Atrial Fibrillation 2016
Quality of Life and Preventing Stroke

The 14 Clinical Challenges
1. Presentation: Complexity vs Simplicity (ESC)  (2)
2. Etiology: General vs Specific  (2)
3. AC Rx: When / Bridge / NSAID vs SCI / NSR  (2)
4. Aging: TE & Bleeding vs Warfarin  (2)
5. AF / Stent: Triple Rx vs Double Rx  (2)
6. Warf. / NOACs: Efficacy vs Safety  (2)
7. Ablat. Yes / No AC vs LAA Closure  (2)

ACC / AHA / HRS - JACC 2014; 64: 2246 - ESC - EHJ 2013; 34:1471
1a). Acute & Chronic Management Of AF

D Kotecha et. al. . Eur Heart J. 2016;37:2851
Death And Stroke In Patients In 47 Countries 1 Yr After Presenting With AF: A Cohort Study

RE-LY AF (JS Healey et. al.) Lancet 2016; 388: 1161.
Death And Stroke In Patients In 47 Countries 1 Yr After Presenting With AF: A Cohort Study

**Bar Chart**
- **Proportion of individuals with outcome (%)**
- **Outcomes**: Heart failure, Infection, Stroke, Respiratory failure, Cancer, Sudden death, Myocardial infarction, Others, Unknown
- **Proportion**:
  - Heart failure: 30%
  - Infection: 10%
  - Stroke: **30%** (highlighted)
  - Respiratory failure: 5%
  - Cancer: 5%
  - Sudden death: 5%
  - Myocardial infarction: 5%
  - Others: 10%
  - Unknown: 5%

**Reference**
RE-LY AF (JS Healey et. al.) Lancet 2016; 388: 1161.
1b). Integrated Care For AF?
1. ECG screening and monitoring whenever AF might be suspected.

2. Physician-patient relationship are critical in decision making.

3. CHADS-VASc score. With a score \( \geq 2 \) in male and \( \geq 3 \) in female patients, AC is clearly recommended, while in a score of 1 in males and 2 in females, AC should be considered.

4. Bleeding risks should be minimized, hypertension controlled, antiplatelet or NSAID therapy should be of short duration, alcohol use moderated, and anaemia treated and normalized.

5. Use perioperative oral beta-blockers for the prevention of postoperative AF, and restore SR by CV in postoperative AF.

*EHJ 2016; 37:2893*
<table>
<thead>
<tr>
<th></th>
<th>AF - CLINICAL CHALLENGES (14) - 2016</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>Presentation: Complexity vs Simplicity (ESC) (2)</td>
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**References:**

ACC / AHA / HRS - JACC 2014; 64: 2246 - ESC - EHJ 2013; 34: 1471
1). General Etiologies of AF – Think !!!!!

2a). **Gross Mechanisms of AF**

**Atrial Fibrillation and Stroke**

**Focal Electrical Disease**
- Risk Factor
  - Reduced LA/PA Appendage Velocities
  - Atrial Dilatation/Myopathy = Arrhythmia Burden
  - Hypercoagulability
  - Stasis
  - Endothelial Dysfunction

**Systemic Disease Symptom**
- Risk Marker
  - Obesity
  - Metabolic Syndrome
  - Sleep Apnea
  - Diabetes
  - Hypertension

**Temporal Association AF & Stroke**
- As needed Anticoagulation Plausible
- Focal Therapy -> Lower Risk
- Rhythm Treatments -> Lower Risk

**Poor Temporal Association AF & Stroke**
- Systemic Therapy -> Lower Risk
- Risk Persists Despite Rhythm Treatment

*TJ Bunch et. al. Eur Heart J. 2016;37:2890*
2b). Mechanisms of AF Initiation At The Pulmonary Veins

Strands of fibres poorly coupled to left atrial tissue

PV ion currents/APs:
- Small $I_{K1}$, reduced RMP
- Small $I_{Ca,L}$, larger $I_{Kr/Ks}$, reduced AP duration

Abrupt changes in fibre orientation promoting conduction delays and block

PV ion currents/APs:
- Small $I_{Ks}$, Na$^+$ channels inactivated
- Small $I_{Ca,L}$, larger $I_{Kr/Ks}$, larger $I_{Sk}$, reduced AP duration, ERP

2c). Molecular Mechanisms of Focal Ectopic Firing In Paroxysmal AF
Molecular Mechanisms of Re-entry In Paroxysmal AF

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**ACC / AHA / HRS - JACC 2014; 64: 2246** - **ESC - EHJ 2013; 34:1471**
### Components of CHA₂DS₂-VASc

