Disclosures:

Advisor and Speaker: Abbott, Boheinger, MSD, Pfizer, Menarini, Bayer, AstraZeneca, Merck, Servier.

No Disclosures for this presentation.
ATRIAL FIBRILATION

• Globally Atrial Fib. varies from 30-35 millions in the planet.
• Is the most common Arrhythmia in the world: increasingly aging population, more Hypertension, more HF, more diabetics.....
• Stroke is a devastating consequence
The new concept in AFib

Pathophysiology of Atrial Fibrillation

- Inflammation
- Mitral regurgitation
- ↓ compliance
- LVH
- Diastolic dysfunction
- ↑ stretch-activated channels
- ↑ dispersion of refractoriness
- ↑ pulmonary vein focal/discharges?

Increased vulnerability to atrial fibrillation?
The new concept in AFib

Pathophysiology of Atrial Fibrillation

- Inflammation
- Mitral regurgitation
- Atrial dilatation/stretch
- LVH
- Diastolic dysfunction
- Stretch-activated channels
- Dispersion of refractoriness
- Pulmonary vein focal/discharges?

Increased vulnerability to atrial fibrillation?
ATRIAL FIB. IS A SISTEMIC DISEASE WITH SISTEMIC CONSEQUENCES
ATRIAL FIB. IS A PROGRESSIVE DISEASE

Progression of AF

From first onset to permanent
From uncomplicated to significant comorbidities/consequences

Sinus Rhythm
Asymptomatic AF episode
Symptomatic AF episode

CV outcomes
(Stroke, Death, Hospitalization)
ATRIAL FIBRILATION: CONTEMPORARY MANAGEMENT STRATEGIES

Enrique Melgarejo R., MD, FACC, FESC
President Colombian Society of Cardiology
Emeritus Professor Military Hospital, Nueva Granada University, Bogota, Colombia.
Member HRA.
Sody Award Jackson Memorial Hospital, U of Miami
QUESTIONS DILEMMAS AND PROBLEMS IN MANAGEMENT OF ATRIAL FIB 2017

STILL WE DON´T HAVE ANSWERS FOR THOSE...

Enrique Melgarejo R., MD, FACC, FESC
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Emeritus Professor Military Hospital, Nueva Granada University, Bogota, Colombia
Member HRA,
Sody Award Jackso Memorial Hospital, U of Miami
ADVANCES

NOACs
First question:
Which is the meaning of “Non Valvular Atrial Fibrilation”?

• Valvular AF refers to AF that occurs in the presence of mechanical prosthetic heart valves or moderate to severe mitral stenosis (usually of rehumatic origin).
• These patients were excluded from NOACs trials.
SECOND QUESTION:
IS IT POSSIBLE TO USE NOACS IN:

<table>
<thead>
<tr>
<th>Eligible</th>
<th>Contra-indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical prosthetic valve</td>
<td>✓</td>
</tr>
<tr>
<td>Moderate to severe mitral stenosis (usually of rheumatic origin)</td>
<td>✓</td>
</tr>
<tr>
<td>Mild to moderate other native valvular disease</td>
<td>✓</td>
</tr>
<tr>
<td>Severe aortic stenosis</td>
<td>✓</td>
</tr>
<tr>
<td>Limited data. Most will undergo intervention</td>
<td></td>
</tr>
<tr>
<td>Bioprosthetic valve$^a$</td>
<td>✓</td>
</tr>
<tr>
<td>(except for the first 3 months post-operatively)</td>
<td></td>
</tr>
<tr>
<td>Mitral valve repair$^a$</td>
<td>✓</td>
</tr>
<tr>
<td>(except for the first 3–6 months post-operatively)</td>
<td></td>
</tr>
<tr>
<td>PTAV and TAVI</td>
<td>✓</td>
</tr>
<tr>
<td>(but no prospective data; may require combination with single or double antiplatelets; consider bleeding risk)</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>✓</td>
</tr>
<tr>
<td>(but no prospective data)</td>
<td></td>
</tr>
</tbody>
</table>
THIRD QUESTION: IS ATRIAL FIB. A PREVENTIVE DISEASE?

YES!

