New indications: Is heart failure a viable new potential indication for anti-thrombosis therapy

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Occult Thromboembolism in HF

- Autopsy data
  - 50% incidence of thromboemboli in HF without anticoagulation\(^1\)
  - 104 IDC patients with 18% vs. 0% thromboemboli without vs. with anticoagulation\(^2\)
  - 37% incidence in IDC\(^3\)
  - IDC and no cardiac thrombus 20% incidence of unrecognized cerebral damage associated with cognitive defects as well\(^4\)

\(^1\)Spodick DH, Littmann D. *Am J Cardiol* 1958;1:610-623.
Virchow’s Triad
Predisposing Conditions for Thromboembolism

- Hypercoagulable state

  - Increased procoagulant factors

  - Venous stasis

  - Increased markers of endothelial damage and inflammation

  - Endothelial damage/dysfunction

  - Abnormal blood flow

  - Immobility

  - Low cardiac output

  - Low cardiac output

  - Abnormalities in the vessel wall

  - Abnormalities in blood constituents

Thrombotic events
Heart failure as a pro-thrombotic state

**Hematological**

- Platelets (↑Beta-thromboglobulin, ↑P-selectin, ↑PECAM-1 and ↑Osteonectin)
- Coagulation cascade (↑TAT and ↑FPA)
- Fibrynolitic pathway (↑D-dimer, ↑PAI-1 and ↑TNF)
- Activated Protein C (APC)

**Endothelial dysfunction** (↓NO, ↑Endothelin, ↑RAS)
Rationale for Antithrombotic Therapy in Chronic HF

- Prevention of VTE
- Prevention of systemic embolism
- Prevention of stroke
- Prevention of coronary thrombosis
- Retarding progression of HF
**HELAS**

Aspirin vs. warfarin (IHD); warfarin vs. placebo (nIHD)

Small, NS

<table>
<thead>
<tr>
<th>Population</th>
<th>Primary Endpoint</th>
<th>N</th>
<th>Length of Follow-Up</th>
<th>Primary Endpoint Event Rate per 100 patient years:</th>
<th>RR (95% CI), P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease cohort: Heart failure (NYHA II-IV, LVEF &lt;35%) and history of MI</td>
<td>Non-fatal stroke, peripheral or pulmonary embolism, recurrent MI, rehospitalization, exacerbation of heart failure or all-cause death</td>
<td>197</td>
<td>18.5-21.9 months</td>
<td>Placebo or Control: IHD/ASA: 14.9 Warf: 15.7 DCM/P: 14.8 Warf: 8.9</td>
<td>Efficacy differences not evaluated due to small numbers</td>
</tr>
</tbody>
</table>
### WASH

Aspirin 300 mg/d vs. warfarin (INR 2.0-3.0) vs. no therapy. PROBE Small, NS

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</thead>
<tbody>
<tr>
<td>Clinical HF, LVEF ≤35% (or large LVDD) (≤7% with afib)</td>
<td>Death, non-fatal MI, non-fatal stroke</td>
<td>279</td>
<td>27 ± 1 months (627 patient-years)</td>
<td>No therapy</td>
<td>ASA: No therapy vs. ASA or warfarin: 1.09 (0.63-1.89)</td>
</tr>
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<td>ASA vs. no ASA: 1.16 (0.74-1.85)</td>
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<td>Warfarin vs. no warfarin: 0.88 (0.54-1.43)</td>
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<td>ASA vs. warfarin: 1.21 (0.7-2.09)</td>
</tr>
</tbody>
</table>
## WATCH

Aspirin 162 mg/d vs. clopidogrel 75 mg/d vs. warfarin (INR 2.0-3.5)

