Stroke Prevention in AF with Kidney Disease: Challenges and Opportunities

MINTU TURAKHIA, MD MAS

Senior Director of Innovation and Research
Center for Digital Health
Stanford University

Chief, Cardiac Electrophysiology
VA Palo Alto Health Care System

mintu@stanford.edu
@leftbundle

Stanford MEDICINE
Disclosures

- Research support
  - VA, NIH
  - Janssen, Medtronic, iRhythm, Boehringer Ingelheim, AstraZeneca
- Advisor/Consultant
  - St Jude Medical, Medtronic, Daiichi Sankyo, Zipline Medical, Precision Health Economics, Cyberheart, thryva, AliveCor, Armetheon, Abbott, Myokardia, Nokia
- Lecture honoraria
  - Medtronic, St Jude Medical
Prevalence of AF

- Most common sustained arrhythmia in clinical practice
- 4% of the population over age 60; 10% over age 80

Miyasaka Y. Circulation 2006;114:119-125
Naccarelli GV. Am J Cardiol. 2009.
Prevalence of AF (per 100,000)

Chugh SS et al, Circulation, 2014
Deaths attributable to AF

AF-associated mortality, stratified

AF is the most expensive cardiac dx

- Direct annual cost age < 65: $6.65 billion
- Medicare spending for new AF: $15.7 billion
  - Mainly due to complications (stroke, CHF, MI, tachycardia)
- Direct and indirect cost of stroke: $58 billion

FIGURE 3: MEDICARE IS THE PRIMARY PAYER FOR AFIB ACROSS ALL SETTINGS OF CARE

Avalere report, 2009
Stroke shortens lifespan the most

Framingham Heart Study

Average Remaining Life Expectancy at Age 60 (Men)

- Healthy
- History of Cardiovascular Disease: -7.4 years
- History of AMI: -9.2 years
- History of Stroke: -12 years

**Physiology**
- Loss of coordinated atrial activity
- Impaired emptying, stasis, hypercoagulability, clot formation

**Implications for stroke risk**
- 15% of 700,000 strokes/year in U.S.
- Risk if untreated: 3-12%/yr
- Stroke from AF has higher severity, disability and mortality (larger territory)

**Therapies can prevent stroke in AF**
First, there was \text{CHADS}_2

- 1 point for each of the following:
  - Congestive heart failure
  - Hypertension
  - Age $\geq$ 75
  - Diabetes
- 2 points for prior Stroke/TIA

\text{(Gage BF, JAMA 2001; AHA 2006 guidelines; ACCP 2012 guidelines)}
National Registry of AF (NRAF)

- Source of CHADS$_2$ data
- Quality improvement Medicare registry
- 1733 inpatients, age 65-95, discharged from a hospital with AF
- 7 hospitals from stroke belt states
- ICD9 codes, not chart review
- Max follow-up: 2.7 years
- CKD not assessed
- Non-generalizable
Validation: how good is CHADS2?

- c-statistic = 0.56-0.62
- (0.50 = pure chance)
- Substantial misclassification
- Untreated “low risk” patients who get strokes
- Treated “high risk” patients who bleed

(Fang M, JACC 2006)
Why did CHADS$_2$ survive this long?

- **Specific**, not sensitive
- Warfarin was too risky to be broadly used
  - High INR+uncontrolled BP+ASA = ICH
- As warfarin management improved (and ICH decreased), goal was to find a **high sensitivity** risk tool

Turakhia M, *Circ Qual Care Outcomes*, 2013
Then came CHA$_2$DS$_2$-VASc…

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age $\geq 75$</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/thrombo-embolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease$^a$</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–74</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e. female sex)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Maximum score</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>

$^a$Adjusted stroke rate according to CHA$_2$DS$_2$-VASc score

Support for this approach comes from various published analyses. In the present guidelines, we have tried to de-emphasize the use of anticoagulation. Then came CHA$_2$DS$_2$-VASc…

The Stroke in AF Working Group performed a comparison of published risk-stratification schemes to predict stroke in patients with AF. Most had substantial, clinically relevant differences among published schemes. The CHADS$_2$ score categorized most subjects of patients assigned to individual risk categories varied widely across the schemes. The CHADS$_2$ score categorized most subjects as ‘low risk’, 1–2 as ‘moderate risk’, and 3 or greater as ‘high risk’. Also, the CHADS$_2$ score does not include many stroke risk factors. CHA$_2$DS$_2$-VASc extends the CHADS$_2$ scheme by considering additional factors, and 1 point each is assigned for age 65–74 years, a history of stroke or TIA, or age $\geq 75$ (doubled), diabetes, or systemic embolism. Importantly, prescription of an antithrombotic therapy on the basis of the presence (or absence) of stroke risk factors does not translate to better outcomes in AF patients in routine care.

Table 7

<table>
<thead>
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</tr>
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$^a$Adjusted stroke rate according to CHA$_2$DS$_2$-VASc score

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA$_2$DS$_2$-VASc (e.g. LV EF < 40%)

See text for definitions.

