Zoom in on atrial fibrillation
NEW ORAL ANTICOAGULANTS: FOCUS ON EDOXABAN
October 16 2015 – 16:15-18:00
Arazzi Room

Real-life data from PREFER in AF Registry
Raffaele De Caterina

October 16, 2015 – 16:55-17:15, 15 min. + 5 min. disc.
Prof. Raffaele De Caterina
Conflicts of Interest

• Co-author ESC Guidelines on Atrial Fibrillation 2010-2012
• Steering Committee member, National Coordinator for Italy, and Co-author of APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE-AF, Re-DUAL PCI
• Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck
NOACs in atrial fibrillation - Timelines

- RE-LY
  - August 2009
- AVERROES
  - February 2011
- ROCKET-AF
  - August 2011
- ARISTOTLE
  - August 2011
- ENGAGE-AF
  - November 2013
And after the big trials?

- «Field» experience: Registries and post-registration surveys (Phase IV studies)
Why Registries/post-marketing surveillance?

- Registries allow a snapshot of treatment behaviors...
- When run consecutively registries allow a dynamic view of treatment changing pattern
- ...and may guide educational efforts, identifying unmet needs and areas where to focus future interventions
- But they should NOT to be used strictly to «confirm» efficacy or safety as derived from controlled trials!
- They can however provide «reassurance» that data from trials are applicable to «the real world»
- Or document an inappropriate/insufficient/excessive use, thus guiding corrections and educational efforts
PREFER in AF: Aims

- The current ESC guidelines for the management of AF (focused update 2012) recommend a NOAC for the prevention of thromboembolism in non-valvular AF

<table>
<thead>
<tr>
<th>ESC Guideline Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs is recommended</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Where OAC is recommended, one of the NOACs should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on net clinical benefit</td>
<td>IIa</td>
<td>A</td>
</tr>
</tbody>
</table>

- The PREFER in AF registry was designed to describe how patients with AF are currently managed in Europe

NOAC, non-VKA oral anticoagulant; VKA, vitamin K antagonist

PREFER in AF was a prospective, observational, multicentre study conducted in 7 EU countries.

Consecutive patients were enrolled from January 2012 to January 2013, with final $N=7243 \ (\geq 18 \text{ years of age}; \text{provided written informed consent; history of AF})$.

Patients were assessed at baseline and at a 1-year follow-up visit (demographics, risk factors, diagnosis, treatment, AF events and anticoagulation therapy; quality of life and treatment satisfaction).

For regional comparisons, Germany, Austria and Switzerland were combined into one pre-specified region (DACH).

Types of VKAs and sites of INR measurement across Europe

DACH, Germany, Austria and Switzerland

Adequacy of INR control

- Adequate INR control is defined as at least 2 of 3 INR values in therapeutic range (2.0 to 3.0)
  - 72.1% of all patients had adequate INR control
  - Adequate INR was overestimated by physicians in all countries
Data from a global AF registry: INR control by region

Adapted from Healey et al. Presentation at ESC 2011
http://www.escardio.org/congresses/esc-2011/congress-reports/Pages/711-6-AF-registry-global.aspx
## Patient demographics

- In PREFER in AF, patient characteristics
  
  - Were comparable across the different countries and to other registries\(^1\,\text{--}^4\)
  
  - At baseline, \textbf{30.0\% of patients had paroxysmal AF, 24.0\% had persistent AF, 7.2\% had long-standing persistent AF and 38.8\% had permanent AF}\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>France (n=1532)</th>
<th>DACH (n=1771)</th>
<th>Italy (n=1888)</th>
<th>Spain (n=858)</th>
<th>UK (n=1194)</th>
<th>Total (N=7243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years] (mean)</td>
<td>72.9</td>
<td>71.9</td>
<td>70.9</td>
<td>70.5</td>
<td>70.7</td>
<td>71.5</td>
</tr>
<tr>
<td>Male (%)</td>
<td>59.3</td>
<td>63.0</td>
<td>57.0</td>
<td>56.0</td>
<td>64.5</td>
<td>60.1</td>
</tr>
<tr>
<td>Height [cm] (mean)</td>
<td>169.1</td>
<td>171.7</td>
<td>167.3</td>
<td>165.5</td>
<td>171.5</td>
<td>169.2</td>
</tr>
<tr>
<td>Weight [kg] (mean)</td>
<td>78.3</td>
<td>84.0</td>
<td>76.2</td>
<td>76.9</td>
<td>86.5</td>
<td>80.3</td>
</tr>
<tr>
<td>BMI [kg/m(^2)] (mean)</td>
<td>27.3</td>
<td>28.4</td>
<td>27.2</td>
<td>28.1</td>
<td>29.3</td>
<td>27.9</td>
</tr>
<tr>
<td>Chronic kidney disease [%]</td>
<td>10.1</td>
<td>14.9</td>
<td>12.5</td>
<td>12.7</td>
<td>14.0</td>
<td>12.9</td>
</tr>
</tbody>
</table>