ASA and clopidogrel double-blind, warfarin open-label

Large, NS

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<tr>
<th>Population</th>
<th>Primary Endpoint</th>
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<th>Primary Endpoint Event Rate</th>
<th>RR (95% CI), P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA II-IV, LVEF ≤35%, sinus rhythm</td>
<td>All-cause mortality, non-fatal MI, and non-fatal stroke</td>
<td>1587</td>
<td>21 months (median), 3073 patient-years of exposure</td>
<td>ASA: 20.7%</td>
<td>Warfarin vs. ASA: 0.98 (0.86-1.12, P=0.77)</td>
</tr>
<tr>
<td></td>
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<td>Clopidogrel 21.6%</td>
<td>Clopidogrel vs. ASA: 1.08 (0.83-1.40, P=0.57)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Warfarin 19.6%</td>
<td>Warfarin vs. clopidogrel: 0.89 (0.68-1.16, P=0.39)</td>
</tr>
</tbody>
</table>
**WARCEF**

**Warfarin (INR 2.0-3.5) vs. Aspirin 325 mg/d**

**Double-blind, double dummy**

NS

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<thead>
<tr>
<th>Population</th>
<th>Primary Endpoint</th>
<th>N</th>
<th>Length of Follow-Up</th>
<th>Primary Endpoint Event Rate per 100 patient-years</th>
<th>RR (95% CI), P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class I-IV</td>
<td>Ischemic stroke, intracerebral hemorrhage, or death from any cause</td>
<td>2305</td>
<td>3.5 ± 1.8 years</td>
<td>Aspirin 7.93, Warfarin 7.47</td>
<td>Warfarin vs. ASA 0.93 (0.79-1.10), P=0.4</td>
</tr>
<tr>
<td>LVEF ≤35%; sinus rhythm</td>
<td></td>
<td></td>
<td>8225 patient years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Post hoc, SOLVD

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary Endpoint</th>
<th>N</th>
<th>Length of Follow-Up</th>
<th>Primary Endpoint Event Rate</th>
<th>RR (95% CI), P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet n=3017 vs.</td>
<td>All-cause mortality</td>
<td>6512</td>
<td>41.4 months</td>
<td>No antiplatelet: 997 (28.5%)</td>
<td>Antiplatelet vs. no antiplatelet: 0.82 (0.73-0.92, P=0.0006) adjusted</td>
</tr>
<tr>
<td>No antiplatelet n=3495</td>
<td></td>
<td></td>
<td></td>
<td>Antiplatelet: 548 (18.2%)</td>
<td></td>
</tr>
<tr>
<td>Warfarin n=861 vs.</td>
<td>All-cause mortality</td>
<td>6513</td>
<td>41.4 months</td>
<td>No warfarin: 1334 (23.6%)</td>
<td>Warfarin vs. no warfarin: 0.76 (0.65-0.89, P=0.0006) adjusted</td>
</tr>
<tr>
<td>No warfarin n=5652</td>
<td></td>
<td></td>
<td></td>
<td>Warfarin: 210 (24.4%)</td>
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</tbody>
</table>
Anticoagulation recommended for heart failure patients:
- With chronic or paroxysmal AF or flutter (IA, warfarin)
- With prior systemic or pulmonary embolic events (IIA, warfarin)
- With recent large anterior MI or LV thrombi (IIA, short term warfarin)
- At risk for venous thromboembolism in hospitalized patients with risk factors (IA, LMWH or UFH)

Anticoagulation possibly beneficial (but unproven)
- In other patients with ventricular thrombi (IIB)

Anticoagulation not recommended
- In other patients with non-ischemic CM (IB)

Aspirin for prevention of vascular events
- Recommended at 75 – 162 mg QD in CAD patients (IC, warfarin and possibly clopidogrel alternatives, IIB)
- Not recommended in non-ischemic CM (IB)
Unanswered questions

- Although anticoagulation is effective in preventing VTE, does it prevent heart failure events that may be caused, precipitated, or aggravated by thrombotic mechanisms and lead to further worsening of heart failure?

- Do newer agents such as dabigatran, apixaban, or rivaroxaban offer advantages over warfarin that might translate into differences in clinical outcomes?