Table 8

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</tr>
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</table>

$^a$Adjusted stroke rate according to CHA$_2$DS$_2$-VASc score

bBased on Lip GY, et al. Chest. 2010


KDIGO
Weaknesses of CHA$_2$DS$_2$-VASc

- CHADS2 score gets reclassified upward
  - Age, CAD, female
- Few stroke events in derivation
- European Heart Survey
  - 1,577 of 5,333 untreated AF patients from cardiology practices in 35 countries
- 2003-2004
- 1-year follow up

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$-VASc score</th>
<th>Patients (n=7329)</th>
<th>Adjusted stroke rate (%/year)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>422</td>
<td>1.3%</td>
</tr>
<tr>
<td>2</td>
<td>1230</td>
<td>2.2%</td>
</tr>
<tr>
<td>3</td>
<td>1730</td>
<td>3.2%</td>
</tr>
<tr>
<td>4</td>
<td>1718</td>
<td>4.0%</td>
</tr>
<tr>
<td>5</td>
<td>1159</td>
<td>6.7%</td>
</tr>
<tr>
<td>6</td>
<td>679</td>
<td>9.8%</td>
</tr>
<tr>
<td>7</td>
<td>294</td>
<td>9.6%</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>6.7%</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>15.2%</td>
</tr>
</tbody>
</table>

R₂CHADS₂: Yet another score

- Derivation: ROCKET-AF (rivaroxaban vs. warfarin)
- Validation: Kaiser
- Adding GFR<60 improves discrimination and reclassification
  - c-statistic 0.74
- AHA/ACC/HRS 2014 guidelines did not endorse

(Piccini J, Circulation 2012)
Q: What is this patient’s annual risk of stroke?

- **Risk factors**
  - Age 67
  - Female
  - Carotid disease
  - GFR < 60

- CHADS$_2$: 0 (low)
- CHA$_2$DS$_2$-VASc: 3 (med)
- R$_2$CHADS$_2$: 2 (med)

**Answer choices:**
1. Very low (< .5%)
2. Low (~1-2%)
3. Medium (~3-6%)
4. High (~8-18%)
So why did new guidelines go with CHA$_2$DS$_2$-VASc?

- Calibrated for high sensitivity
- Contemporary therapy has tilted in favor of having a low treatment threshold
  - Low bleeding risk with DOACs
  - Warfarin: less ICH, major bleeding now
The biggest limitation of the CHADS-based scores is the diagnosis of AF itself

- AF defined by treatment, not disease
  - Reimbursement codes, mostly hospitalized patients
- Transient or lone AF not well represented
- Diagnosis creep
  - Device-detected AF
  - Ambulatory ECG
  - Episodic detection with wearables
How much AF should be treated?

- 30 seconds?
- 1 minute?
- 6 minutes?
- 6 hours?
- Depends on vascular risk?

- Is this a condemnation to lifelong therapy?
Subclinical Atrial Fibrillation and the Risk of Stroke

Jeff S. Healey, M.D., Stuart J. Connolly, M.D., Michael R. Gold, M.D., Carsten W. Israel, M.D., Isabelle C. Van Gelder, M.D., Alessandro Capucci, M.D., C.P. Lau, M.D., Eric Fain, M.D., Sean Yang, M.Sc., Christophe Bailleul, M.D., Carlos A. Morillo, M.D., Mark Carlson, M.D., Ellison Themeles, M.Sc., Elizabeth S. Kaufman, M.D., and Stefan H. Hohnloser, M.D., for the ASSERT Investigators*

METHODS
We enrolled 2580 patients, 65 years of age or older, with hypertension and no history of atrial fibrillation, in whom a pacemaker or defibrillator had recently been implanted. We monitored the patients for 3 months to detect subclinical atrial tachyarrhythmias (episodes of atrial rate >190 beats per minute for more than 6 minutes) and followed them for a mean of 2.5 years for the primary outcome of ischemic stroke or systemic embolism. Patients with pacemakers were randomly assigned to receive or not to receive continuous atrial overdrive pacing.
Subclinical atrial tachyarrhythmias (AT) (> 6 minutes) in 10% by 3 months
AT associated with clinical AF (HR 5.6)
AT associated with ischemic stroke/SE (HR 2.5)
But, population attributable risk low: 13% (Healey JS, NEJM 2012)

Panel A shows the risk of electrocardiographically documented clinical atrial tachyarrhythmias after the 3-month visit, according to whether subclinical atrial tachyarrhythmias were or were not detected between enrollment and the 3-month visit. Panel B shows the risk of ischemic stroke or systemic embolism after the 3-month visit, according to whether subclinical atrial tachyarrhythmias were or were not detected between enrollment and the 3-month visit. The insets show the same data on an enlarged y axis.
Mechanisms of stroke in AF are diverse