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
<th>CHA₂DS₂-VASc Score</th>
<th>Annual Risk of Stroke (%)</th>
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<tbody>
<tr>
<td><strong>Cardiac failure</strong></td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>HTN</strong></td>
<td>1</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Age ≥75 y</strong></td>
<td>2</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>1</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>2</td>
<td>4</td>
<td>4.0</td>
</tr>
<tr>
<td><strong>Vascular disease (MI, PAD, aortic atherosclerosis)</strong></td>
<td>1</td>
<td>5</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>Age 65-74 y</strong></td>
<td>1</td>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td><strong>Sex category (female)</strong></td>
<td>1</td>
<td>7</td>
<td>9.6</td>
</tr>
<tr>
<td><strong>Age 65-74 y</strong></td>
<td>1</td>
<td>8</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>Sex category (female)</strong></td>
<td>1</td>
<td>9</td>
<td>15.2</td>
</tr>
</tbody>
</table>


**ATRIA - HA van den Ham et.al. J Am Coll Cardiol 2015;66:1851– Points by Age**
AC When ?- The Prevention Of Stroke.

V Fuster, JS Chinitz, Circ. 2012; 125: 2285
Swedish AF Cohort Register (L Friberg, GYH Lip et al) Circ. 2012; 125: 2298
A/C Prevention - Emboli >>>> Bleeding, Thrombosis > Bleeding
Cumulative Hazard Rates Of Embolic Events According To The Pattern Of AF Occurrence

**Persistent vs. Paroxysmal:**
Hazard ratio, 1.43 (95% CI, 1.04–1.96), P value, 0.03

**Permanent vs. Paroxysmal:**
Hazard ratio, 2.04 (95% CI, 1.60–2.61), P value, <0.001

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Years</th>
</tr>
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<tbody>
<tr>
<td>Paroxysmal</td>
<td>0.00</td>
</tr>
<tr>
<td>Persistent</td>
<td>0.00</td>
</tr>
<tr>
<td>Permanent</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>1226</td>
</tr>
<tr>
<td>Persistent</td>
<td>846</td>
</tr>
<tr>
<td>Permanent</td>
<td>2909</td>
</tr>
<tr>
<td></td>
<td>2.00</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>766</td>
</tr>
<tr>
<td>Persistent</td>
<td>502</td>
</tr>
<tr>
<td>Permanent</td>
<td>1975</td>
</tr>
<tr>
<td></td>
<td>3.00</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>604</td>
</tr>
<tr>
<td>Persistent</td>
<td>386</td>
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<tr>
<td>Permanent</td>
<td>1505</td>
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<td>4.00</td>
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<tr>
<td>Paroxysmal</td>
<td>310</td>
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<tr>
<td>Persistent</td>
<td>174</td>
</tr>
<tr>
<td>Permanent</td>
<td>685</td>
</tr>
</tbody>
</table>

T Vanassche, SJ Connolly et al. Eur Heart J. 2015;36:281
1b) Bridging AC and Associated Outcomes During AC Interruption in Patients With AF

The ORBIT-AF is a prospective, observational registry study of US outpatients with AF. Of 7372 patients treated with oral A/C, 2803 overall interruption events occurred in 2200 patients or 30% at a median follow-up of 2 years. Bridging A/C were used in 24% (n=665), predominantly LMW heparin (73%, n=487) and unfractionated heparin (15%, n=97). Bridged patients were more likely to have had prior cerebrovascular events (22% versus 15%; \( P=0.0003 \)) and mechanical valve replacements (9.6% versus 2.4%; \( P<0.0001 \)); however, there was no difference in \( \text{CHA}_2\text{DS}_2\text{-VASc} \) scores (scores \( \geq 2 \) in 94% versus 95%; \( P=0.5 \)). Bleeding events were more common in bridged than nonbridged patients (5.0% versus 1.3%; \( P<0.0001 \)). The incidence of MI, stroke or systemic embolism, major bleeding, hospitalization, or death within 30 days was also significantly higher in patients receiving bridging (13% versus 6.3%). These data do not support the use of routine bridging, and additional data are needed to identify best practices concerning A/C interruptions.

\textit{ORBIT=AF (BA Steinberg et al.), Circulation 2015; 131:488}
### NSAID Exposure in Patients on Antithrombotic Rx
#### Risks For Serious Bleeding At 3 Mo & 2 Yrs

<table>
<thead>
<tr>
<th>Antithrombotic Treatment</th>
<th>Serious Bleeding (3 mo)</th>
<th>Absolute Risk Difference (95% CI)</th>
<th>Serious Bleeding (2 y)</th>
<th>Absolute Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No NSAID</td>
<td></td>
<td>1.9 (1.6–2.3)</td>
<td></td>
<td>1.3 (1.0–1.6)</td>
</tr>
<tr>
<td>NSAID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OAC plus single antiplatelet</strong></td>
<td></td>
<td>2.6 (1.6–3.7)</td>
<td></td>
<td>1.8 (1.1–2.6)</td>
</tr>
<tr>
<td>No NSAID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OAC</strong></td>
<td></td>
<td>2.5 (2.1–3.0)</td>
<td></td>
<td>1.9 (1.4–2.3)</td>
</tr>
<tr>
<td>No NSAID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Single antiplatelet</strong></td>
<td></td>
<td>2.1 (1.7–2.5)</td>
<td></td>
<td>1.4 (1.0–1.8)</td>
</tr>
<tr>
<td>No NSAID</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>NSAID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No treatment</strong></td>
<td></td>
<td>1.6 (1.3–2.0)</td>
<td></td>
<td>1.0 (0.7–1.3)</td>
</tr>
<tr>
<td>No NSAID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td></td>
<td></td>
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</tbody>
</table>

