Rheumatic Valve-Associated AF: Selecting the Best Anticoagulant Strategy

Thursday | October 27, 2022 | 12:00pm – 1:00pm ET

Presenter: Geoffrey Barnes, MD, MSc (Webinar Co-Chair)

Panelists: Arthur L. Allen, PharmD, CACP (Webinar Co-Chair)
Stuart J. Connolly, MD
Deborah Kwon, MD
Presenters

Arthur Allen, PharmD, CACP
Anticoagulation Program Manager
VA Salt Lake City Health Care System

Geoffrey Barnes, MD, MSc
Associate Professor of Medicine
University of Michigan School of Medicine

Stuart Connolly, MD
Professor emeritus, Department of Medicine
McMaster University
Principal Investigator
Population Health Research Institute (PHRI)

Deborah Kwon, MD
Director of Cardiac MRI
Cleveland Clinic
Disclosures & Notification of Support

Acknowledgement of Financial Commercial Support:

The speakers have the following relevant financial relationships with commercial interests:

**Arthur Allen**  
AstraZeneca Pharmaceuticals | BMS-Pfizer | Janssen Pharmaceuticals: Speakers Bureau, Scientific/Medical Advisory Board Member

**Geoffrey Barnes**  
Acelis Connected Health | Boston-Scientific | BMS-Pfizer | Janssen

**Stuart Connolly**  
Bayer | BMS-Pfizer | Daiichi Sankyo Company | Javelin Ventures
"Causes" of Atrial Fibrillation

High Income Countries
- Hypertensive Disease
- Congestive heart failure
- Valvular disease (aortic stenosis)
- Obstructive sleep apnea

Low & Middle Income Countries
- Valvular disease
  - Rheumatic heart disease
    - MS, MR, and TR – 70%
    - MS and MR – 52%
    - MS only – 29%
    - MR only – 16%

References:
- NEJM 1982;306:1018-1022
- Am J Cardiol 1996;77:96-98
- Lancet 2016;387:1335-1346
Rheumatic Valve Disease

- Acute rheumatic carditis
  - Pericarditis
  - Myocarditis
  - Valvulitis
    - Mitral & aortic valve regurgitation
    - 10% of cases have "severe" valvulitis

- Chronic valve disease
  - Almost always involved MV
    - Mitral stenosis most common
  - Detected age 20-50
    - Women > men

- Etiology
  - Group A streptococcus pharyngeal infection
  - Usually age 5-15 years

Lancet 2016;387:1335-1346
Eur Heart J 2015;36:1115-1122a
All studies of DOAC & AFib excluded rheumatic valve disease and/or moderate-severe MS
Prior RCTs in AF: DOAC > VKA
  - Similar or better stroke prevention
  - Less bleeding

RCTs of DOAC vs. VKA → excluded rheumatic heart disease

AF patients with vs. without rheumatic heart disease
  - Younger
  - Female > male
  - Advanced valvular disease

<50% of pts with Rheum-AF are prescribed VKA
  - Only 1/3 achieve therapeutic INR

INVICTUS TRIAL - Rationale

NEJM 2022;387:978-988
Patients with RHD-AF with one of:
- Mitral Stenosis (valve area <2cm²)
- CHA₂DS₂-VASc score ≥2
- LA Appendage clot on imaging

1:1

Rivaroxaban 20mg od (n=2275)
(15 mg od if CrCl 15-49 ml/min)

VKA (n=2256)
(INR 2-3)
Primary Outcome
• Stroke/systemic embolism

Additional Primary Outcomes (protocol amendment)
• MI
• Death from vascular cause

Primary Safety Outcome
• ISTH major bleeding

All outcomes independently adjudicated

Statistical Design
• Non-inferiority study
• Margin at HR 1.186
• 80% power with 4500 patients
• Plan to continue until 1079 primary outcome (composite) events
INVICTUS TRIAL – Countries Participating

138 centers in 24 countries
## INVICTUS TRIAL – BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n=2275)</th>
<th>VKA (n=2256)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>50.7</td>
<td>50.3</td>
</tr>
<tr>
<td>Female sex</td>
<td>1648 (72.4)</td>
<td>1626 (72.1)</td>
</tr>
<tr>
<td>Mitral valve stenosis</td>
<td>1927 (85.5)</td>
<td>1903 (85.2)</td>
</tr>
<tr>
<td>CHF</td>
<td>879 (38.6)</td>
<td>866 (38.4)</td>
</tr>
<tr>
<td>HTN</td>
<td>522 (22.9)</td>
<td>535 (23.7)</td>
</tr>
<tr>
<td>DM</td>
<td>158 (6.9)</td>
<td>132 (5.9)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>248 (10.9)</td>
<td>257 (11.4)</td>
</tr>
<tr>
<td>CAD</td>
<td>32 (1.4)</td>
<td>20 (0.9)</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc Score 0-1</td>
<td>978 (43)</td>
<td>993 (44)</td>
</tr>
</tbody>
</table>