- Cardioembolic
- Atheroembolic
- Small vessel
Vascular risk factors also predict AF, stroke

- In patients with CHD/CHF but without AF, CHADS2 and other scores predict...
  - Left atrial dysfunction, LA appendage clot
  - Ischemic stroke
  - Incident AF

**Absolute risk of ischemic stroke after 1-y follow-up, %**

- Without atrial fibrillation
- With atrial fibrillation

**In Heart Failure**

- CHA2DS2-VASc Score
- Absolute risk of ischemic stroke

**Figure 2. Absolute Risks and Relative Risks by CHA2DS2-VASc Score Components During the First Year**

**Relative Risk of Death After 1-y Follow-up, %**

- With atrial fibrillation
- Without atrial fibrillation

**Relative Risk of Ischemic Stroke After 1-y Follow-up, %**

- With atrial fibrillation
- Without atrial fibrillation

**Relative Risk of Thromboembolism After 1-y Follow-up, %**

- With atrial fibrillation
- Without atrial fibrillation

---

Azarbal F / Whooley MA / Turakhia M, Am J Cardiol 2014
Welles C / Whooley MA / Turakhia M, JACC 2011
Welles C / Whooley MA / Turakhia M, Am Heart J 2013
Wong J / Whooley MA / Turakhia M, Am Heart J 2014
Melgaard L, JAMA 2015
AF correlates with brain disease

- Manhattan Cohort Study subset (CABL)
- n = 455 without stroke history; all received MRI
- LA volume and LA function also associated with brain ischemic lesions

### Univariate correlates of subclinical cerebrovascular disease

<table>
<thead>
<tr>
<th></th>
<th>SBI</th>
<th>Log-WMHV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (SE)</td>
<td>P value</td>
</tr>
<tr>
<td>Age</td>
<td>0.06 (0.01)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male sex</td>
<td>-0.2 (0.3)</td>
<td>0.46</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.02 (0.03)</td>
<td>0.47</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.9 (0.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.5 (0.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>-0.03 (0.27)</td>
<td>0.90</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.6 (0.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CAD</td>
<td>0.7 (0.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>0.1 (0.3)</td>
<td>0.70</td>
</tr>
<tr>
<td>LV mass</td>
<td>0.02 (0.004)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>2.4 (1.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>-0.03 (0.01)</td>
<td>0.07</td>
</tr>
<tr>
<td>LV diastolic dysfunction</td>
<td>0.5 (0.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>MV regurgitation (&gt; mild)</td>
<td>0.9 (0.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.01 (0.01)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Values in table are parameter estimates (B) and relative standard error (SE). SBI: Silent brain infarcts. WMHV: White matter hyperintensities volume. BMI: Body mass index. CAD: Coronary artery disease. MV: Mitral valve.
Watchman 4-year data
Strokes still occur

579 of 707 (82%) of randomized pts
AF temporally discordant

- ASSERT
  - 1 of 51 stroke patients had AF at time of stroke
  - 25 (49%) had no AT/AF (including post-stroke)
  - Median time to AF was 339 days prior
- In larger device cohorts, AF does transiently increase risk but attributable risk is low
- AF also discordant with ICH on OAC

What is the mechanism of ischemic stroke?

Do NOACs prevent strokes that are not cardioembolic?

Are competing risks sufficiently offset

Other vascular risk factors
Trials in progress

Table 2  Summary of ongoing trials investigating the safety/efficacy of OAC treatment of occult AF

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Primary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTESia</td>
<td>Randomised to either aspirin 81 mg daily (control) or apixaban 5 mg twice daily (intervention)</td>
<td>Incidence of stroke and major bleeding events</td>
</tr>
<tr>
<td>STROKESTOP</td>
<td>Twice-daily ECG screening+OAC treatment if AF detected (single episode duration &gt;30 s, or 2 or more episodes &gt;10 s)</td>
<td>Incidence of stroke and major bleeding events</td>
</tr>
</tbody>
</table>

Treatment
Target specific oral anticoagulants vs. warfarin
Outcome of stroke or systemic embolism

RE-LY
[Dabigatran 150 mg]
Risk Ratio (95% CI)
0.66 (0.53 - 0.82)

ROCKET AF
[Rivaroxaban]
0.88 (0.75 - 1.03)

ARISTOTLE
[Apixaban]
0.80 (0.67 - 0.95)

ENGAGE AF-TIMI 48
[Edoxaban 60 mg]
0.88 (0.75 - 1.02)

Combined
[Random Effects Model]
Risk Ratio (95% CI)
0.81 (0.73 - 0.91)