**Absolute Risk per 1000 Patients (95% CI)**
Silent Cerebral Infarcts (SCI) Cardiac Disease And Procedures

Cardioembolic heart disease
- Atrial fibrillation
- Left ventricular thrombus
- Cardiomyopathy
- Patent foramen ovale

Cardiac procedures
- Left heart catheterization
- CABG surgery
- Transcatheter aortic valve implantation
- Pulmonary vein isolation
- Closure of patent foramen ovale

Stroke
Cognitive decline
Dementia
Depression

F Gaita et. al. J Am Coll Cardiol 2013;62:1990 (Italy)
### silent cerebral ischemia in AF correlation with cognitive function

#### Table: Cognitive Function Scores

<table>
<thead>
<tr>
<th>Domains</th>
<th>Controls (N = 90)</th>
<th>PRX AF (N = 90)</th>
<th>PER AF (N = 90)</th>
<th>p PRX / controls</th>
<th>p PER / controls</th>
<th>p PRX/PER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domains</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Immediate Memory</td>
<td>92.4 ± 15.4</td>
<td>86.2 ± 13.8</td>
<td>82.9 ± 11.5</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>2-Visuospatial abilities</td>
<td>95.6 ± 17.5</td>
<td>89.9 ± 14.7</td>
<td>87.1 ± 16.9</td>
<td>0.02</td>
<td>&lt; 0.01</td>
<td>0.24</td>
</tr>
<tr>
<td>3-Language</td>
<td>93.8 ± 16.7</td>
<td>89.9 ± 18.2</td>
<td>84.8 ± 14.8</td>
<td>0.14</td>
<td>&lt; 0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>4-Attention</td>
<td>92.9 ± 11.4</td>
<td>88.8 ± 9.1</td>
<td>88.1 ± 8.7</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>0.59</td>
</tr>
<tr>
<td>5-Delayed memory</td>
<td>101.4 ± 21.2</td>
<td>96.6 ± 16.6</td>
<td>94.9 ± 15.6</td>
<td>0.09</td>
<td>0.02</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>93.5 ± 11.7</td>
<td>88.7 ± 14.7</td>
<td>87.7 ± 14</td>
<td>0.02</td>
<td>&lt; 0.01</td>
<td>0.64</td>
</tr>
</tbody>
</table>

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*F Gaita et. al. J Am Coll Cardiol 2013;62:1990 (Italy)*

2b). **LAA Structure / Function – Stroke in NSR**

**Cardiac Imaging For Assessment**

J Romero et. al. Nat Rev Cardiol. 2014;11:470

**ENGAGE AF** (DK Gupta et al.) EHJ 2014; 35:1457 – *LA Function / NSR ?*


**IMPACT** (DT Martin et al.) EHJ; 2015; 36:1660- *LV Function / NSR ?*
ATs detected by implanted devices are often AF/AFI associated with stroke. We randomized 2718 patients with dual-chamber and biventricular defibrillators to start and stop AC based on remote rhythm monitoring vs. usual office-based follow-up with AC determined by standard clinical criteria. Although AT burden was associated with thromboembolism, there was no temporal relationship between AT and stroke. In other words, in patients with implanted defibrillators, the strategy of early initiation and interruption of anticoagulation based on remotely detected AT did not prevent thromboembolism and bleeding.

**IMPACT** (DT Martin et al.) Eur Heart J 2015; 36:1660
Temporal Relationship of AF & Thromboembolism

**IMPACT Trial**

**AF Burden (0 to 100%, log scale)**

**Months from TE**

**IMPACT** (DT Martin et. al.) EHJ J. 2015;36:1660
AF - CLINICAL CHALLENGES (14) - 2016

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**ACC / AHA / HRS - JACC 2014; 64: 2246 - ESC - EHJ 2013; 34:1471**
1) NVAF - ODDS OF INTRACRANIAL HEMORRHAGE & AGE IN 145 CASE-PATIENTS (INR 2.0-3.0) AND 870 CONTROLS

MC Fang et al., Ann Intern Med 2004; 141:745 (UCSF, Boston, Oakland)
2) The Net Clinical Benefit Of Warfarin By Age Group

Relative Benefits Of Oral AC Vs. No Oral AC (Antiplatelet Therapies Or No) With $\text{CHA}_2\text{DS}_2\text{-VASc}$ And HAS-BLED Scores

ESC Thrombosis Working Group (F Andreotti et. al.) Eur Heart J. 2015;36:3238
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**ACC / AHA / HRS - JACC 2014; 64: 2246  -  ESC - EHJ 2013; 34:1471**
In the WOEST trial, 573 patients were randomized to dual therapy with oral anticoagulation and clopidogrel (75 mg daily) or to triple therapy with oral anticoagulation, clopidogrel and aspirin 80 mg daily. Treatment was continued for one month after bare metal stenting and one year after drug eluting stent placement.