- Are all these drugs safe in patients with heart failure considering the prevalence of renal impairment in this population and the lack of a reversal agent?
Control Arm Annual Mortality in Chronic HF trials

Adapted from Skali H et al. Circulation 2006
AHFS vs. ACS event rate

CV Mortality or HF Hospitalisation

PLATO:

CV Death + MI + Stroke :

11%

Peto-Peto Wilcoxon Test: \( P = 0.55 \)

TLV 30 mg

PLACEBO

EVEREST

1 year rate > 50%

Peto-Peto Wilcoxon Test: \( P = 0.55 \)

<table>
<thead>
<tr>
<th>Months In Study</th>
<th>TLV 30 mg</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2072</td>
<td>2061</td>
</tr>
<tr>
<td>3</td>
<td>1562</td>
<td>1532</td>
</tr>
<tr>
<td>6</td>
<td>1146</td>
<td>1137</td>
</tr>
<tr>
<td>9</td>
<td>834</td>
<td>819</td>
</tr>
<tr>
<td>12</td>
<td>607</td>
<td>597</td>
</tr>
<tr>
<td>15</td>
<td>396</td>
<td>385</td>
</tr>
<tr>
<td>18</td>
<td>271</td>
<td>255</td>
</tr>
<tr>
<td>21</td>
<td>149</td>
<td>143</td>
</tr>
<tr>
<td>24</td>
<td>58</td>
<td>55</td>
</tr>
</tbody>
</table>

Proportion Without Event
Where are the unmet needs?

Maggioni PA et al. 2011
AHFS: An Acute EVENT
The ACS model

Pre-admission
“Golden Hours”
22%

In-Patient
4-27%

Post-Discharge
1-year Mortality 25%
1-year Re admissions 25%

Zannad et al EJHF 2008
Target patient population: HHF Post discharge

- Event rates are highest
- Increased risk of thromboembolism
- Greatest unmet need in terms of event reduction.
- No proven therapies
- Common troponin release suggesting that pathophysiology may be amenable to antithrombotic intervention

BUT...

- May be at particularly high risk of bleeding
- Presents with more comorbidities
- Common significant renal impairment may limit the testing of renally eliminated antithrombotic agents (i.e. dabigatran, rivaroxaban, and apixaban)
Study Design: Overview

Hospitalization

Acute Care

≥36 hrs

≤7 days

First Dose

(Randomization)

Treatment Period
Anticoagulant X vs. Placebo (+SOC)

24 Weeks

Follow-up Visit

Index Event
HFNEF rather than HFPEF

- Event rates are similar
- Including both may facilitate enrollment
- However, in HFPEF
  - Hospitalizations commonly related to comorbidities and diseases of the elderly
  - Multiple pathophysiological processes, which may confound the ability to detect potential efficacy of a drug.
  - Atrial fibrillation more common in HFPEF
  - Bleeding risk is likely high given the higher proportion of elderly patients.
Ischemic rather than Non-Ischemic Etiology.

- ischemic heart failure
  - Overall event rates are generally higher
  - Higher thrombotic risk

- Non-ischemic patients with dilated cardiomyopathy are at high risk of intracardiac thrombi
Enhancing Population Risk.

- Evidence of cardiac dilatation (increase the underlying risk of thrombotic events)
- Recent hospitalization (within 6 or 12 months)
- Elevated BNP in the absence of a hospitalization,
- Patients shortly after discharge from a heart failure (or cardiovascular) hospitalization
Study Drug, the case for new OAC.

- Global underuse of warfarin for VTE prophylaxis
- Newer agents have practical advantages over warfarin
  - standardized dosing
  - elimination of INR testing
- Dosing strategy should account for the risk related to renal impairment or in the frail elderly
- Short half-life may increase thrombotic risk if dose missed
- Thrombin may have detrimental direct cellular effects.
- A direct thrombin and/or factor Xa inhibitor may interrupt such adverse pathophysiologic processes, as demonstrated experimentally
Placebo Versus Active Control, Background Therapy.