Heterogeneity P=0.13.
P<0.0001

N=58,541

<table>
<thead>
<tr>
<th></th>
<th>RE-LY (Dabigatran)</th>
<th>ROCKET-AF (Rivaroxaban)</th>
<th>ARISTOTLE (Apixaban)</th>
<th>ENGAGE AF TIMI 48 (Edoxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Renal Excretion</td>
<td>80%</td>
<td>35%</td>
<td>27%</td>
<td>50%</td>
</tr>
<tr>
<td>Efficacy % Warfarin vs. OAC (CVA or SE)</td>
<td>1.69 vs. 1.11, p&lt;.001 150 mg shown</td>
<td>2.42 vs. 2.12, p=.12 2.2 vs 1.7 on treatment</td>
<td>1.60 vs. 1.27, p &lt; .001 303</td>
<td>1.80 vs. 1.57, p=.08 (1.5 vs. 1.18 on treatment) *High-dose (60 mg)</td>
</tr>
<tr>
<td>Major Bleeding %</td>
<td>3.57 vs. 3.32, p=0.31</td>
<td>3.45 vs. 3.6, p=0.58</td>
<td>3.09 vs. 2.13, p&lt;.001</td>
<td>3.43 vs. 2.75, p&lt;.001</td>
</tr>
<tr>
<td>ICH%</td>
<td>0.74 vs. 0.30, p&lt;.001</td>
<td>0.74 vs. 0.49, p&lt;.019</td>
<td>0.47 vs. 0.24, p&lt;.001</td>
<td>0.85 vs. 0.39, p&lt;.001</td>
</tr>
<tr>
<td>All-cause mortality %/yr</td>
<td>4.13 vs. 3.64, p = 0.051 NNT = 204</td>
<td>4.91 vs. 4.52, p=NS</td>
<td>3.94 vs 3.52, p = 0.05 NNT = 238</td>
<td>4.35 vs. 3.99, p=0.08 NNT = 277</td>
</tr>
<tr>
<td>Conclusion vs. warfarin</td>
<td>Superior efficacy, similar bleeding, less ICH</td>
<td>Non-inferior on efficacy and safety measures</td>
<td>Superior efficacy, less major bleeding and ICH, lower mortality</td>
<td>Non-inferior on efficacy; less bleeding</td>
</tr>
</tbody>
</table>

## Dosing in chronic kidney disease

<table>
<thead>
<tr>
<th>Agent</th>
<th>Standard AF Dose (Prescribing info)</th>
<th>Renal Dosing</th>
<th>Trial and Other Experience</th>
</tr>
</thead>
</table>
| **Dabigatran** | 150mg Twice Daily (CrCl > 30ml/min) | 75mg Twice Daily (CrCl 15-30ml/min) | • RE-LY trial: 150mg or 110mg BID if CrCl > 30ml/min  
• No trial experience in pts w/ CrCl < 30ml/min  
• 75mg dose not studied in RCTs  
• European dosage:  
  • 150mg BID if CrCl >50ml/min  
  • 110mg BID if CrCl 30-50ml/min  
  • Contraindicated if CrCl < 30ml/min |
| **Rivaroxaban** | 20mg Once Daily (CrCl > 50ml/min) | 15mg Once Daily (CrCl 15-50ml/min) | • ROCKET-AF trial:  
  • 20mg Daily if CrCl > 50ml/min  
  • 15mg Daily if CrCl 30-50ml/min  
  • No trial experience in pts w/ CrCl < 30ml/min |
| **Apixaban** | 5mg Twice Daily | | • ARISTOTLE trial: Renal dose studied as per prescribing information.  
• No trial experience in pts w/ CrCl < 25ml/min  
• No trial experience with ESRD patients |
| **Edoxaban** | 60mg Once Daily (CrCl 50-95ml/min) **BLACK BOX WARNING:** Avoid use if CrCl > 95ml/min | 30mg Once Daily (CrCl 15-50ml/min) | • TIMI-ENGAGE: Randomized to 60mg or 30mg Daily  
  • Dose halved if  
    • CrCl 30-50ml/min, Weight ≤ 60kg, or  
    • Concomitant verapamil, quinidine, or dronedarone (strong P-gp inhibitors)  
• No trial experience in pts w/ CrCl < 30ml/min  
• Worse outcomes in patients with CrCl > 95ml/min |

**Bottom Line:** None have been evaluated in randomized trials for CrCl < 25-30 or dialysis ESRD trials in development.
Issues

- Treatment benefit in CKD subgroups?
- Treatment harm?
- Stability of kidney function?
  - How often should CrCl be assessed?
  - Titration of ACE/ARB?
- Cockroft-Gault vs MDRD or CKD-EPI
### Pivotal NOAC trials and CKD