### Notes:
- **NEJM 2022;387:978-988**
- This table summarizes baseline characteristics for the INVICTUS trial comparing Rivaroxaban (n=2275) and VKA (n=2256). The data shows comparisons across various demographic and condition categories, including age, sex distribution, valve stenosis, heart failure (CHF), hypertension (HTN), diabetes (DM), prior stroke, coronary artery disease (CAD), and the CHA₂DS₂-VASc Score.
## INVICTUS TRIAL – ANTICOAG MANAGEMENT

<table>
<thead>
<tr>
<th>Year of Visit</th>
<th>Rivaroxaban</th>
<th>VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>88.7</td>
<td>98</td>
</tr>
<tr>
<td>Year 2</td>
<td>84.4</td>
<td>97.7</td>
</tr>
<tr>
<td>Year 3</td>
<td>81.2</td>
<td>97.1</td>
</tr>
<tr>
<td>Year 4</td>
<td>79</td>
<td>96.4</td>
</tr>
</tbody>
</table>

Permanent discontinuation:
- Riva 23% (1/3 for valve surg)
- VKA 6%

<table>
<thead>
<tr>
<th>Year of Visit</th>
<th>INRs between 2-3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>33.2</td>
</tr>
<tr>
<td>Year 1</td>
<td>59.0</td>
</tr>
<tr>
<td>Year 2</td>
<td>65.3</td>
</tr>
<tr>
<td>Year 3</td>
<td>65.1</td>
</tr>
<tr>
<td>Year 4</td>
<td>64.1</td>
</tr>
</tbody>
</table>

NEJM 2022;387:978-988
INVICTUS TRIAL – PRIMARY OUTCOME

Stroke, Systemic Embolism, MI, Death from Vascular/Unknown Cause

Proportional hazards assumption not met

Hazard ratio, 1.25 (95% CI, 1.10–1.41)

NEJM 2022;387:978-988
INVICTUS TRIAL – SECONDARY OUTCOMES

Ischemic Stroke

- Rivaroxaban
- VKA

Hazard ratio, 1.24 (95% CI, 0.92–1.68)

Death

- Rivaroxaban
- VKA

Hazard ratio, 1.23 (95% CI, 1.09–1.40)

NEJM 2022;387:978-988
## INVICTUS TRIAL – SAFETY OUTCOMES

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban N=2265</th>
<th>VKA N=2251</th>
<th>HR 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>0.7 (40)</td>
<td>0.8 (56)</td>
<td>0.76 (0.51-1.15)</td>
<td>0.18</td>
</tr>
<tr>
<td>- Life-threatening</td>
<td>0.4 (22)</td>
<td>0.5 (31)</td>
<td>0.77 (0.44-1.32)</td>
<td>0.31</td>
</tr>
<tr>
<td>- Intracranial</td>
<td>0.1 (8)</td>
<td>0.2 (14)</td>
<td>0.63 (0.26-1.50)</td>
<td>0.27</td>
</tr>
<tr>
<td>- Fatal</td>
<td>0.1 (4)</td>
<td>0.2 (15)</td>
<td>0.29 (0.10-0.88)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
• In RHD-AF, VKA reduced ischemic stroke and mortality without increase in bleeding as compared to rivaroxaban

• VKAs should be standard of care for RHD-AF

• Mortality benefit of VKA in RHD requires further study
Questions for Dr. Connolly

• What was your motivation for conducting this study?

• How did you select sites for enrollment?
  • Why not include any Canadian, American, or European sites?

• How should we interpret primary outcome results given that “proportional hazards assumption was not met”?

• How do these results impact your practice in Canada?
  • How should we apply them to our practice in USA?
Dr. Kwon:
• What are features of “rheumatic” mitral stenosis on echo?
• How often do these echo findings represent clinically-significant RHD?
• How do you apply findings from INVICTUS to your practice in Ohio?
Questions?
Thank You to Our Presenters!

Arthur Allen, PharmD, CACP
Anticoagulation Program Manager
VA Salt Lake City Health Care System

Geoffrey Barnes, MD, MSc
Associate Professor of Medicine
University of Michigan School of Medicine

Stuart Connolly, MD
Professor emeritus, Department of Medicine
McMaster University
Principal Investigator
Population Health Research Institute (PHRI)

Deborah Kwon, MD
Director of Cardiac MRI
Cleveland Clinic
**Newly Updated Rapid Resource**

Direct Oral Anticoagulant (DOAC) Drug-Drug Interaction Guidance

Resource updates include a new algorithm on how to find and utilize info on a drug/drug interaction!
Abstract Submissions Now Open!
Abstracts Due December 5, 2022

17th National Conference on Anticoagulation Therapy
April 1-3, 2023
San Francisco, CA

Register by November 30th for discounted early bird rate!

acforum.org/2023
Awards & Scholarships

➢ Abstract Research Award
➢ IDEA Initiative Scholarship

Awards include:
• Complimentary registration to National Conference
• $1,000 Travel Stipend

Applications due November 1, 2022

Visit our conference website at: acforum.org/2023
This webinar is brought to you, in part, by the support of the following companies:

AstraZeneca  Janssen  Bristol Myers Squibb  Pfizer  ABIOMED  Acelis Connected Health  Boston Scientific  Coag-Sense  werfen  acforum.org