BECAUSE THERE ARE RISK FACTORS!
Cardiovascular and other conditions independently associated with atrial fibrillation (1)

<table>
<thead>
<tr>
<th>Characteristic/comorbidity</th>
<th>Association with AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic predisposition (based on multiple common gene variants associated with AF)</td>
<td>HR range 0.4–3.2</td>
</tr>
<tr>
<td>Older age</td>
<td></td>
</tr>
<tr>
<td>50–59 years</td>
<td>HR: 1.00 (reference)</td>
</tr>
<tr>
<td>60–69 years</td>
<td>4.98 (95% CI 3.49–7.10)</td>
</tr>
<tr>
<td>70–79 years</td>
<td>7.35 (95% CI 5.28–10.2)</td>
</tr>
<tr>
<td>80–89 years</td>
<td>9.33 (95% CI 6.68–13.0)</td>
</tr>
<tr>
<td>Hypertension (treated vs. none)</td>
<td>HR 1.32 (95% CI 1.08–1.60)</td>
</tr>
<tr>
<td>Heart failure vs. none</td>
<td>HR 1.43 (95% CI 0.85–2.40)</td>
</tr>
<tr>
<td>Valvular heart disease vs. none</td>
<td>RR 2.42 (95% CI 1.62–3.60)</td>
</tr>
<tr>
<td>Myocardial infarction vs. none</td>
<td>HR 1.46 (95% CI 1.07–1.98)</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>(reference: euthyroid)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>HR 1.23 (95% CI 0.77–1.97)</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>RR 1.31 (95% CI 1.19–1.44)</td>
</tr>
<tr>
<td>Overt hyperthyroidism</td>
<td>RR 1.42 (95% CI 1.22–1.63)</td>
</tr>
<tr>
<td>Obesity (body mass index)</td>
<td>HR:</td>
</tr>
<tr>
<td>None (&lt;25 kg/m²)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Overweight (25–30 kg/m²)</td>
<td>1.13 (95% CI 0.87–1.46)</td>
</tr>
<tr>
<td>Obese (≥31 kg/m²)</td>
<td>1.37 (95% CI 1.05–1.78)</td>
</tr>
<tr>
<td>Diabetes mellitus vs. none</td>
<td>HR 1.25 (95% CI 0.98–1.60)</td>
</tr>
</tbody>
</table>

HR = hazard ratio; RR = risk ratio

www.escardio.org/guidelines
Cardiovascular and other conditions independently associated with atrial fibrillation (2)

<table>
<thead>
<tr>
<th>Characteristic/comorbidity</th>
<th>Association with AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>RR:</td>
</tr>
<tr>
<td>FEV1 ≥80%</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>FEV1 60–80%</td>
<td>1.28 (95% CI 0.79–2.06)</td>
</tr>
<tr>
<td>FEV1 &lt;60%</td>
<td>2.53 (95% CI 1.45–4.42)</td>
</tr>
<tr>
<td>Obstructive sleep apnoea vs. none</td>
<td>HR 2.18 (95% CI 1.34–3.54)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>OR:</td>
</tr>
<tr>
<td>None</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Stage 1 or 2</td>
<td>2.67 (95% CI 2.04–3.48)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>1.68 (95% CI 1.26–2.24)</td>
</tr>
<tr>
<td>Stage 4 or 5</td>
<td>3.52 (95% CI 1.73–7.15)</td>
</tr>
<tr>
<td>Smoking</td>
<td>HR:</td>
</tr>
<tr>
<td>Never</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Former</td>
<td>1.32 (95% CI 1.10–1.57)</td>
</tr>
<tr>
<td>Current</td>
<td>2.05 (95% CI 1.71–2.47)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>RR:</td>
</tr>
<tr>
<td>None</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>1–6 drinks/week</td>
<td>1.01 (95% CI 0.94–1.09)</td>
</tr>
<tr>
<td>7–14 drinks/week</td>
<td>1.07 (95% CI 0.98–1.17)</td>
</tr>
<tr>
<td>15–21 drinks/week</td>
<td>1.14 (95% CI 1.01–1.28)</td>
</tr>
<tr>
<td>&gt;21 drinks/week</td>
<td>1.39 (95% CI 1.22–1.58)</td>
</tr>
<tr>
<td>Habitual vigorous exercise</td>
<td>RR:</td>
</tr>
<tr>
<td>Non-exercisers</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>&lt;1 day/week</td>
<td>0.90 (95% CI 0.68–1.20)</td>
</tr>
<tr>
<td>1–2 days/week</td>
<td>1.09 (95% CI 0.95–1.26)</td>
</tr>
<tr>
<td>3–4 days/week</td>
<td>1.04 (95% CI 0.91–1.19)</td>
</tr>
<tr>
<td>5–7 days/week</td>
<td>1.20 (95% CI 1.02–1.41)</td>
</tr>
</tbody>
</table>
Risk Factors for Stroke and AF