#### Table 1  Selected patient characteristics of the included trials

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Trial</th>
<th>Dab 110 mg</th>
<th>Dab 150 mg</th>
<th>Warfarin</th>
<th>Apix</th>
<th>Warfarin</th>
<th>Riva</th>
<th>Warfarin</th>
<th>Riva</th>
<th>Warfarin</th>
<th>Edox 30 mg</th>
<th>Edox 60 mg</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance[^5] %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–49 mL/min</td>
<td></td>
<td>19.4</td>
<td>19.2</td>
<td>19.4</td>
<td>16.5</td>
<td>16.6</td>
<td>21.0</td>
<td>20.6</td>
<td>22.1</td>
<td>22.4</td>
<td>19.3</td>
<td>19.6</td>
<td>19.0</td>
</tr>
<tr>
<td>50–79 mL/min</td>
<td></td>
<td>48.6</td>
<td>48.1</td>
<td>48.5</td>
<td>41.6</td>
<td>41.8</td>
<td>46.6</td>
<td>48.8</td>
<td>51.3</td>
<td>51.3</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>&gt;80 mL/min</td>
<td></td>
<td>32.3</td>
<td>32.0</td>
<td>32.2</td>
<td>41.2</td>
<td>41.4</td>
<td>32.3</td>
<td>31.3</td>
<td>26.6</td>
<td>26.3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

| | Moderate renal impairment (95 % CI) | | Mild renal impairment (95 % CI) | | Non renal impairment (95 % CI) | |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Safety** | | | | | |
| Dabigatran 110 [39] | 0.99b (0.77–1.28) | 0.76 (0.62–0.94) | 0.61c (0.44–0.84) | |
| Dabigatran 150 [39] | 1.01b (0.79–1.30) | 0.91 (0.75–1.11) | 0.84c (0.62–1.13) | |
| Rivaroxaban [40] | 0.98b (0.84–1.14) | NR | 1.04d (0.96–1.13) | |
| J-ROCKET [41] | 1.22b (0.78–1.91) | NR | 1.07d (0.80–1.43) | |
| Apixaban [30] | 0.50a (0.38–0.66) | 0.77 (0.65–0.94) | 0.80d (0.61–1.04) | |
| Edoxaban 30 [9] | 0.31b (0.23–0.42)c | NR | 0.55d (0.46–0.65)c | |
| Edoxaban 60 [9] | 0.63b (0.50–0.81)c | NR | 0.88d (0.76–1.03)c | |
| **Efficacy** | | | | | |
| Dabigatran 110 [39] | 0.85b (0.59–1.24) | 0.93 (0.70–1.23) | 0.84d (0.54–1.32) | |
| Dabigatran 150 [39] | 0.56b (0.37–0.85) | 0.68 (0.50–0.92) | 0.67d (0.42–1.09) | |
| Rivaroxaban [40] | 0.84b (0.57–1.23) | NR | 0.78d (0.63–0.98) | |
| J-ROCKET [41] | 0.82b (0.25–2.69) | NR | 0.36d (0.14–0.93) | |
| Apixaban [30] | 0.79a (0.55–1.14) | 0.74 (0.56–0.97) | 0.88c (0.64–1.22) | |
| Edoxaban 30 [9] | 1.17b (0.92–1.45)c | NR | 1.10d (0.92–1.32)c | |
| Edoxaban 60 [9] | 0.86b (0.68–1.15)c | NR | 0.87d (0.82–1.05)c | |
Subgroup analyses of NOAC trials

- For CrCl $\leq$ 50 mL/min
On-Treatment Outcomes in Patients With Worsening Renal Function With Rivaroxaban Compared With Warfarin
Insights From ROCKET AF

Table 2. Baseline Characteristics by Renal Function Over the Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n=12612)</th>
<th>SRF Patients (n=9292)</th>
<th>WRF Patients (n=3320)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized to rivaroxaban, % (n)</td>
<td>50 (6253)</td>
<td>49 (4565)</td>
<td>51 (1688)</td>
<td>0.090</td>
</tr>
<tr>
<td>Age, y</td>
<td>73 (65, 78)</td>
<td>72 (65, 78)</td>
<td>73 (66, 78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female, % (n)</td>
<td>39 (4959)</td>
<td>38 (3555)</td>
<td>42 (1404)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Table 3. Outcomes by Renal Function Over the Course of the Study On-Treatment Period

