Antiplatelet and anticoagulant drugs in patients with heart failure

Gerasimos Filippatos, MD
President Elect
Heart Failure Association
Disclosures

• None related to this subject

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Pooled Results of 3 Early Trials of Anticoagulants in HF

Thromboembolism

Prevalence

• There is a wide variation in prevalence estimates for clinical events (stroke, pulmonary, and peripheral thromboembolism) ranging from 3% to 50%

Incidence

• In incidence estimates, ranging from 1.5 to 3.5 per 100 patient years
Ischemic Stroke in Chronic Heart Failure

J Card Fail 2007

<table>
<thead>
<tr>
<th>Years</th>
<th>Ref</th>
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<td>&gt;1-2</td>
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<td>Dunkman I</td>
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<td>Dunkman II</td>
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<td>&gt;3-4</td>
<td>Andersson</td>
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<td>McMurray</td>
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<td>&gt;4-5</td>
<td>Setaro</td>
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<td>Remme</td>
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</table>

Stroke rate/1,000

18
Clinical Investigations

Silent Strokes in Patients With Heart Failure

THOMAS SIACHOS, MD, ADRIAN VANBAKEL, MD, DAVID S. FELDMAN, MD, WALTER UBER, PharmD, KIT N. SIMPSON, DrPH, AND NAVEEN L. PEREIRA, MD FACC

Charleston, South Carolina

ABSTRACT

Background: The prevalence of asymptomatic strokes detected by brain imaging in a large cohort of patients with congestive heart failure (CHF) and reduced ejection fraction (EF) is unknown.

Methods and Results: The present study was conducted to assess the prevalence of cerebrovascular accidents (CVA) diagnosed by routine brain imaging in neurologically asymptomatic patients with CHF who were being evaluated for heart transplantation. A comprehensive review of clinical data in a consecutive case series of 168 adult patients being evaluated was conducted. Patients at a high risk of having cerebral infarction (i.e., history of transient ischemic attack or stroke, paroxysmal or chronic atrial fibrillation, intracardiac thrombi, and prosthetic valves) were excluded. Brain imaging was performed as part of a routine pre-heart transplant evaluation protocol. The prevalence of silent ischemic strokes was 34%. Multiple logistic regression analysis revealed a 2.3 (95% CI 1.05–5.03) times increased risk of silent strokes if a patient was African American. Traditional risk factors such as age, gender, hypertension, and diabetes mellitus were not predictive of CVA in this population.

Conclusion: Patients with CHF and a left ventricular EF less than 20% being evaluated for heart transplantation have a high prevalence of ischemic CVA. The role of anticoagulation in this high-risk group of patients should be further explored.

Key Words: Congestive heart failure, Stroke, Heart transplantation.
In HF patients The Rate of PE Is High And Complicates the Course of the Disease

- >9% of HF patients have PE diagnosed clinically
- 24% of patients dying of heart disease have a PE diagnosed at autopsy
- Acute PE complicates AHF, increasing the length of hospital stay and the chance of death or rehospitalization at 3 months

Darze et al., Chest 2007;
Pulido et al., Chest 2006;129:1282-1287
Bleeding Risk

• Petitti et al, in a retrospective study, concluded that the RR for major hemorrhage in patients with treated HF was 1.4 compared with patients without HF, after controlling for age and sex.
Antithrombotic therapy in HF patients

• Treatment of hospitalized patients with Heart Failure. When, whom, how long?
  ▪ Hospitalized Patients with Heart Failure in the ward?
  ▪ AHF patients in the ICCU
• Heart Failure patients on Atrial Fibrillation
• Heart Failure Patients on Sinus Rhythm?
Practice guidelines

• ACCP
  – LDUH* or LMWH recommended in general medical patients with clinical risk factors for VTE (including cancer, bed rest, HF, and severe lung disease) (Grade 1A)

• International Consensus Statement
  – LMWH recommended for hospitalized patients with chronic respiratory disease or HF (Grade A)

* LDUH: UFH 5,000 U SC BID or TID
## Guideline implementation

### ADHERE registry

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 62,018)</th>
<th>Academic (n = 16,546)</th>
<th>Nonacademic (n = 45,472)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LMWH</strong></td>
<td>21</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td><strong>SC UFH</strong></td>
<td>10</td>
<td>19</td>
<td>7</td>
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<tr>
<td><strong>Warfarin</strong></td>
<td>27</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td><strong>IV UFH</strong></td>
<td>10</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td><strong>No anticoagulant reported</strong></td>
<td>32</td>
<td>23</td>
<td>35</td>
</tr>
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</table>
Adjudicated Symptomatic Venous Thromboembolism or Death Related to Venous Thromboembolism during the Treatment Period. NEJM 2011

