure
- Asymptomatic
- Had TEE + other

17 of 52 had Thrombus = 33%
111 patients

Monagle et al. Journal of the American College of Cardiology, Volume 58, Issue 6, 2 August 2011

22% had clot cumulatively
45 Year Tricuspid Atresia
AP Fontan

1 in 5 had silent PE

J Am Coll Cardiol
2003;41:2252–8
Stroke Risk

- **12% prevalence** when looking proactively on MRI scanning
- **Clinical stroke burden – 5.8%**

Thrombosis associated with significant risk to the patient
What do we know about longitudinal characteristics of thrombophilia
Some patients likely have a longer “honeymoon” than others
Can we Predict the Late Hazard
Biomarkers & risk factors for thrombosis

- Factor VIII/vWF
- Protein C
- Protein S
- Antithrombin
- D-dimer
- Inflammation
- Factor V<sub>Leiden</sub>
- Prothrombin G20210A
- Thrombin generation potential
- Fibrinogen
- Factor XI

- Obesity
- Cigarette smoking
- Estrogen Containing OCPs
- Orthopedic surgery
- Major pelvic/abdominal surgery
- PAI-1
- Homocysteine
- Lipoprotein(a)
- C4b binding protein
- Antiphospholipid antibodies
- Male Sex
Can we predict when this “honeymoon” comes to an end – D dimers

D-DIMER

- An elevated **D-dimer** after stopping anticoagulation strongly correlates with recurrence in adults with unprovoked VTE.

**D-DIMER**

<table>
<thead>
<tr>
<th>Duration of follow-up (years)</th>
<th>Cumulative incidence of recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>10%</td>
</tr>
<tr>
<td>4</td>
<td>30%</td>
</tr>
<tr>
<td>6</td>
<td>60%</td>
</tr>
</tbody>
</table>

- HemosIL D-dimer
  - > 230 ng mL\(^{-1}\)
  - ≤ 230 ng mL\(^{-1}\)

**Blood coagulation abnormalities and the usefulness of D-dimer level for detecting intracardiac thrombosis in adult Fontan patients**

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**ABSTRACT**

Background: Coagulation abnormalities are associated with a high incidence of intracardiac thrombus (ICT) and systemic thromboembolism in Fontan patients. The biomarker for detecting ICT is currently unknown.

Methods: We retrospectively investigated the underlying coagulation abnormalities and useful biomarkers to screen ICT in adult Fontan patients. We measured various biomarkers of blood coagulation, fibrinolysis, and platelet activity in 122 Fontan patients (Fontan group; median age 37 (27-50) years) and compared them to those in 30 patients with atrial septal defect (ASD group; 31 (24-40) years).

Results: Regardless of whether the patient had ICT, the Fontan group showed significantly lower levels of anti-thrombin III, thrombomodulin, and D-dimer, lower protein C and protein S activities, and significantly higher levels of thrombin-antithrombin complex and s-fibrinogen inhibitor complex than the ASD group. Among various biomarkers, D-dimer level measured by latex immunomassay was significantly higher in the patients with ICT (thrombin group, n = 23) than in the patients without ICT (non-thrombus group, n = 100). Receiver operating characteristic curve analysis revealed that the appropriate cut-off D-dimer level for ICT was 1.8 ng/mL, with a negative predictive value of 95%.

Cut-Off 1.8 ug/ml

Takeuchi D et al, Int J Cardiol. 2016 Dec 1;224:139-144
Can we predict when this “honeymoon” comes to an end – Factor 8


Elevated FVIII activity and risk of Thrombotic Complications

FVIII activity tended to correlate with central venous pressure


Adjusted $R^2 = 0.74$, $P = .003$

$y = 12.7 \times \text{SVCp} - 28$
What are potential Treatment Approaches?
Option #1: Simply commit every patient with a Fontan to indefinite therapeutic anticoagulation.

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Problems with this approach

• Therapeutic anticoagulation: 2 – 3% yearly risk of major bleeding

• Poorly managed Warfarin may increase thrombosis risk.

• Need more data on NOAC’s

• Lifestyle limitations that come with anticoagulation
Option 2: Risk Stratified approach based on the published literature – Anticoagulate those with a thrombophilic profile
What I do in our Fontan Clinic

• Family and/or personal history of thrombosis
• Review old imaging studies for thrombosis
• Risk Factors for the specific Fontan circulation of the patient
  • Stents
  • Cyanosis
  • Prior clot
  • Stasis
  • Blind ending PA pouch
  • Mitral stenosis in HLHS
What I do in our Fontan Clinic

• Screen for
  • aspirin resistance
  • AT 3
  • D-Dimer
  • Signs of active inflammation [hs CRP]
  • Exclude common thrombophilias [vWF], Protein C and S

• High Risk Patients
  • Anticoagulation [warfarin or DOAC]
Effect of High TTR - > 80% WARFARIN

Only One Thrombotic Event During 52.92 Patient Years

Figure 3: Patient Years Spent Within, Above, and Below The Therapeutic Range During Clinic Management

- 52.92 total patient years of clinic therapy
- 44.67 Years
- 5 Years
- 3.25 Years

Time Within
Time Above
Time Below

NOTE Registry

Apixaban Trial - PHN

Rivaroxaban Safety Trial
Conclusions

• Fontan is a highly thrombophilic state
• There is a bimodal hazard for thrombosis
• Thrombosis is associated with poor outcomes
• There are identified risk factors for thrombosis
• Options of treatment are an empiric approach to formal anticoagulation
• Or a tailored approach once thrombophilia becomes evident
• More data is needed – join us in gathering it!
27th International Symposium on Adult Congenital Heart Disease
Presented by the Heart Institute at Cincinnati Children's & Children's National Health System, Washington, D.C.

Upcoming Deadlines

- Early registration: Thursday, June 1
- Abstract submissions: Friday, June 9

To submit abstracts and to register, please visit www.cincinnatichildrens.org/ACHDsymposium.

September 14-16, 2017
The Westin Cincinnati
Downtown Cincinnati, OH

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