### Bleeding events (TIMI criteria)

<table>
<thead>
<tr>
<th></th>
<th>Dual therapy (%)</th>
<th>Triple therapy (%)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All bleeding Events</td>
<td>19.5</td>
<td>44.9</td>
<td>0.36 (0.26-0.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shin thrombosis</td>
<td>1.5</td>
<td>3.2</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Significant reduction in minor bleeding, < Major bleeding (NS)

**WOEST (W DeWilde et al.) NEJM 2012**
2). Preventing Bleeding in Pts with AF-PCI

Group 1 - LD rivaroxaban (15 mg once daily) plus a P2Y12 inhibitor for 12 Mo

Group 2 - VLD rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, 12 Mo

Group 3 - D-adjusted vitamin K antagonist plus DAPT for 1, 6, or 12 months.

PIONEER AF-PCI (CM Gibson et. al.) NEJM 2016 (In Press)
Prevention of CV Events in Pts with AF-PCI

Group 1 - LD rivaroxaban (15 mg once daily) plus a P2Y12 inhibitor for 12 Mo

Group 2 - VLD rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, 12 Mo

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PIONEER AF-PCI (CM Gibson et al.) NEJM 2016 (In Press)
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<tr>
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<td>Efficacy vs Safety</td>
<td>(2)</td>
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<td>7. Ablat. Yes / No</td>
<td>AC vs LAA Closure</td>
<td>(2)</td>
</tr>
</tbody>
</table>

**ACC / AHA / HRS - JACC 2014; 64: 2246 - ESC - EHJ 2013; 34:1471**
New Oral Anticoagulants - 1) Efficacy & 2) Safety

Stroke or systemic embolism

- W vs placebo
- W vs W_{low-dose}
- W vs aspirin
- W vs aspirin + clopidogrel
- W vs ximelagatran
- W vs dabigatran 110
- W vs rivaroxaban
- W vs dabigatran 150
- W vs apixaban 5

Intracranial hemorrhage

- W vs dabigatran 110
- W vs rivaroxaban
- W vs dabigatran 150
- W vs apixaban 5

Major bleeding

- W vs dabigatran 110
- W vs rivaroxaban
- W vs dabigatran 150
- W vs apixaban 5

Favors warfarin

Favors other treatment

Dialogues in Cardiovascular Medicine 2012;17:189
2a). **NOACs - Kidney & Prosthetic Heart Valves**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHADS(_2)-VASc</strong> score recommended to assess stroke risk</td>
<td>I</td>
</tr>
<tr>
<td>With prior stroke, TIA, or CHADS(_2)-VASc score (\geq 2), oral anticoagulants recommended. Options include:</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>I</td>
</tr>
<tr>
<td>Dabigatran, rivaroxaban, or apixaban</td>
<td>I</td>
</tr>
<tr>
<td><strong>Evaluate renal function before initiation of direct thrombin or factor Xa inhibitors, and reevaluate when clinically indicated and at least annually</strong></td>
<td>I</td>
</tr>
<tr>
<td>Direct thrombin dabigatran and factor Xa inhibitor rivaroxaban are not recommended in patients with AF and end-stage CKD or on dialysis because of a lack of evidence from clinical trials regarding the balance of risks and benefits</td>
<td>III: No Benefit</td>
</tr>
<tr>
<td>Direct thrombin inhibitor dabigatran should not be used with a mechanical heart valve</td>
<td>III: Harm</td>
</tr>
</tbody>
</table>

*CT January et. al. J. Am. Coll. Card. 2014; 64: e1*

*J. Am. Coll. Card. 2016 Sept 27 - VKA 75% - Apixaban 2.5-5mg bid*
<table>
<thead>
<tr>
<th>Kidney Function</th>
<th>Major Bleeding (Events per 100 Patient-Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl ≥60 ml/min</td>
<td>6.2 (4.1-8.9)</td>
</tr>
<tr>
<td>CrCl 30-59 ml/min</td>
<td>8.3 (5.1-12.8)</td>
</tr>
<tr>
<td>CrCl &lt;30 ml/min</td>
<td>30.5 (17.0-50.3)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>54-100</td>
</tr>
</tbody>
</table>
# Characteristics of Warfarin & NOAC Agents

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<th>Warfarin</th>
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<td>HR (95% CI) of major bleeding referent to warfarin, CrCl &lt;50 ml/min</td>
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<td>0.50 (0.38-0.66)</td>
<td>0.98 (0.84-1.14)</td>
<td>1.01 (0.79-1.30)</td>
<td>0.76 (0.58-0.98)†</td>
</tr>
</tbody>
</table>
Efficacy And Safety Of NOAC Vs Warfarin In Moderate CKD From RCT In AF

A Qamar et. al. Circulation. 2016;133:1512
F Del-Carpio Munoz et al., Am J Cardiol 2016; 117:69
When available, idarucizumab is likely to be the treatment of choice for patients who present with dabigatran-induced uncontrolled or life-threatening bleeding or for those who require urgent surgery or invasive procedures. Other reversal agents are in development to reverse other NOACs. These include andexanet alfa, a recombinant truncated form of enzymatically inactive factor Xa, which binds and reverses the anticoagulant action of the factor Xa inhibitors, and PER977 (ciraparantag), a synthetic small molecule that is reported to bind to all of the NOACs.