![Graph showing patients at risk for events over time for Apixaban and Enoxaparin.](image-url)
Antithrombotic therapy in HF patients

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• Heart Failure Patients on Sinus Rhythm?
### Recommendations

The $\text{CHA}_2\text{DS}_2$-$\text{VASC}$ and $\text{HAS-BLED}$ scores (Tables 17 and 18) are recommended to determine the likely risk–benefit (thrombo-embolism prevention vs. risk of bleeding) of oral anticoagulation.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>The $\text{CHA}_2\text{DS}_2$-$\text{VASC}$ and $\text{HAS-BLED}$ scores (Tables 17 and 18) are recommended to determine the likely risk–benefit (thrombo-embolism prevention vs. risk of bleeding) of oral anticoagulation.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>An oral anticoagulant is recommended for all patients with paroxysmal or persistent/permanent AF and a $\text{CHA}_2\text{DS}_2$-$\text{VASC}$ score $\geq 1$, without contraindications, and irrespective of whether a rate- or rhythm-management strategy is used (including after successful cardioversion).</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>
**Atrial Fibrillation and Heart Failure in Cardiology Practice: Reciprocal Impact and Combined Management From the Perspective of Atrial Fibrillation: Results of the Euro Heart Survey on Atrial Fibrillation**
Robby Nieuwlaat, Luc W. Eurlings, John G. Cleland, Stuart M. Cobbe, Panos E. Vardas, Alessandro Capucci, José L. López-Sendón, Joan G. Meeder, Yigal M. Pinto, and Harry J.G.M. Crijns
*J. Am. Coll. Cardiol.* 2009;53;1690-1698

<table>
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<tr>
<th>Antithrombotic drugs</th>
<th>No HF (n = 3,482)</th>
<th>HF (n = 1,816)</th>
<th>p</th>
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<tr>
<td>Oral anticoagulation</td>
<td>63</td>
<td>68</td>
<td>0.001</td>
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<tr>
<td>Antiplatelet drug</td>
<td>32</td>
<td>33</td>
<td>0.155</td>
</tr>
<tr>
<td>Heparin</td>
<td>5</td>
<td>7</td>
<td>0.002</td>
</tr>
<tr>
<td>None</td>
<td>10</td>
<td>6</td>
<td>&lt;0.001</td>
</tr>
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</table>
Do we need a new anticoagulant in heart failure?

- **Warfarin/Vitamin K Antagonists**
  - Slow onset and offset of effect
  - Unpredictable anticoagulation
  - Protein binding
  - Drug interactions
  - Require frequent coagulation lab test monitoring just to keep patient in therapeutic range
Point of action of novel oral anticoagulants in the coagulation cascade.

Steffel J, Braunwald E Eur Heart J 2011;eurheartj.ehr052
<table>
<thead>
<tr>
<th>Study</th>
<th>Anticoagulant</th>
<th>% HF</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PETRO</td>
<td>Dabigatran vs. warfarin</td>
<td>29.3%</td>
<td>Not known subgroup analysis</td>
</tr>
<tr>
<td>RE-LY</td>
<td>Dabigatran vs. warfarin</td>
<td>32%</td>
<td>No difference</td>
</tr>
<tr>
<td>Phase II</td>
<td>AZD0837</td>
<td>38%</td>
<td>Not subgroup analysis. Not powered to look at stroke and systemic embolic events</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>Rivaroxaban vs. warfarin</td>
<td>62%</td>
<td>No differences across pre-specified subgroups have been reported.</td>
</tr>
<tr>
<td>AVERROES</td>
<td>Apixaban vs. aspirin</td>
<td>39%</td>
<td>No difference</td>
</tr>
<tr>
<td>Phase II</td>
<td>Tecarfarin (ATI-5923)</td>
<td>9.1%</td>
<td>Small group</td>
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<tr>
<td>ARISTOTLE</td>
<td>Apixaban vs. warfarin</td>
<td>35.5%</td>
<td>No difference</td>
</tr>
</tbody>
</table>

Filippatos et al 2013
For the subgroup of symptomatic heart failure no significant interaction was seen with the treatment effect of dabigatran (at either dose).