- The risk factors for stroke in AF are very similar to the risk factors that lead to the development of AF

CDC website: Atrial Fibrillation Fact Sheet
It is crucial to control the risk factors. Not only ablation and drugs!

**LEGACY** - Sustained weight loss in obese patients with symptomatic AF is associated with:

1. A dose-dependent effect on long-term freedom from AF (6-fold)
2. A reduction in LA volume and LVH
3. Lower BP & lipids
4. Improved glycaemic control
5. A reduction in hsCRP
FIRST DILEMMA
Trombosis vs. hemorragia.

the fear persist!
DILEMMA

Stroke prevention in atrial fibrillation

- Mechanical heart valves or moderate or severe mitral stenosis
  - Yes
  - No
    - Estimate stroke risk based on number of CHA2DS2-VASc risk factors
      - 0:
        - No antithrombotic treatment (IIb)
      - ≥1:
        - Oral anticoagulation indicated
          - Assess for contra-indications
          - Correct reversible bleeding risk factors
          - LAA occluding devices may be considered in patients with clear contra-indications for OAC (IIbC)
          - NOAC (IA)b
          - VKA (IA)c

*Includes women without other stroke risk factors
b IIaB for women with only one additional stroke risk factor
c IIb for patients with mechanical heart valves or mitral stenosis

www.escardio.org/guidelines
European Heart Journal - doi:10.1093/eurheartj/ehw310
Performance and Validation of a Novel Biomarker-Based Stroke Risk Score for Atrial Fibrillation

- 8356 patients with 16,137 person-years of follow-up in anticoagulated patients with AF in the RE-LY study.

- ABC risk score, which incorporates age, biomarkers (hs-cTn and NT-proBNP), and clinical history of prior stroke.

- The biomarker-based ABC stroke score is an improved decision-making tool for patients with AF, specially for CHA$_2$DS$_2$VASc score <2.

http://dx.doi.org/10.1161/CIRCULATIONAHA.116.022802
Published Ahead of Print: August 28, 2016
Effectiveness and Safety of Standard-Dose Nonvitamin K Antagonist Oral Anticoagulants and Warfarin Among Patients With Atrial Fibrillation With a Single Stroke Risk Factor: A Nationwide Cohort Study

Gregory Y. H. Lip, MD; Flemming Skjøth, MSc, PhD; Peter Brunnum Nielsen, MSc, PhD; Jette Nordström Kjellgaard, BSc; Torben Bjerregaard Larsen, MD, PhD

RESULTS Of 14,020 participants, 5,511 (36.7%) were women, and the median age for participants was 66.5 years. For the principal effectiveness end point of ischemic stroke/systemic embolism, no significant differences of the NOACs compared with treatment with warfarin across strata were evident. For the end point of "any bleeding," this was significantly lower for treatment with apixaban (hazard ratio [HR], 0.35; 95% CI, 0.17-0.72) and dabigatran (HR, 0.48; 95% CI, 0.30-0.77) compared with warfarin in the main analysis, and was not significantly different for treatment with rivaroxaban vs warfarin (HR, 0.84; 95% CI, 0.49-1.44). There was broad consistency across most subgroups in the sensitivity analyses and whether 1- or 2.5-year follow-up periods were analyzed. However, falsification end points nerally did not falsify, indicating the possible presence of residual confounding across these comparisons, presumably related to selective prescribing and unobserved covariates.

