Cardiology Update: Atrial Fibrillation, Stroke, Cognitive Decline

T. Jared Bunch, FACC, FHRS

Professor of Medicine
Clinical Cardiac Electrophysiology
University of Utah Health Sciences Center
Disclosures

• Boehringer-Ingelheim – Institutional Grant – Cognitive AF trial
• Boston Scientific – Institutional Grant - PLUG MRI trial
• Altathera – Institutional Grant – Sotalol Economics analysis

• No unlabeled or unapproved use discussed
Projected Prevalence of AFib in U.S.

Impact of Olmsted County Incidence Data

Projected number of persons with AF (millions)

Year


5.1 5.9 6.7 7.7 8.9 10.2 11.7 13.1 14.3 15.2 15.9

Proportion Aged ≥80 Yr

2000 2025 2050

% 0 20 40 60 80

37 36 53


Apx 30% Higher
RESEARCH PAPER

Lifetime risk of common neurological diseases in the elderly population

Suvian Licheri,1 Sirwan K L Darweesh,1 Frank J Wolters,1,2 Lana Fan1,2, Ali Heshmatollahi1,2 Ural Mutlu1,2, Peter J Koudstaal1,2 Jan Heeringa,1 Maarten J G Leening1,2,3, M Kamran Iqram1,2, M Arfan Iqram1

![Venn diagram showing the lifetime risk of dementia, stroke, and Parkinson's disease among men and women.](image-url)
Spectrum of Brain Injury in Patients with Atrial Fibrillation

- Clinical and Subclinical Strokes
- Clinical and Subclinical Bleeds
- Repetitive Micro Bleeds and/or Clots
- Cerebral Hypotension/Hypoperfusion

- Atrophy and Volume loss
  - Gray Matter Changes
  - Amyloid Plaques

Circulating Levels of Biomarkers of Cerebral Injury in Patients with Atrial Fibrillation and no history of stroke/TIA/cranial injury

Potential Biomarkers of Brain Injury

- Tight Junctions
- Neuron
- Microglia
- Astrocyte
- Leaky Junctions – From Clots or Bleeds
- Proteins Released With Injury
- Clot
- Biomarkers Cross the Blood Brain Barrier

Normal Function

Ischemic Brain Injury

Adapted from Kawata et al (2016)

myelin basic protein

myelin oligodendrocyte
Perspective of Brain Injury in Atrial Fibrillation Management

Rhythm vs Ablation

LAA Occlusion

Anticoagulation

Contemporary view of EP

Disabling Stroke

Ischemic Stroke (other – stroke/TIA)

Clinical Stroke (focal neuro deficit)
Moving Beyond Clinical/Disabling Stroke As An Endpoint in Atrial Fibrillation Management

Relationships of Overt and Silent Brain Lesions With Cognitive Function in Patients With Atrial Fibrillation

David Coren, MD, MPH,1,2,8 Nicolas Rodondi, MD, MAS,8,9 Andreas Müller, MD,1,9 Juerg H. Beer, MD,6
Peter Ammann, MD,1 Giorgio Moschovitis, MD,1 Angelo Auricchio, MD, PhD,1 Daniel Hayoz, MD,1 Richard Kobza, MD,1 Dipen Shah, MD,1,9 Jan Novak, MD,1 Jürg Schlüchter, MD,1 Marcello Di Valentino, MD,1 Stefanie Aeschbacher, PhD,1,4,5 Steffen Blum, MD,1,2 Pascal Meyre, MD,1,2 Christian Sticherling, MD,1,2 Leo H. Bonati, MD,2 Georg Ebert, MD,10 Ellisavet Moutzouri, MD,1,11 Urs Fischer, MD, MS,1 Andreas U. Monsch, PhD,1 Christoph Stippich, MD,1 Jens Wuerfel, MD,1 Tim Simneck, MD,1,11 Michael Coslovsky, PhD,1 Matthias Schwenklenks, PhD, MPH,7 Michael Kühne, MD,1,2,3,4 Stefan Oswald, MD,1,2,3,4 for the Swiss-AF Study Investigators

1,737 AF Patients (most >65 yrs) Data from Enrollment MRI
Incidence of Stroke is Directly Dependent on Diagnostic Methods Used and Traditional Stroke Symptoms Correlate Inconsistently with Infarcts on MRI

Patients with Atrial Fibrillation (>65 years)

Clinical Stroke/TIA Symptoms at 2 Years

Brain MRI at 2 Years

2.3% Incidence

5.5% Incidence

2.4x Increase

Are "Silent" Strokes Really Silent?