- An adequately powered, placebo controlled trial of antithrombotic therapy in heart failure has not been conducted.
- No universally accepted standard of care anticoagulant therapy in HF and sinus rhythm
- Sufficient clinical equipoise exists to justify a placebo controlled trial in this setting.
- Use of aspirin in patients with HF, controversial
- Aspirin mandatory treatment of patients with coronary artery disease
- A placebo-controlled study on top of background standard therapy (including aspirin in CAD) would be the most optimal approach.
Single Versus Multiple Doses.

- Dosing issues studied in phase II?
- No reliable pharmacodynamic markers to predict efficacy and safety. Adaptive design not helpful
- Potential for bleeding not widely studied in HF.
  - higher risk due to chronic low cardiac output, hepatic congestion, or poor hepatic perfusion,
- Renal impairment exposes to longer half-lives of renally eliminated agents.
- FDA recommends that more than 1 dose should be studied in phase III to adequately assess the balance between efficacy and safety.
Primary Endpoint.

- Composite of all-cause mortality, nonfatal MI, and nonfatal stroke.

- Include some measure of hospitalization (all-cause, cardiovascular, or heart failure) as a component of the primary endpoint?
  - a meaningful endpoint, burdensome to patients
  - economically relevant
  - predicts subsequent mortality.

- How could it be influenced by thrombosis?
  - Coronary micro-thrombi = Progresssion of HF
  - Many PE present as Worsening HF
Embolic Rates in CHF and AF

Rates per 100 patient-years

<table>
<thead>
<tr>
<th>Trial</th>
<th>All Emboli</th>
<th>Stroke</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-HeFT*</td>
<td>2.3</td>
<td>1.8</td>
<td>14%</td>
</tr>
<tr>
<td>SOLVD*</td>
<td>1.9</td>
<td>1.3</td>
<td>12%</td>
</tr>
<tr>
<td>AF trials (all pts)</td>
<td>5.0</td>
<td>4.5</td>
<td>5%</td>
</tr>
<tr>
<td>AF trials (high-risk)</td>
<td></td>
<td></td>
<td>6 – 17%/y</td>
</tr>
</tbody>
</table>

* Includes AF patients (some anticoagulated)

PE: Undiagnosed and Common Cause of Death in Hospitalized Patients

- PE may account for up to 10% of inhospital mortality
- 75% of fatal PE *not* associated with recent surgery
- 10% of symptomatic PE cause death within 1 h
  - 1-week survival following PE only 71%
- In most cases of fatal PE in hospitalized patients, PE *not* diagnosed before autopsy
  - A number of ‘HF’ admissions may be related to PE
Primary Endpoint. Combined arterial (MI, stroke) and venous outcomes?

- One way to reduce the estimated sample size
- Both arterial and venous thromboses are hypothesized to contribute to the pathogenesis of heart failure and the burden of the disease.
- Pulmonary embolism may be misdiagnosed as HF worsening.
- Venous and pulmonary thromboembolism are risk factors for worse outcome in heart failure
- Could both components contribute equally?
Ancillary Studies.

- Biomarker studies may be critical to understand why and how antithrombotic therapy works (or does not work).
- Measurement of thrombin generation curves in total blood or platelet-rich plasma.
- Such data would help to determine the global hypercoagulable state in this population.
- At this time, these *in vitro* tests remain limited to small populations and need to be implemented in prospective large studies.
Optimal HF thrombosis trial with a NOAC

- Post discharge, low EF, IHD with high BNP
- Placebo controlled, on top of aspirin up to 160 mg
- 2 Doses (or one single dose decided from ACS, VTE or AF trials and HF subgroup analyses)
- Primary endpoint: Composite of all-cause mortality, nonfatal MI, and nonfatal stroke.
- Secondary endpoint: HF hospitalization, VTE, PE