CONCLUSIONS AND RELEVANCE In this Danish cohort study of patients with atrial fibrillation and a single stroke risk factor, there was no difference between NOACs compared with treatment with warfarin in terms of the risk of having an ischemic stroke/systemic embolism. For "any bleeding," this was lower for treatment with apixaban and dabigatran compared with warfarin. These data do not allow for a definitive statement of the comparative effectiveness or safety of NOACs because of the possible residual confounding that was unmasked with falsification outcomes.
PROBLEMS in AF 2017

• There is evidence of underuse of anticoagulants for AF after 10 years of DOACs.
• Inconsistent approach to cardiovascular risk factors
• Inadequate treatment for concomitant comorbidities.
• In Real Life studies, DOACs are used in sub-therapeutic dosis
• Anticoagulation is used thinking in preventing bleeding complications more than in preventing tromboembolism. Stroke is “God´s design”; bleeding is a medical complication”!

Fear to anticoagulation persist!
ANOTHER PROBLEM: ARE ALL NOACS THE SAME?
All NOACs are equal, but some are more equal than others....

Dr Puneet Kakar MRCP LLM MSc
Consultant Stroke physician
Epsom general hospital
Choose the OAC drug considering the patient profile and/or preferences

- Recurrent stroke/TIA despite well controlled VKA
  - Consider agent with superior efficacy for preventing both IS and haemorrhagic stroke
  - D150

- Patient has moderate to severe renal impairment CrCl 15–49 ml min⁻¹
  - D110

- GI symptoms or dyspepsia
  - Also consider increased risk of bleeding
  - A

- GI symptoms or dyspepsia
  - A

- High risk of bleeding (HAS-BLED ≥3)
  - Consider agent with lowest bleed incidence
  - A

- Patient preference for once daily dosing
  - A

- Asian patients
  - Consider agents with reduced risk of ICH and major haemorrhage in Asian populations
  - A

- Less likely to do well on VKA (SAME-TT, R₂ score ≥2)
  - Avoid ‘trial’ of warfarin and consider NOAC upfront
  - A

If CrCl < 15 ml min⁻¹, use VKA
**Question:**

How to adjust the dose of DOACS in CKD?

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Study</th>
<th>Excretion</th>
<th>Dosages and renal adjustment</th>
</tr>
</thead>
</table>
| Dabigatran | RE-LY 75 | Mostly renal | CrCl > 30 ml/min : 150 mg orally twice daily  
CrCl 15- 30 ml/min : 110 mg orally twice daily  
CrCl < 15 ml/min : Avoid |
| Rivaroxaban | ROCKET AF[57] | Partially renal | CrCl > 50 ml/min : 20 mg orally once daily  
CrCl 15 - 50 ml/min : 15 mg orally once daily  
CrCl < 15 ml/min : Avoid |
| Apixaban | ARISTOTLE[58] AVERROES[58] | Partially renal | Recommended dose: 5 mg orally twice daily  
No dose adjustment required in patients with mild, moderate, or severe renal impairment alone. In patients with at least 2 of the following:  
- age ≥80 years  
- body weight ≤60 kg  
- serum creatinine ≥1.5 mg/dL. The recommended dose is 2.5 mg orally twice daily  
CrCl < 15 ml/min : Avoid |

Among the 1,473 patients with a renal indication for dose reduction, 43.0% were potentially overdosed. These patients were associated with a higher risk of major bleeding (hazard ratio [HR], 2.19; 95% confidence interval [CI], 1.07-4.46), but no significant difference in stroke. Among the 13,392 patients without a renal indication for dose reduction, 13.3% were potentially underdosed.

The apixaban underdosed patients were associated with a higher risk of stroke (HR, 4.87; 95% CI, 1.30-18.26), but no significant difference in bleeding. The rivaroxaban and dabigatran underdosed patients were not associated with any stroke.
CENTRAL ILLUSTRATION: Prevalence and Impact of Inappropriate NOAC Dosing

WHETHER TO INTERRUPT DOAC THERAPY

CONSIDERATIONS

No clinically important risk

Low

Uncertain, intermediate, or high

Procedural bleed risk?

Perform the procedure uninterrupted, but time it at DOAC interval trough.

INCREASED PATIENT BLEED RISK?