For the subgroup of symptomatic HF or \( \text{EF} \leq 40\% \) no significant interaction was seen with the treatment effect of apixaban (\( P:0.50 \) for the primary outcome and \( p:0.30 \) for the major bleeding)
Pharmacokinetics and pharmacodynamics of rivaroxaban and its effect on biomarkers of hypercoagulability in patients with chronic heart failure

Mihai Gheorghiade, MD, An Thyssen, PhD, Robert Zolynas, DVM, MBA, Venkatesh K. Nadar, MD, Barry H. Greenberg, MD, Mandeep Mehra, MD, Xiang Sun, PhD, Hong Tian, PhD, Alexei N. Plotnikov, MD, and Paul Burton, MD

• In this trial they evaluated the PK and PD of rivaroxaban in patients with AHF and CHF receiving single and multiple once-daily doses of rivaroxaban 10 mg.
• They hypothesized that it would also reduce biomarkers of hypercoagulability in patients with HF. The effect of rivaroxaban on circulating levels of the hypercoagulability biomarkers DD, F1.2 and TAT was examined

J Heart Lung Transplant 2011;30:218–26
Rivaroxaban has similar PK/PD in patients with either acute or chronic HF. In patients with HF, rivaroxaban clearance appeared to be decreased compared with healthy young subjects, resulting in an approximately 1.8-fold increased AUC. This may partly be because patients with HF frequently have reduced liver and kidney function.
Gaps in Evidence

- Safety and efficacy of new agents in heart failure? Especially Hospitalized patients

- Real life epidemiological data (AHF vs CHF, HFPEF vs systolic HF, advanced HF, etc)

- Where to use the new agents
Antithrombotic therapy in HF patients

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- Heart Failure Patients on Sinus Rhythm?
Warfarin therapy in Heart Failure
Based on clinical practice guidelines

ESC 2008
- HF with AF
- HF with previous thrombo-embolism
- HF with intracardiac thrombus

ACC/AHA
- HF with AF
- HF with previous thrombo-embolism
- HF with mobile LV thrombus
- MI with mural thrombus (with or without HF)

HFSA
- HF with AF
- HF with previous thrombo-embolism (stroke, TIA, PE)
- HF with LV thrombus depending on the characteristics of the thrombus, such as its size, mobility, and degree of calcification
- MI with thrombus or large recent anterior MI with low EF (with or without HF)
HF and SR

Reasons for anti-coagulation

• Reduction of hypercoagulation
• Reduction of thrombembolic events
• Reduction of sudden cardiac death
• Reduction of total mortality
Thromboprophylaxis in Heart Failure on Sinus Rhythm

Data derived from retrospective analyses of clinical trials

• CONSENSUS suggested that long-term anticoagulation with warfarin was associated with lower mortality in heart failure
  • N Engl J Med 1987

• A retrospective analysis of the SOLVD trials showed a reduction in all cause mortality, death or hospitalization for heart failure associated with warfarin use
  • J Am Coll Cardiol 1998

• In the SAVE trial warfarin use was associated with an 81% reduction in stroke risk

• V-HeFT and SCD-HeFT were not positive

Fundamental & Clinical Pharmacology 2009
The American Journal of the Medical Sciences 2010
Retrospective studies of antiplatelet therapy

• In the SAVE study patients on aspirin had a 56% lower incidence of stroke following MI
• In the SOLVD trial aspirin use was associated with a lower incidence of thromboembolic events in women (53% RRR) but not in men
• By contrast, a lack of benefit of aspirin use was found in the V-HeFT I and II

The American Journal of the Medical Sciences 2010
Impact of Anticoagulation on Outcome in HF patients: Randomized Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Primary Endpoint</th>
<th>Primary Result %</th>
<th>Hospitalization %</th>
<th>Bleeding %</th>
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<tbody>
<tr>
<td>WASH</td>
<td>WvAvP</td>
<td>279</td>
<td>D/MI/CVA</td>
<td>26/32/26</td>
<td>47/64/48</td>
<td>4/1/0</td>
</tr>
<tr>
<td>WATCH</td>
<td>WvAvC</td>
<td>1587</td>
<td>D/MI/CVA</td>
<td>19.8/20.5/21</td>
<td>16.1/22.2/18.3</td>
<td>5.6/3.6/2.5</td>
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<tr>
<td>HELAS</td>
<td>WvA DCM</td>
<td>197</td>
<td>D/MI/CVA/Hosp/PE</td>
<td>15.7/14.9/8.9/14.8</td>
<td>2.4/3.2/4.4/5.9</td>
<td>4.8/0/4.4/0</td>
</tr>
<tr>
<td></td>
<td>WvP IHD</td>
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<tr>
<td>WARCEF</td>
<td>WvA</td>
<td>~2860</td>
<td>D/CVA</td>
<td></td>
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Prospective Studies - Problems...