JW Eikelboon et al., Circ 2015; 132:2412 – ESC Rome, 2016 Sept
<table>
<thead>
<tr>
<th></th>
<th>Clinical Challenges</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Presentation: Complexity vs Symplcity (ESC)</td>
<td>ACC / AHA / HRS - JACC 2014; 64: 2246</td>
</tr>
<tr>
<td>2.</td>
<td>Etiology: General vs Specific</td>
<td>ESC - EHJ 2013; 34:1471</td>
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<td>3.</td>
<td>AC Rx: When / Bridge / NSAID vs SCI / NSR</td>
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<tr>
<td>4.</td>
<td>Aging: TE &amp; Bleeding vs Warfarin</td>
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<td>5.</td>
<td>AF / Stent: Triple Rx vs Double Rx</td>
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<td>6.</td>
<td>Warf. / NOACs: Efficacy vs Safety</td>
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</tr>
<tr>
<td>7.</td>
<td>Ablat. Yes / No AC vs LAA Closure</td>
<td></td>
</tr>
</tbody>
</table>
1a). AF Burden - After Catheter Ablation
Several Strategies (Linq Recorder etc)

El Charitos et al. Circulation. 2012;126:806 (Luebeck, Germ.)
1b). \( \text{CHA}_2 \text{DS}_2 \)-VASc (Recurrent AF) in Predicting Clinical Outcomes in AF After Catheter Ablation

T-F Chao et al., JACC 2011; 58:2380 (Japan) – 565 Pts
2). Primary Efficacy Outcome of Watchman LAA Closure For Embolic Protection In AF PROTECT AF Over 60 Months

- RP Whitlock et. al. Circulation. 2015;131:756
Bleeding Risk, Ischemic Stroke Risk, Indications for Left Atrial Appendage Closure

---

**A**

Proportion of patients (%)

HAS-BLED score

0-1 2 3 4 5 6

---

**B**

Proportion of patients (%)

CHA$_2$DS$_2$-VASc score

0-1 2 3 4 5 6 7 8 9

---

**C**

Proportion of patients (%)

High risk of bleeding
Indication for DAPT
History of GI bleeding
History of intracranial bleeding
History of other bleeding
Risk of falls
Labile NR

---

KC Koskinas et. al. J AmColl Cardiol Intv 2016;9:1374
<table>
<thead>
<tr>
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<th>AF - CLINICAL CHALLENGES (14) - 2016</th>
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<td>Presentation: Complexity vs Symplicity (ESC) (2)</td>
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ACC / AHA / HRS - JACC 2014; 64: 2246 - ESC - EHJ 2013; 34:1471
1a). Prevalence of Adults With AF
The European Union Between 2000 And 2060

BP Krijthe et. al. Eur Heart J. 2013;34:2746

Over Age 50 yr.- AF: 1/2 1st yr of Age, -
1b). Stroke: A Significant Cause Of Poor Health

- Stroke accounts for nearly 10% of all deaths worldwide.

- The number of strokes per year is predicted to rise dramatically as the population ages.

- About 30% strokes are cardioembolic & 15% relate to AF.

- Strokes in patients with AF are more severe and have worse outcomes than strokes in people without AF.

- AF almost doubles the death rate from stroke. AF increases the risk of remaining disabled following stroke by almost 50%.

ESC Guidelines EHJ 2010;31:2369 - Working Group Report, EU 2010
The aim of this study was to assess predictors of adverse 1-week outcomes and determine the effect of LAA) morphology following LAA closure (LAAC) with Amplatzer devices. Between 2009 and 2014, 500 consecutive patients with AF ineligible or at high risk for oral AC underwent LAAC using Amplatzer devices. Procedure-and device-related major adverse events (MAEs) were defined as the composite of death, stroke, major or life-threatening bleeding, serious pericardial effusion, device embolization, major access-site vascular complication, or need for CV surgery within 7 days following the intervention. Early procedural success was 97.8%, and MAEs occurred in 29 patients (5.8%). Independent predictors of MAEs included device repositioning and LVEF<30%, with no effect of device type & size or LAA morphology.
# Baseline Predictors of Device- and Procedure-Related Major Adverse Events Within 7 Days

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<tr>
<th>Predictor</th>
<th>Univariate Analysis</th>
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<td>6.82</td>
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<td>OAC at baseline</td>
<td>2.19</td>
<td>0.95-5.03</td>
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Rates of Major Adverse Events Within 7 Days Stratified on Patient & Device-Related Characteristics