Traditional Clinical Symptoms

No Traditional Clinical Symptoms

Deficiencies of cognitive operations, semantic memory, language production and mental flexibility are present with testing at 2 years

Brain Injury in Patients with Atrial Fibrillation

1. "Clinical" Stroke/TIA diagnosis significantly underestimated incidence
2. "Silent" Strokes is a misnomer and these infarcts impact function when targeted testing is used

Incidence (%) of various dementia types with and without atrial fibrillation, showing statistically significant differences with p-values <0.0001 for each comparison. Bunch TJ, Heart Rhythm J, 2010.
Golive AS, Bunch TJ. Am J Cardiol
## Odds Ratios for Association of AF based on Age and Dementia Type

<table>
<thead>
<tr>
<th>Dementia</th>
<th>Overall</th>
<th>≤70</th>
<th>70-79</th>
<th>80-89</th>
<th>≥90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>1.73</td>
<td>2.22</td>
<td>1.68</td>
<td>1.31</td>
<td>------</td>
</tr>
<tr>
<td></td>
<td>p=0.001</td>
<td>p=0.004</td>
<td>p=0.02</td>
<td>p=0.45</td>
<td>--------</td>
</tr>
<tr>
<td>Senile</td>
<td>1.39</td>
<td>3.34</td>
<td>1.60</td>
<td>0.93</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>p=0.005</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p=0.004</td>
<td>p=0.41</td>
</tr>
<tr>
<td>Alzheimers</td>
<td>1.06</td>
<td>2.30</td>
<td>1.07</td>
<td>0.81</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>p=0.59</td>
<td>p=0.001</td>
<td>p=0.68</td>
<td>p=0.29</td>
<td>p=0.37</td>
</tr>
<tr>
<td>Nonspecific</td>
<td>1.44</td>
<td>2.87</td>
<td>1.49</td>
<td>0.96</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p=0.001</td>
<td>p=0.77</td>
<td>p=0.44</td>
</tr>
</tbody>
</table>
Mechanisms of Cognitive Decline and Dementia in Patients with Atrial Fibrillation

The timing, use, and efficacy of anticoagulation is critical

Micro and Macro Emboli/Bleeds

Disruptions of blood/brain barrier/Cytotoxicity

Cellular Apoptosis Cytotoxicity Volume Loss

Mediators
Inflammation, Oxidative Stress, Vascular Disease, Genetic Risks

Cerebral Hypoperfusion

Arteriolar Hypotension Capillary Hypertension

Cellular Apoptosis Cytotoxicity Volume Loss

Rhythm, Rate, and Cerebral Perfusion Strategies May Impact Risk
Less dementia with oral anticoagulation in atrial fibrillation

Leif Friberg and Märten Rosenqvist

Department of Clinical Sciences, Karolinska Institute, Stockholm, Sweden

Accepted March 2017; revised April 2017; accepted September 2017

Intermountain Healthcare
AF Pts (Warfarin)
Dementia Risk in AF Patients on Warfarin by TTR
(2,693 pts, no prior dementia, following by CPAS

Average number of draws per patient was 44.2 ± 39.4
Association of anticoagulant therapy with risk of dementia among patients with atrial fibrillation

Daehoon Kim1, Pil-Sung Yang2, Eunsun Jang1, Hae Tae Yu1, Tae-Hoon Kim1, Jae-Sun Uhm1, Jong-Youn Kim1, Jung-Hoon Sung3, Hui-Nam Pak1, Moon-Hyoun Lee4, Gregory Y. H. Lip3,5, and Boyoung Joung1,4,6

GIRAF trial

RCT: 200 patients aged 70 years or older – follow-up 2 years

- No patients developed dementia
- Cognitive scoring assessments were identical in both treatment groups (<1 point difference).
Impact of Anticoagulation Therapy on the Cognitive Decline and Dementia in Patients with Non-Valvular Atrial Fibrillation: The Cognitive Decline and Dementia In Patients with Non-Valvular Atrial Fibrillation (CAF) Trial

**Study Enrollment**
- Anticoagulation Initiation for Atrial Fibrillation
- Meets Inclusion and Exclusion Requirements
- Documented Atrial Fibrillation without Rheumatic or Prosthetic Valvular Heart Disease
- CHADS<sub>2</sub> or CHA<sub>2</sub>S<sub>2</sub>-VASc Score ≥ 2
- No history of clinically diagnosed form of dementia

**1:1 Randomization**
- Dabigatran Etexilate vs Warfarin

**Dabigatran Etexilate**
- 150 mg BID (CrCL > 30 mL/min) or
- 75 mg BID (CrCL 15-30 mL/min).
  - Assessment of kidney function every 6 months.