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>SRF Patients, Event Rate per 100 patient-years (95% CI) (Total Events, n)</th>
<th>WRF Patients, Event Rate per 100 patient-years (95% CI) (Total Events, n)</th>
<th>HR (95% CI), WRF Versus SRF Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or systemic embolism</td>
<td>1.82 (1.60–2.04) (262)</td>
<td>2.37 (1.68–3.07) (45)</td>
<td>1.25 (0.89–1.75)</td>
<td>0.19</td>
</tr>
<tr>
<td>Vascular death</td>
<td>1.41 (1.21–1.60) (203)</td>
<td>2.21 (1.54–2.88) (42)</td>
<td>1.47 (1.05–2.06)</td>
<td>0.026</td>
</tr>
<tr>
<td>MI</td>
<td>0.93 (0.77–1.09) (134)</td>
<td>1.22 (0.72–1.72) (23)</td>
<td>1.19 (0.75–1.90)</td>
<td>0.47</td>
</tr>
<tr>
<td>Stroke/embolism/vascular death/MI</td>
<td>3.87 (3.55–4.19) (557)</td>
<td>5.66 (4.59–6.74) (107)</td>
<td>1.40 (1.13–1.73)</td>
<td>0.0023</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.93 (1.70–2.15) (279)</td>
<td>3.10 (2.31–3.89) (59)</td>
<td>1.49 (1.12–1.98)</td>
<td>0.0067</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.24 (1.06–1.42) (179)</td>
<td>1.63 (1.06–2.21) (31)</td>
<td>1.25 (0.83–1.87)</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Safety outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major or NMCR bleeding</td>
<td>11.44 (10.87–12.01) (1529)</td>
<td>11.97 (10.34–13.61) (206)</td>
<td>1.05 (0.90–1.21)</td>
<td>0.55</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.16 (2.87–3.45) (451)</td>
<td>3.69 (2.82–4.56) (69)</td>
<td>1.08 (0.83–1.40)</td>
<td>0.59</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0.28 (0.19–0.36) (40)</td>
<td>0.26 (0.03–0.49) (5)</td>
<td>0.98 (0.37–2.56)</td>
<td>0.96</td>
</tr>
<tr>
<td>Critical organ bleeding</td>
<td>0.96 (0.82–1.14) (141)</td>
<td>0.74 (0.35–1.12) (14)</td>
<td>0.68 (0.38–1.21)</td>
<td>0.19</td>
</tr>
<tr>
<td>Transfusion ≥2 U</td>
<td>0.73 (0.59–0.87) (105)</td>
<td>1.11 (0.63–1.58) (21)</td>
<td>1.34 (0.81–2.22)</td>
<td>0.25</td>
</tr>
<tr>
<td>Hemoglobin decrease ≥2 g/dL</td>
<td>2.21 (1.96–2.45) (316)</td>
<td>2.72 (1.97–3.46) (51)</td>
<td>1.08 (0.78–1.48)</td>
<td>0.64</td>
</tr>
<tr>
<td>ICH</td>
<td>0.63 (0.50–0.76) (91)</td>
<td>0.68 (0.31–1.05) (13)</td>
<td>1.00 (0.54–1.83)</td>
<td>0.99</td>
</tr>
<tr>
<td>NMCR bleeding</td>
<td>8.56 (8.07–9.06) (1159)</td>
<td>8.53 (7.16–9.90) (149)</td>
<td>1.02 (0.86–1.21)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; ICH, intracranial hemorrhage; MI, myocardial infarction; NMCR, nonmajor clinically relevant; SRF, stable renal function; and WRF, worsening renal function.
INR control (VA TREAT-AF cohort)

n=57,337

Yang F / Turakhia M, in press
providing written informed consent before study entry. Regulatory authorities and ethics committees. All patients or active liver disease. Haemorrhage, creatinine clearance less than 30 mL/min, valve disorder, recent stroke, increased risk of artery disease. Exclusion criteria included severe heart of age with diabetes mellitus, hypertension, or coronary fraction (<40%); at least 75 years of age; or at least 65 years congestive heart failure or reduced left ventricular ejection following: previous stroke or transient ischaemic attack; documented atrial fibrillation and at least one of the clinical centres in 44 countries. Inclusion criteria were patients treated with warfarin used as an approximation groups, the average TTR each centre achieved in its relation to the quality of INR control. In the absence of any primary and secondary outcomes of the RE-LY trial in control. We therefore did a prespecified assessment of the findings for countries and sites with better mean INR standards for such treatment. As in previous multicentre clinical practice often show even lower means. The detailed design and primary results of RE-LY have been published. Patients were recruited from countries and sites with better mean INR correspond well to contemporary warfarin group of RE-LY correspond well to contemporary standards for such treatment. Therefore, the overall standards of anticoagulation in the dabigatran dose but not to warfarin dose. Randomisation and masking

![INR control by country](image)

**TTR < 58:**
Warfarin no better than aspirin

(Wallentin L, Lancet 2010)
The ongoing GENETIC-AF (Genetically Targeted Therapy for the Prevention of Symptomatic Atrial Fibrillation in Patients With Heart Failure) clinical trial will test the hypothesis that genotype-directed bucindolol therapy is superior to metoprolol for the prevention of symptomatic AF in patients with HF.

CATHETER ABLATION FOR RHYTHM AND SYMPTOM CONTROL

ABLATION TECHNIQUE.

Given the limitations of current antiarrhythmic drug therapy, clinicians have shown great interest in the use of nonpharmacological rhythm control interventions in patients with AF and HF. The role of catheter ablation is not simply to restore and maintain sinus rhythm, but more importantly, to ameliorate symptoms and improve QOL. The percutaneous technique, at a minimum, employs circumferential ablation and hence electrical isolation of the pulmonary veins and their connection to atrial myocardium. Additional ablation, such as linear ablation and/or focal ablations of areas with evidence of scar, fractionation, or rotor-perpetuation, may be employed, too, depending upon the type of AF and degree of left atrial disease (Fig. 3) (54–56).