CHADS\textsubscript{2} $< 3$ vs. $\geq 3$; p=0.87

HASBLED $< 3$ vs. $\geq 3$; p=0.51

Device: Amulet vs. ACP; p=0.74

Lone LAAC: Yes vs. No; p=0.47

First 250 patients vs. Latest 250 patients; p=0.85

KC Koskinas et al. J Am Coll Cardiol Intv 2016;9:1374
Baseline Predictors of Patients-Related Major Adverse Events Within 7 Days

**E**
- Device repositioning, p=0.58
- Change of device size, p=0.65
- No procedure success, p=0.51
- Device embolization, p=0.42

**F**
Proportion of patients with MAE (%)

- Chickenwing
- Windsock
- Cauliflower
- Cactus

p=0.78

KC Koskinas et. al. J AmColl Cardiol Intv 2016;9:1374
Rates of Major Adverse Events Within 7 Days Stratified on Patient & Device-Related Characteristics

KC Koskinas et. al. J AmColl Cardiol Intv 2016;9:1374
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<td>36%</td>
<td>80%</td>
<td>50%</td>
</tr>
<tr>
<td>Removal with 4 h of hemodialysis</td>
<td>&lt;1%</td>
<td>7%</td>
<td>&lt;1%</td>
<td>50%-60%</td>
<td>9%</td>
</tr>
<tr>
<td>Volume of distribution, l (66)</td>
<td>8</td>
<td>21</td>
<td>50</td>
<td>50-10</td>
<td>107</td>
</tr>
<tr>
<td>Reversal agent</td>
<td>Vitamin K, FFP, 4F-PCC</td>
<td>4F-PCC</td>
<td>4F-PCC</td>
<td>Idarucizumab</td>
<td>4F-PCC</td>
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<td>1.01 (0.79-1.30)</td>
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</table>
Pharmacokinetics of NOAC Agents

**A**
- Apixaban
  - Parent drug (87% bound)
  - CYP3A4/5 and P-glycoprotein
  - Inactive metabolite (50-60% of dose)
  - 6% cleared with dialysis
  - 27% renal elimination

**B**
- Rivaroxaban
  - Parent drug (95% bound)
  - CYP3A4/5 and CYP2J2 metabolized
  - 51% inactive metabolite
  - 7% feces
  - 36% renal elimination

**C**
- Dabigatran etexilate
  - Parent drug (35% bound)
  - Metabolized in liver
  - 50-60% cleared with dialysis
  - 80% renal elimination

**D**
- Edoxaban
  - Parent drug (55% bound)
  - CYP3A4
  - 10% metabolite
  - 40% bile elimination
  - 9% cleared with dialysis
  - 50% renal elimination

KE Chan et al. J Am Coll Cardiol 2016;67:2888
Use of NOAC Agents in Patients With Advanced CKD and on Dialysis: Substantial and Growing

KE Chan et. al. J Am Coll Cardiol 2016;67:2888
Catheter Ablation Methods

Event-free Survival for the Primary Efficacy and Safety End Points in the Intention-to-Treat Cohort

A Primary Efficacy End Point

- Hazard ratio, 0.96 (95% CI, 0.76–1.22)
- P<0.001 for noninferiority

C Primary Safety End Point

- Hazard ratio, 0.78 (95% CI, 0.52–1.18)
- P=0.24

Catheter Ablation Methods
Repeat Ablations

**Figure A**

- **Repeat Ablation**
  - Number of Events
  - Days Since Index Ablation

**Figure B**

- **Freedom From Repeat Ablation**
  - Days Since Index Ablation
  - Log-Rank P-value = 0.03

**No. at Risk**

- **CRYOBALLOON**
  - 374
  - 343
  - 301
  - 221
  - 149
  - 84
  - 20

- **RFC**
  - 376
  - 341
  - 302
  - 213
  - 135
  - 72
  - 22

Locations Of Atrial Tachycardia That Initiated AF In 45 Patients Reported In 1998

Atrial Fibrillation
Editor: Stanley Nattel
2014

ACC / AHA / HRS - JACC 2014; 64: 2246
ESC - EHJ 2013; 34:1471
### 2) AF Symptoms / Etiology

ESC Guidelines (P Kirchhof, AJ Camm et al) EHJ **2013;34:1471** – **ANSD !!!**

<table>
<thead>
<tr>
<th>EHRA class</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>EHRA I</td>
<td>‘No symptoms’</td>
</tr>
<tr>
<td>EHRA II</td>
<td>‘Mild symptoms’; normal daily activity not affected</td>
</tr>
<tr>
<td>EHRA III</td>
<td>‘Severe symptoms’; normal daily activity affected</td>
</tr>
<tr>
<td>EHRA IV</td>
<td>‘Disabling symptoms’; normal daily activity discontinued</td>
</tr>
</tbody>
</table>
2a). Obesity - Peri-atrial EAT Volume Indexes (CT) AF Events According To LA Volume Index

K Nakanishi et. al. Circ J 2012;76:2748 (Osaka) - Adipocytokines
HS Abed et. al. JAMA. 2013;310:2050 - < Weight, < AF-Australia 2015
# Clinical Studies Showing An Association Of Obesity With AF