**Warfarin**
- Dose-adjusted warfarin (INR: 2.0-3.0).
  - Standard warfarin follow-up and education based upon system criteria.

**Clinic Care and Follow-Up**
- Baseline: Mini-Mental Status Evaluation, Hachinski Ischemic scale, cognitive subscale of the Alzheimer’s Disease Assessment Scale, Disability Assessment for Dementia, Quality of Life Improvement as assessed by Minnesota Living with Heart Failure Scale and the Anti-Clot Treatment Scale Quality of Life Survey.
- Follow-up surveys: 3, 6, 12, 18, 24 months: All scores and scales assessed at baseline (only one survey will be administered at the 3-month visit: Hachinski Ischemic Scale only).

**MRI Subgroup**
- Baseline: MRI with Volume Measurements.
- 24 Months: MRI with Volume Measurements.

**Alzheimer’s Disease Assessment Scale**
- Baseline: p=0.42
- 24 Months: p=0.80

**Disability Assessment for dementia Scale**
- Baseline: p=0.78
- 24 Months: p=0.78

**Hachinski Ischemic Score**
- Baseline: p=0.80
- 24 Months: p=0.39

*p-values reflect differences in scores at 24 months
Impact of Anticoagulation Therapy on the Cognitive Decline and Dementia in Patients with Non-Valvular Atrial Fibrillation: The Cognitive Decline and Dementia In Patients with Non-Valvular Atrial Fibrillation (CAF) Trial

- GDF-15, pg/ml
- Cystatin C, ng/ml
- Prothrombin fragments 1+2, nmol/L
- CRP, mg/L
- Antithrombin-III/SerinC1, μg/ml
- P-Selectin, ng/ml
- Protein S, μg/mL
- Factor 8, ng/ml
- MMP 9, ng/ml
- Neprilysin, ng/ml
- BNP, pg/ml
- CCL23, pg/ml
- ESAM, ng/ml
- vWF, μg/ml
- D-dimer, ng/mL
- Protein C, ng/ml
- Cardiac troponin T, pg/ml
- AntiBeta 2 Glycoprotein I IgG, U/ml
- AntiBeta 2 Glycoprotein I IgM, U/ml
- Anti-Cardiolipin, U/ml

Dabigatran Warfarin
### Comparison of clinical data from the PROTECT AF and PREVAIL AF and DOAC Trials

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF LAA closure</th>
<th>PREVAIL AF LAA closure</th>
<th>PROTECT AF Warfarin</th>
<th>Apixaban (ARISTOTLE)</th>
<th>Rivaroxaban (ROCKET AF)</th>
<th>Edoxaban (ENGAGE AF)</th>
<th>Dabigatran (RELY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>72</td>
<td>74</td>
<td>73</td>
<td>70</td>
<td>73</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>CHADS2</td>
<td>2.2</td>
<td>2.6</td>
<td>2.3</td>
<td>2.1</td>
<td>3.5</td>
<td>2.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Major or minor bleeding (%)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>18.1</td>
<td>14.9</td>
<td>16.9</td>
<td>16.4</td>
</tr>
<tr>
<td>Major bleeding (%)</td>
<td>3.5</td>
<td>--</td>
<td>4.1</td>
<td>2.1</td>
<td>3.6</td>
<td>2.8</td>
<td>3.1</td>
</tr>
<tr>
<td>Stroke/systemic embolism (%)</td>
<td>2.3</td>
<td>2.3</td>
<td>2.7</td>
<td>1.3</td>
<td>1.7</td>
<td>1.6</td>
<td>1.1</td>
</tr>
</tbody>
</table>
Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke


6 Table S1: Anticoagulation during follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Left Atrial Appendage Occlusion</th>
<th>No Left Atrial Appendage Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any anticoagulation</td>
<td>Vitamin K antagonist</td>
</tr>
<tr>
<td>Discharge</td>
<td>83.4%</td>
<td>64.8%</td>
</tr>
<tr>
<td>One Year</td>
<td>79.6%</td>
<td>44.6%</td>
</tr>
<tr>
<td>Two Years</td>
<td>77.2%</td>
<td>39.2%</td>
</tr>
<tr>
<td>Three Years</td>
<td>75.3%</td>
<td>38.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Occlusion (N=2379)</th>
<th>No Occlusion (N=2397)</th>
<th>Comparison†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of participants (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke or systemic embolism</td>
<td>114 (4.8)</td>
<td>168 (7.0)</td>
<td>0.67 (0.53 to 0.88)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>109 (4.6)</td>
<td>164 (6.9)</td>
<td>0.66 (0.52 to 0.84)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>6 (0.3)</td>
<td>7 (0.3)</td>
<td>0.86 (0.29 to 2.55)</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any stroke or systemic embolism</td>
<td>127 (5.3)</td>
<td>187 (7.8)</td>
<td>0.67 (0.54 to 0.84)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>113 (4.7)</td>
<td>176 (7.4)</td>
<td>0.63 (0.50 to 0.80)</td>
</tr>
</tbody>
</table>
Mechanisms of Cognitive Decline and Dementia in Patients with Atrial Fibrillation

The timing, use, and efficacy of anticoagulation is critical

Cerebral Hypoperfusion

Micro and Macro Emboli/Bleeds

Disruptions of blood/brain barrier/Cytotoxicity

Cellular Apoptosis Cytotoxicity Volume Loss

Mediators
Inflammation, Oxidative Stress, Vascular Disease, Genetic Risks

Rhythm, Rate, and Cerebral Perfusion Strategies May Impact Risk

Arteriolar Hypotension Capillary Hypertension

Cellular Apoptosis Cytotoxicity Volume Loss

Circulation 2020 – in Press
Examples of percentile, hypoperfusion and hypertensive event evaluation

(a–b) Example of percentile evaluation in the case of $P_{\text{dm, left}} (p(P_{\text{dm, left}})$ is the probability density function). SR thresholds (5% SR and 95% SR, dashed lines) individuate the 5th and 95th percentiles in SR (panel a, blue areas), while they correspond to the 27th and 91st percentiles in AF (panel b, red areas). (c) Example of hypoperfusion lasting 2 beats ($Q_{\text{dm, left}}$). Average flow rate per beats are represented by green horizontal lines, while the 5th percentile SR threshold is displayed through the dashed blue horizontal line. (d) Example of hypertensive event lasting 3 beats ($P_{\text{dm, left}}$). Average pressure per beats are reported with black horizontal lines, while the dashed blue horizontal line represents the 95th percentile SR threshold.

Evidence for Rate Control

Patients in Longstanding Persistent Atrial Fibrillation with No Baseline History of Dementia

S. Scarsoglio et al J. R. Soc. Interface 14: 20170180
Before AV Node Ablation

Rete mirabile complex of veins and arteries

In the neck of the dog, protects the brain when the body overheats during hunting.

MRI Cerebrovascular Reserve Assessment and Quantification:

Pre Diamox
Post Diamox

https://en.wikipedia.org/wiki/Rete_mirabile
Changes in Average Cerebrovascular Reserve in the Gray and White Brain Matter

Baseline
3 Month
6 Month

Gray Matter Reserve Blood Flow
White Matter Reserve Blood Flow

Percent of Pre-Diamox Blood Flow

8 Animals
Evidence for Rhythm Control

Improved brain perfusion after electrical cardioversion of atrial fibrillation

Marianna Gardarsdottir¹, Sigurdur Sigurðsson², Thor Aspelund²,³, Valdis Anna Gardarsdottir⁴, Lars Forsberg⁵, Vilmundur Gudnason²,³, and David O. Arnar ²,⁴,⁶

![Image of brain perfusion before and after cardioversion]

- Sustained AF
- Cardioverted to SR

Before cardioversion  After cardioversion
Impact of Atrial Fibrillation Ablation
Intermountain Experience

- 3 Year Success Rate (no antiarrhythmics, no AF recurrences): 64.4%
- Repeat procedure: 1,162 (27.6%)

Less dementia after catheter ablation for atrial fibrillation: a nationwide cohort study

Daehoon Kim, Pil-Sung Yang, Jung-Hoon Sung, Eunsun Jang, Hee Tae Yu, Tae-Hoon Kim, Jae-Sun Uhm, Jong-Youn Kim, Hui-Nam Pak, Moon-Hyoung Lee, Gregory Y.H. Lip, and Boyoung Joung