Ablation of complex fractionated atrial electrograms as an adjunct to pulmonary vein isolation (PVI) has been demonstrated to increase freedom from AF compared with PVI alone (55,57). Several investigators have demonstrated that the focal impulse and rotor modulation (FIRM) technique, distinct from PVI, can successfully identify ablative targets, called rotors, and terminate or slow AF and improve arrhythmia-free outcomes compared with conventional ablation alone (56,57). As our understanding of the mechanisms behind AF initiation and propagation continues to advance, durable targets for novel therapies are evolving in tandem (58).

ABLATION VERSUS ANTIARRHYTHMIC DRUG THERAPY.

Although the efficacy of catheter ablation varies according to the underlying severity and duration of AF, multiple studies have established its superiority in those patients with recurrent AF despite antiarrhythmic drug therapy (59,60). Meta-analysis of clinical trials have concluded PVI to be superior to antiarrhythmic drug therapy as a second-line therapy for maintaining sinus rhythm, improving physical functioning, and potentially, reducing readmission rates for patients with symptomatic AF (60,61). Initial studies comparing antiarrhythmic drug therapy versus catheter ablation as initial therapy in treatment-naive patients with paroxysmal AF have revealed conflicting results (62,63); hence, catheter ablation is not typically employed as first-line therapy. However, a recent clinical trial demonstrated a significant attributable benefit to catheter ablation compared with antiarrhythmic therapy as first-line therapy for preventing recurrent atrial tachyarrhythmias at 2 years (64). Notably, these studies were not primarily performed in patients with HF, and many of the antiarrhythmic medications used are contraindicated in patients with HF. To date, there are no studies investigating catheter ablation as first-line treatment for AF in HF patients. Although some trials include freedom from antiarrhythmic drugs as a therapeutic endpoint of catheter ablation, it should be noted that the 2 interventions may be synergistic or even necessary to ameliorate AF-associated symptoms and potentially restore sinus rhythm.

EFFICACY AND OUTCOMES FOR CATHETER ABLATION.

Importantly, studies citing the highest success rates of catheter ablation are composed primarily of middle-aged men with few comorbidities and often included repeat or redo ablation procedures. A smaller number of trials have been performed in dedicated cohorts with AF and concomitant HF.

Table 1 details and reviews the available CENTRAL ILLUSTRATION: The Physiological Relationship Between Atrial Fibrillation and Heart Failure

<table>
<thead>
<tr>
<th>Shared Risk Factors:</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, coronary disease, diabetes, hypertension, chronic kidney disease, obesity, sleep apnea and tobacco use</td>
<td></td>
</tr>
<tr>
<td>Cellular calcium dysregulation</td>
<td></td>
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<tr>
<td>Renin-angiotensin-aldosterone system activation</td>
<td></td>
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<tr>
<td>Increased filling pressures</td>
<td></td>
</tr>
<tr>
<td>Increased focal triggers, pulmonary vein ectopy, substrate remodeling, rotor formation and reentry</td>
<td></td>
</tr>
<tr>
<td>Conduction slowing</td>
<td></td>
</tr>
<tr>
<td>*Action potential duration heterogeneity</td>
<td></td>
</tr>
<tr>
<td>**Decreased effective refractory period</td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td></td>
</tr>
<tr>
<td>Left atrial stretch</td>
<td></td>
</tr>
<tr>
<td>Tachycardia-mediated cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Decreased cardiac output</td>
<td></td>
</tr>
<tr>
<td>Ventricular dysfunction</td>
<td></td>
</tr>
<tr>
<td>Rapid/irregular ventricular rate</td>
<td></td>
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<tr>
<td>Loss of atrial systole</td>
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</tbody>
</table>
patients discharged following decompensated HF with concurrent contraindication receive oral anticoagulation: 68% of concurrent appropriate anticoagulation. At best, two-thirds of patients with atrial fibrillation–chronic kidney disease with co-existent heart failure–atrial fibrillation.

Anticoagulation dilemmas in patients with renal impairment (57% with CrCl < 60 mL/min). A recent study found a similar proportion of patients with severe renal impairment (57% with CrCl < 15 mL/min).

CHARM trial: (candesartan in HF)

Severity of renal impairment in patients with heart failure (HF) and atrial fibrillation (AF). We examined the severity and variation in renal function amongst patients with AF compared with those without AF, the difference being more pronounced.