HELAS-Study: ASS vs Warfarin & Placebo vs Warfarin
- stopped early due to recruitment problems

WASH-Study: ASS vs Warfarin vs no Therapy
- pilot study for WATCH (too small)
- **aspirin**: increase in hospitalisation due to CHF

WATCH-Study: ASS vs Warfarin vs Clopidogrel
- stopped early due to recruitment problems
- no difference between groups for primary endpoint
- **aspirin**: increase in hospitalisation due to CHF
- **warfarin**: increase of severe bleeding complications
WARCEF
Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction Trial

• PI’s: Shunichi Homma & John L.P. Thompson (Columbia Univ.)
• Hypothesis: Warfarin is superior to aspirin for preventing death & stroke in CHF patients with low LVEF
• Population: planned 3400 pts NYHA I-IV, LVEF ≤35% & SR
• Intervention: Aspirin 325mg or warfarin (INR 2.5-3.0), double-blind
• 1. EP: Death or ischemic stroke or intracerebral hemorrhage
• Patients & FU: n=2305, recruited Oct ’02 – Jan ’10, end of follow-up: Jan ’11 (mean 3.5 yrs)
• Sponsor: NINDS (NIH)
Primary Outcome:
Death, ischemic stroke or intercerebral hemorrhage

INR in Warfarin group:
INR 2.0–3.5 for 62.6% if time INR <2.0 for 27.1% of time

Rates of the primary outcome
W: 7.47 per 100 pat-yrs
A: 7.93 per 100 pat-yrs
HR 0.93 (0.79–1.10)
P = 0.40

Figure 1. Cumulative Incidence of the Primary Outcome.
The primary outcome was the time to the first event in the composite endpoint of ischemic stroke, intracerebral hemorrhage, or death from any cause.
Conclusions in WARCEF

- No overall difference for primary outcome
- Suggestive benefit of warfarin for primary outcome at 4 years and beyond
- Warfarin reduces ischemic stroke risk throughout follow-up
- More major hemorrhage with warfarin, but intracerebral and intracranial hemorrhage similar
- No difference for the Main Secondary Outcome (Primary Outcome + MI + HF hospitalisation)
Thrombo-embolism and antithrombotic therapy for heart failure in sinus rhythm. A Joint Consensus Document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis

Gregory Y.H. Lip¹, Piotr Ponikowski², Felicita Andreotti³, Stefan D. Anker⁴, Gerasimos Filippatos⁵, Shunichi Homma⁶, Joao Morais⁷, Patrick Pullicino⁸, Lars H. Rasmussen⁹, Francisco Marin¹⁰, and Deirdre A. Lane¹
Consensus statements (1)

- In HF, thromboembolic complications contribute to mortality and morbidity.
- Associated comorbidities such as AF, should be proactively looked for.
  - In patients with AF, oral anticoagulation is recommended.
  - The CHA$_2$DS$_2$-VASc and HAS-BLED scores should be used to determine the likely risk-benefit ratio of oral anticoagulation.
Consensus statements (2)

• If anticoagulation is used, the combination of an oral anticoagulant with an anti-platelet agent is not recommended in patients with chronic (> 12 months after an acute event) coronary or other arterial disease, because of a high risk of serious bleeding and the lack of clear benefit.

• In the absence of a specific indication, such as documented coronary artery disease, aspirin should not be initiated.

• Given no overall benefit of warfarin on rates of death and stroke, with an increase in major bleeding – despite the potential for a reduction in ischaemic stroke – there is currently no compelling reason to routinely use warfarin for all HF patients in sinus rhythm.
Consensus statements (3)

- Anticoagulation may potentially be considered by some clinicians in the following HF patient groups:
  - HFrEF with previous thromboembolism (stroke, TIA, venous thromboembolism)
  - newly diagnosed intracardiac thrombus
  - right heart failure with pulmonary hypertension
  ...but evidence is limited and more research is needed to ascertain the long-term risk-benefit ratio

- Registry data, to estimate the risk of stroke among contemporary HF patients and to identify relevant risk factors, may prove useful.
How to implement anti-coagulation according to the guidelines

„The best physician for a patient with HF would be one with excellent training, extensive experience, and superb judgment with regard to all aspects of the disease. He or she would not necessarily follow guidelines slavishly.”

J.N. Cohn, Circ Heart Fail 2008;1:87-88