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before matching Ablation (N = 9119)</th>
<th>Medical therapy (N = 17 978)</th>
<th>ASD</th>
<th>After matching Ablation (N = 5863)</th>
<th>Medical therapy (N = 5863)</th>
<th>ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent medication†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>1757 (19.3)</td>
<td>3057 (17.0)</td>
<td>5.9%</td>
<td>1120 (19.1)</td>
<td>1107 (18.9)</td>
<td>0.6%</td>
</tr>
<tr>
<td>P2Y12 inhibitor</td>
<td>875 (9.6)</td>
<td>1028 (5.7)</td>
<td>14.6%</td>
<td>469 (8.0)</td>
<td>462 (7.9)</td>
<td>0.4%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>5079 (55.7)</td>
<td>12 590 (70.0)</td>
<td>30.0%</td>
<td>3609 (61.6)</td>
<td>3594 (61.3)</td>
<td>0.5%</td>
</tr>
<tr>
<td>NOAC</td>
<td>384 (4.2)</td>
<td>368 (2.0)</td>
<td>12.5%</td>
<td>186 (3.2)</td>
<td>200 (3.4)</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

*AD: Alzheimer’s disease, VaD: Vascular dementia
2000-2021 Optum Clinformatics database

55,255 total patients with 19,684 patients in the CA cohort and 35,571 in the AAD cohort (propensity-matched)

Age: 67.35 (10.16), CHADS2 Vasc: 3.77 (1.64)  
Oral anticoagulation: 77.7%

Emily P. Zeitler – ACC 2022
Cumulative Incidence of Dementia by AF Treatment (2010 and forward)

- AAD
- CA

p < 0.0001

Years after Index Episode
Atrial Fibrillation Catheter Ablation Improves 1-Year Follow-Up Cognitive Function, Especially in Patients With Impaired Cognitive Function

See Editorial by Rosman et al

BACKGROUND: Although atrial fibrillation (AF) has a risk of cognitive dysfunction, it is not clear whether AF catheter ablation improves or worsens cognitive function. This prospective case-control study sought to assess the 1-year serial changes in the cognitive function with or without AF catheter ablation.

METHODS: We evaluated the Montreal Cognitive Assessment score in 308 patients (71.4% male, 60.4±9.1 years of age, 34.1% persistent AF, who underwent AF ablation (ablation group) and 50 AF patients on

Moo-Nyun Jin, MD*, Tae-Hoon Kim, MD*, Ki-Woon Kang, MD, PhD Hye-Tae Yu, MD, PhD Jee-Sun Uhm, MD, PhD Boyoung Young, MD, PhD Moon-Hyo Yong Lee, MD, PhD Eisu Kim, MD, PhD† Hui-Nam Pak, MD, PhD†
New Look at What Matters

Coronary Artery Disease

- Troponins, CA score, Stress tests, EF
- To Prevent
- Disabling MI/Death

Atrial Fibrillation

- Disabling CVA/Death
CHA₂DS₂-VASc scores and Intermountain Mortality Risk Scores for the joint risk stratification of dementia among patients with atrial fibrillation

Kevin G. Graves, MPH,*  ‡ Helda T. May, PhD, MSPh, ‡ Victoria Jacobs, PhD,*
Kirk U. Knowlton, MD,* ‡ Joseph B. Muhlstein, MD,* ‡ Donald L. Lappe, MD,* ‡
Jeffrey L. Anderson, MD,* ‡ Benjamin D. Horne, PhD, MStat, MPH,* ‡
T. Jared Bunch, MD, FHRS* ‡

Demographic Based Risk Assessment

**CHA₂DS₂-VASc score**
- Age >65, Age >75
- Hypertension
- Diabetes
- Stroke/TIA
- Sex (female)
- Congestive Heart Failure
- Vascular Disease

Biomarker/Physiologic Based Risk Assessment

**Intermountain Mortality Risk Score (IMRS)**
- Complete Blood Count Components
- Basic Metabolic Profile Components
For each 5 fl-wide histogram bin, boxes are 25th to 75th percentiles of RBC count, black line is median RBC count, and whiskers are 2.5th to 97.5th percentiles of RBC count. Predictors of morbidity and mortality included the following RBC size metrics: %Macro: Percentage of RBCs with extreme macrocytic volume >120 fL; %Micro: Percentage of RBCs with extreme microcytic volume <60 fL; RDW: Red cell distribution width (also called RDW-CV), calculated as one standard deviation (SD) of the RBC volumes (about 68.2% of RBCs are within 1 SD of the mean) divided by the mean corpuscular volume (MCV); RDW-sd: RDW-size distribution, calculated as the width of the curve at 20% height (shown here as 20% of the height of the median RBC count of the histogram bin with the highest RBC count).
Thank You

Jared.bunch@hsc.utah.edu

@tjaredbunch