<table>
<thead>
<tr>
<th>Baseline eGFR (mL/min)</th>
<th>Very severe (&lt; 15 mL/min)</th>
<th>Severe (15-30 mL/min)</th>
<th>Moderate (30-50 mL/min)</th>
<th>Mild (50-80 mL/min)</th>
<th>Normal (&gt; 80 mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-40</td>
<td>0.0</td>
<td>2.6</td>
<td>8.0</td>
<td>20.3</td>
<td>32.3</td>
</tr>
<tr>
<td>40-50</td>
<td>2.0</td>
<td>6.7</td>
<td>16.7</td>
<td>34.1</td>
<td>41.8</td>
</tr>
<tr>
<td>50-60</td>
<td>5.7</td>
<td>11.3</td>
<td>20.1</td>
<td>36.5</td>
<td>43.8</td>
</tr>
<tr>
<td>60-70</td>
<td>11.2</td>
<td>21.5</td>
<td>30.9</td>
<td>42.3</td>
<td>48.6</td>
</tr>
<tr>
<td>70-80</td>
<td>20.3</td>
<td>33.4</td>
<td>45.6</td>
<td>50.2</td>
<td>53.0</td>
</tr>
<tr>
<td>80-90</td>
<td>32.3</td>
<td>47.7</td>
<td>59.9</td>
<td>64.2</td>
<td>64.1</td>
</tr>
</tbody>
</table>

The Authors

Hawkins NM, *Eur J Heart Fail*, 2016
What about bleeding risk?

Patient factors affecting bleeding risk

- Age
- Prior major bleeding
- Anemia
- Kidney disease
- Antiplatelet agents, NSAIDS
- Hypertension (SBP > 160)
- Prior stroke
- High alcohol use
- Moderate to severe liver disease
- Low TTR / unstable INRs

These factors also affect risk of stroke

Quality and Coordination of Care
Anticoagulation prescription in new AF: Primary care vs. cardiology in VA system

n = 140,000

CHADS2 score

Nephrology and Cardiology care not coordinated

- In outpatient setting, most patients take on role of care coordinator
- In U.S., bundled payments are disease focused
- Problem of care structure
  - “I defer to the other”
Chronic kidney disease in patients with cardiac rhythm disturbances or implantable electrical devices: clinical significance and implications for decision making-a position paper of the European Heart Rhythm Association endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society

Giuseppe Boriani (Chair, Italy)*, Irina Savelieva (Co-chair, UK), Gheorghe-Andrei Dan (Romania), Jean Claude Deharo (France), Charles Ferro (UK), Carsten W. Israel (Germany), Deirdre A. Lane (UK), Gaetano La Manna (Italy), Joseph Morton (Australia), Angel Moya Mitjans (Spain), Marc A. Vos (The Netherlands), Mintu P. Turakhia (USA), and Gregory Y.H. Lip (UK)

Document reviewers: Bulent Gorenek (Review Coordinator, Turkey), Yoshihide Takahashi (Japan), Dennis Lau (Australia), Mina Chung (USA), Jens Cosedis Nielsen (Denmark), Laurent Fauchier (France), Tatjana Potpara (Serbia), Francisco Marin (Spain), Gulmira Kudaiberdieva (Turkey), Gerhard Hindricks (Germany), Cecilia Linde (Sweden), and Michele Brignole (Italy)
Renal Function in Patients With Atrial Fibrillation Receiving Anticoagulants
The Canaries in the Coal Mine

The past few years have witnessed unprecedented progress in the field of anticoagulation for atrial fibrillation (AF). Since 2010, 4 direct oral anticoagulants (DOACs) have been approved in nonvalvular AF based on pivotal trials. Patients with advanced chronic kidney disease (CKD) are arguably the highest-risk patients receiving anticoagulation from the standpoint of both stroke/systemic embolism and bleeding events. Although patients with estimated creatinine clearance (eCrCl) less than 30 mL/min/1.73m² (to convert to milliliters per second per meters squared, multiply by 0.0167) were excluded from trials, about 15% to 20% of enrollees had stage 3 CKD, providing clinicians representative data to derive meaningful conclusions to guide practice. Prespecified subgroup analysis and meta-analysis concur that the overall trial results (ie, noninferiority of the DOACs vs warfarin in the prevention of stroke/systemic embolism) are applicable to patients with stage 3 CKD, and several agents may actually have specific advantages.¹

Not enough attention has been focused on systemic approaches to recognize and anticipate the fresh challenges that will be posed in the era of the DOACs, particularly in this high-risk population. Publication of challenge rates to monitor renal function during anticoagulation (high- and low-dose dabigatran and warfarin), albeit statistically significant in the warfarin arm,⁵ this observation may lend credence to the notion of warfarin-related nephropathy/glomerulopathy, but more importantly perhaps, indicates the need for temporal monitoring of renal function during anticoagulant therapy for AF, particularly in patients with CKD. Although most clinicians use estimated glomerular filtration rates to monitor renal function in practice, the doses
Summary

- **Challenges**
  - We have enough data to be worried, but not enough to know what to do
  - Trials of every permutation are unlikely
    - Reliance on observational data
    - More precision risk stratification?

- **Opportunities**
  - Defining areas of controversy, gaps in evidence, and a roadmap for research
  - Starting down a longer path of joint recommendations for clinical care and process measures
  - New friends, new collaborations!
Thank you!

mintu@stanford.edu
@leftbundle