<table>
<thead>
<tr>
<th>Study name</th>
<th>Study design</th>
<th>Clinical endpoints</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Abed et al. \(^{43}\)       | 150 obese AF patients randomized to risk factor management (RFM) vs. conventional therapy | Primary: AF symptom burden and severity  
Secondary: AF burden and echocardiographic parameters | RFM results in more marked decrease in body weight and improved cardio-metabolic profile. 
This was associated with improved AF symptom burden, symptom severity, AF burden, and echocardiographic structural parameters |
| ARREST-AF cohort Pathak et al. \(^{44}\) | 149 obese AF patients with \(\geq 1\) cardiac risk factor having ablation were offered RFM. Patients were followed prospectively for | Primary: Recurrent AF  
Secondary: AF frequency, duration and symptoms | RFM in patients having ablation is associated with superior procedural success, improved AF duration, AF frequency, and AF symptom severity. This correlates with weight loss and improved cardio-metabolic risk factor profiles (control vs. RFM group: HR 2.3 (95% CI 1.5–3.6) \(P < 0.001\)). |
| LEGACY cohort Pathak et al. \(^{45}\) | 825 obese AF patients were offered RFM and followed for 34 ± 15 months. Outcomes were assessed in relation to categories of weight loss and weight-fluctuation | Primary: AF burden  
Secondary: Echocardiographic structural parameters | AF burden and symptom severity was most improved in patients with the greatest weight loss (\(>10\%\)). Greatest benefit was observed in patients with stable weights following weight loss. The benefit of weight loss was offset by weight-fluctuation. Weight loss was associated with favourable cardiac structural changes |

HS Abed et. al. JAMA 2013;310:2050  
RK Pathak et. al. JACC 2014;64:2222  
RK Pathak et. al. JACC 2015;65:2159
Mechanisms Underlying Increased AF Risk In Obesity

Increased Epicardial Adiposity

- Oxidative Stress (TLRs and ROS signaling)
- Fibro-fatty Infiltration
  - Adipogenesis (Mature Adipocytes)
  - Fibrosis (MMP-2/7; Activin A)
- Inflammation-Cytokines
  - TNFα, IL-1β, 6, 8

Dysfunctionality in:
- Muscle Activity
- ANS, Ion Channels, Receptors, Gene Expression

Increase in:
- AF Substrate/Triggers

Increased AF burden

2b). **AF Substrate: Towards Specific Fibrotic Atrial Cardiomyopathy**

![Diagram showing box plots comparing collagen I/GAPDH ratios in different cardiac states: SR, Lone AF, and MVD with AF. The comparison between Lone AF and MVD with AF shows statistically significant differences with p-values of 0.01.]

**H Kottkamp Eur Heart J. 2013; 34: 2731**
2c) AF - LAA Morphologies (CT, MRI) – N=932

Chicken Wing LAA Morphology

Windsock LAA Morphology

Cactus LAA Morphology

Cauliflower LAA Morphology

L Di Biase et. al. J Am Coll Cardiol 2012;60:531 (Austin, Foggia, Turin)

J H Yoon et al., Clin Cardiol 2013; 36:235 (Korea) – LA Function > Volume
Novel Genetic Markers Associate With Atrial Fibrillation Risk in Europeans and Japanese

Steven A. Lubitz, MD, MPH,1,2 Kathryn L. Lunetta, PhD,3,4 Honghuang Lui, PhD,5,6 Dan E. Arking, PhD,7 Stella Trompet, PhD,7,8 Guo Li, MS,9 Bouwe P. Krijtje, MSc,10,11 Daniel I. Chasman, PhD,12,13 John Barnard, PhD,14 Marcus E. Kleber, PhD,15 Marcus Dörö, MD,16,17 Koshi Otsuki, PhD,18 Albert V. Smit, PhD,19,20 Stefán Walter, PhD,19 Sund K. Agarwal, MD, PhD,21 Joshua C. Bis, PhD,22 Jennifer A. Brody, BA,22 Lin Y. Chen, MD, MS,23 Brendan M. Everett, MD, MPH,1,25 Ian Ford, PhD,27 Oscar H. Franco, MD, PhD,23,25 Tamara B. Harris, MD,26,25 Albert Hofman, MD, PhD,10,11 Kevin A. Kääb, MD, PhD,20,26 Saagar Mahida, MB, Crn.,26 Sekar Karelsean, MD, MPH,31 Michiaki Kubo, MD, PhD,25 Lenore J. Launer, PhD,28 Peter W. Macfarlane, DSC,29 Jared W. Magnani, MD, MSc,30,31 Barbara McKeown, PhD,32 David D. McManus, MD, ScM,32 Annette Peters, PhD, MPH,32,33 Bruce M. Poole, MD, PhD,32 Leopoldo Molina, MD, MSc,34,35 Lynda M. Rose, MSc,17 Jerome I. Rotter, MD,42 Guenter Silberer, MD,42 Jonathan D. Smith, PhD,42 Noma Sontooshelula, MD, MPH,42,43 David L. Strot, MD,42 Kent D. Taylor, PhD,42 Andreas Tornachatz, MD,42 Tatsuhiko Tsunoda, PhD,42 André G. Uitterlinden, PhD,42,43,44 David R. Van Wagoner, PhD,51 Ulrich Völker, PhD,15,16,25,26 Henry Völzke, MD,17,23 Joanne M. Murabito, MD, ScM,32,45 Monty F. Sinner, MD, MPH,32,45,46 Vilmandur Gudnason, MD, PhD,19,42,46,47 Winfried März, MD,15,25,26 Mina Chung, MD, PhD,29,37 Christine M. Albert, MD, MPH,15,30,32,44 Bruno H. Stricker, MD, PhD,15,30,32,44 Toshihiro Tanaka, MD, PhD,15,30,32,44 Susan R. Heckbert, MD, PhD,15,30,32,44 J. Wouter Jukema, MD, PhD,15,30,44 Alvaro Alonso, MD, PhD,15,30,44 Emilia J. Benjamin, MD, ScM,32,42,46,47 Patrick T. Ellison, MD, PhD,15,32