Yes

No

GUIDANCE

INTERRUPT

GIVE DOAC THERAPY CONTINUOUSLY

GIVE DOAC THERAPY CONTINUOUSLY

WHEN TO INTERRUPT

CONSIDERATIONS

CrCl

Discontinue

CrCl < 15

Discontinue

CrCl < 15

Discontinue

CrCl < 15

Discontinue

CrCl < 15

Discontinue

CrCl < 30

Insufficient data on best practices. Interrupt at least as long as determined by CrCl (Table 2) and possibly longer.

GUIDANCE

Measure CrCl

DTI — direct thrombin inhibitor (dabigatran)

FXa inhibitor — Factor Xa inhibitor (apixaban, edoxaban, rivaroxaban)

CrCl — creatinine clearance

ICH — intracranial hemorrhage

PARENTERAL BRIDGING NOT IndICATED FOR DOACS.

Perform the procedure
ABLATION: A SOLUTION FOR ANTIARRHYTHMIC USE?
Pulmonary Vein Isolation With Versus Without Continued Antiarrhythmic Drug Treatment in Subjects With Recurrent Atrial Fibrillation (POWDER-AF)

Arrhythmias occurred in 2.7% (n=2) patients who continued antiarrhythmic drug therapy, compared with 21.9% (n=16) of those who discontinued therapy (P<0.001).

The freedom from atrial fibrillation in the patients after PVI without drugs was 78%, which confirms a good outcome with cardiac ablation, but by adding drugs, you can reach up to 97% freedom from atrial fibrillation.

In addition, patients who continued AAD had a lower occurrence of repeat ablation (1.3%) vs those who stopped therapy (17.1%; odds ratio [OR] 0.06, 95% CI 0.001–0.46)
Whether to initiate oral anticoagulant therapy in advanced chronic kidney disease patients with atrial fibrillation remains debatable. Although randomized trial data are lacking, observational studies yield controversial results. Keskar and colleagues analyzed data from a Canadian health care system and found that in elderly chronic kidney disease patients with atrial fibrillation, oral anticoagulant therapy did not prevent ischemic strokes, induced hemorrhages, but prolonged life. These paradoxical findings emphasize the dire need for an adequately powered randomized trial.
Does Left Atrial Appendage (LAA) occlusion prevent stroke?

- Left atrial thrombus on echo always in the LAA
- Results with device closure of the LAA mixed
Comparison of Watchman device with new oral anti-coagulants in patients with atrial fibrillation: A network meta-analysis
Do NOACs Prevent Stroke in Rheumatic AF?

- Rheumatic disease common in low-middle income countries
- ‘Global’ trials excluded rheumatic patients
THE PROBLEM WITH EVIDENCE: DELAYED OR NO ANTICOAGULATION… RESULT: DEMENTIA!

- Patients prescribed aspirin and clopidogrel 3 years or more after their initial diagnosis had a more than threefold increase in the risk of dementia (hazard ratio [HR] 3.39, 95% CI 2.4–4.65; P<0.0001).

- Similarly, delays in warfarin therapy were associated with a two-and-a-half times greater risk of developing dementia (HR 2.55, 95% CI 1.59–4.09; P<0.0001).

Dementia rates increase with delays in initiation of anticoagulation treatment for atrial fibrillation. Heart Rhythm Society 2017 Scientific Sessions. May 12, 2017; Chicago, IL. Abstract C-AB30-03
Implications of AF

- How to manage patients with HF, valvular disease, hypertension?
  - AF is present in up to 90% of participants in hypertension trials[a]
  - In patients with hypertension, ACEis and ARBs may reduce AF or its progression
  - If you knew the patient already had AF, is may change how hypertension is treated
- Patients may present with HF and silent AF
  - Treatment with β-blockers,

Conclusions

1) All Risk Factors for CAD and Stroke are the same for AF corresponding to >85%
2) Focus on primary prevention and management of traditional cardiovascular risk factors.
3) The importance for detect AF as early as possible
4) Sub-use and sub-dosis: a problem of Real World.
5) CKD and DOACs need attention,
6) Anticoagulation in Afib. is the hallmark regardless of other management.
7) Atrial fib. induces stroke, HF, dementia and detrimental quality of life.
A Fibrilation

• Requires apply all known and developing

MANAGEMENT STRATEGIES
MEN WERE NOT BORN TO DIE, BUT TO INNOVATE

A. ARENDT