Integrating Genetic, Transcriptomic, and Functional Analyses to Identify 5 Novel Genes for Atrial Fibrillation

Moritz F. Sinner, MD, MPH;1 Nathan R. Tucker, PhD2; Kathryn L. Lunetta, PhD;2 Koshi Otsuki, PhD;2 J. Gustav Smith, MD, PhD;2 Stella Trompet, PhD;2 Joshua C. Bis, PhD;2 Honghuang Lui, PhD;2 Mia K. Chung, MD;2 Jonas B. Nielsen, MD;2 Steven A. Lubitz, MD, MPH;2 Bouwe P. Krijtje, PhD;2 Jared W. Magnani, MSc;2 Jiancheng Yu, MD, PhD;2 Michael H. Gotlib, MD;2 Tatsuhiko Tsunoda, PhD;2 Martina Müller-Nurasyid, PhD;2 Peter Lichtner, PhD;2 Annette Peters, PhD;2 Elena Dolmatova, PhD;2 Michiaki Kubo, MD;2 Jonathan D. Smith, PhD;2 Bruce M. Poole, MD, PhD;2 Nicholas L. Smith, MD;2 J. Wouter Jukema, MD, PhD;2 Daniel I. Chasman, PhD;2 Christine M. Albert, MD, MPH;2 Yusuke Ebana, MD, PhD;2 Tetsushi Furukawa, MD, PhD;2 Peter W. Macfarlane, DSC;2 Tamara B. Harris, MD;2 Lewis Darbar, MD;2 Marcus Dörö, MD;2 Anders G. Holst, MD, PhD;2 Jesper H. Svendsen, MD, DMSc;2 Albert Hofman, MD, PhD;2 Andre G. Uitterlinden, MD, PhD;2 Vilmandur Gudnason, MD;2 Mitsuishi Itohe, MD, PhD;2 Ramesh Malik, PhD;2 Martin Dichtgans, MD, MSc;2 David R. Van Wagoner, PhD;2 META STROKE Consortium;2 AFGen Consortium;2 Emilia J. Benjamin, MD, ScM;2 David J. Miller, MD;2 Olle Melander, MD, PhD;2 Susan R. Heckbert, MD, PhD;2 Ian Ford, PhD;2 Yongmei Liu, MD, PhD;2 John Barnard, PhD;2 Morten S. Olsen, MSc, PhD;2 Bruno H.C. Stricker, MB, PhD;2 Toshihiro Tanaka, MD, PhD;2 Stefan Kääb, MD, PhD;2 Patrick T. Ellison, MD, PhD;2

2d). Genetics in AF – Familial 5%
Strategies For miRNA-Based Therapies


Downregulated miRNAs
- miRNA overexpression
  - miRNA mimic duplex
  - Virus-based overexpression
  - miRNA coding sequence
  - AAA
- Target gene
  - ORF
  - Binding site
  - miRNA level increased to normal

- Downregulation of overexpressed target proteins
- Diseased heart

Upregulated miRNAs
- miRNA knockdown
  - Anti-miRNA oligos
  - miRNA sponge
  - miR-mask
  - Target protection
  - Mask
  - AAA

- Upregulation of downregulated target proteins
- Healthy heart

- Upregulation of selected downregulated target protein
Dabigatran Bound To Idarucizumab

JW Eikelboom et. al. Circulation 2015;132:2412
We performed a meta-analysis of the randomized clinical trials that compared efficacy and safety (major bleeding) outcomes of NOACs compared to W. for the treatment of NVAF and had available data on renal function. Renal function was assessed by baseline estimated GF rate divided in 3 groups: normal [estimated GF rate >80 ml/min], mildly impaired [50 to 80 ml/min], and moderate impairment [<50 ml/min]). We included 4 randomized clinical trials enrolling a total of 58,338 subjects. The use of NOACs was associated with a reduced risk of S/SE and reduced risk of major bleeding compared to Warfarin in subjects with mild or moderate renal impairment suggesting a favorable risk profile of these agents in patients.
Major Complication Rates Across Watchman Clinical Studies

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