DACH, Germany, Austria and Switzerland

Similar stroke and bleeding risks at baseline across European countries\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>France (n=1532)</th>
<th>DACH (n=1771)</th>
<th>Italy (n=1888)</th>
<th>Spain (n=858)</th>
<th>UK (n=1194)</th>
<th>Total (N=7243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CHA}_2\text{DS}_2\text{VASc} ) score (mean)</td>
<td>3.3</td>
<td>3.7</td>
<td>3.3</td>
<td>3.3</td>
<td>3.2</td>
<td>3.4</td>
</tr>
<tr>
<td>Score =1 (%)</td>
<td>9.2</td>
<td>7.1</td>
<td>11.3</td>
<td>11.7</td>
<td>12.8</td>
<td>10.1</td>
</tr>
<tr>
<td>Score ≥2 (%)</td>
<td>83.0</td>
<td>89.6</td>
<td>83.4</td>
<td>81.8</td>
<td>80.2</td>
<td>84.1</td>
</tr>
<tr>
<td>HAS-BLED score (mean)</td>
<td>1.9</td>
<td>2.1</td>
<td>2.1</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Risk factors reported in correlation with \( \text{CHA}_2\text{DS}_2\text{VASc} \) score
DACH, Germany, Austria and Switzerland; TIA, transient ischaemic attack

EuroHeart and PREFER in AF: Improved anticoagulation by CHADS\textsubscript{2}/CHA\textsubscript{2}DS\textsubscript{2}-VASc over time


AP, antiplatelet
Stroke risk and treatment at baseline

- With increasing CHA$_2$DS$_2$-VASc score, more patients received a VKA and VKA + AP
- Still, a large proportion of patients received no anticoagulation despite a high thromboembolic risk

**CHA$_2$DS$_2$-VASc score**

**Treatment by CHA$_2$DS$_2$-VASc score**

Rincon et al. Poster presented at ESC 2014; Poster P3225
**Trends in the antithrombotic management of AF from PREFER in AF**

- Antithrombotic management of patients with AF in Europe has been substantially adapted to ESC guideline recommendations.
- The baseline anticoagulation rate in patients with CHA2DS2-VASc ≥2 was 85.6% and 70.1% in those with CHA2DS2-VASc = 1.
- From baseline to follow up, there was a significant reduction in the use of VKAs while NOAC use rose.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall anticoagulation (%)</td>
<td>82.3</td>
<td>80.0</td>
</tr>
<tr>
<td>VKA alone (%)</td>
<td>66.3</td>
<td>61.8</td>
</tr>
<tr>
<td>NOAC (%)</td>
<td>6.1</td>
<td>12.6</td>
</tr>
<tr>
<td>Direct FXa inhibitor(^a)</td>
<td>1.9</td>
<td>6.0</td>
</tr>
<tr>
<td>Direct thrombin inhibitor(^b)</td>
<td>4.0</td>
<td>6.5</td>
</tr>
<tr>
<td>Long-term VKA + AP (%)</td>
<td>9.9</td>
<td>5.7</td>
</tr>
<tr>
<td>AP alone (%)</td>
<td>11.2</td>
<td>8.0</td>
</tr>
</tbody>
</table>

\(^a\)Rivaroxaban, apixaban; \(^b\)dabigatran

Rincon et al. Presented at ESC 2014; Abstract 86447
Bleeding risk and treatment at baseline

- With increasing HAS-BLED score, fewer patients received VKAs and an increasing proportion received a VKA + AP or AP alone.
Multivariable analysis for factors predicting the non-prescription of VKAs in non-valvular AF

<table>
<thead>
<tr>
<th>Variable Effect</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥75 vs &lt;75</td>
<td>1.64 (1.39-1.96)</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>Gender Female vs Male</td>
<td>1.22 (0.98-1.53)</td>
<td>0.0640</td>
</tr>
<tr>
<td>Type -pAF vs sAF</td>
<td>0.24 (0.18-0.33)</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>Need for assistance -Yes vs No</td>
<td>1.77 (1.18-2.63)</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>Cognitive impairment -Yes vs No</td>
<td>2.09 (1.44-3.03)</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>CHADS2 score -≥2 vs &lt;2</td>
<td>0.29 (0.19-0.43)</td>
<td>≤0.0001</td>
</tr>
<tr>
<td>Modified HAS-BLED score -≥3 vs &lt;3</td>
<td>5.55 (4.74-6.39)</td>
<td>≤0.0001</td>
</tr>
</tbody>
</table>
Conclusions

1. Apparent decrease in the number of non-anticoagulated patients, and clear increase in number of patients treated with NOACs
2. Still many patients with AF eligible to anticoagulation do not receive it
3. Fear of bleeding (high HAS-BLED score and other indicators) as the main reason
Distribution of antithrombotic treatments as a function of thromboembolic risk – PREFER Italian cohort

**Baseline**

De Caterina et al.  

**Follow-Up**

% Patients not on OAC:

- \( \text{CHA}_2 \text{DS}_2 \text{VASc} \geq 1 \) 26%
- \( \text{CHA}_2 \text{DS}_2 \text{VASc} \geq 2 \) 23.9%

% Patients not on OAC:

- \( \text{CHA}_2 \text{DS}_2 \text{VASc} \geq 1 \) 25.3%
- \( \text{CHA}_2 \text{DS}_2 \text{VASc} \geq 2 \) 22.6%
Distribution of antithrombotic treatments as a function of thromboembolic risk – The Italian ATAF Registry
Conclusions

1. Apparent decrease in the number of non-anticoagulated patients, and clear increase in number of patients treated with NOACs

2. Still many patients with AF eligible to anticoagulation do not receive it

3. Fear of bleeding (high HAS-BLED score and other indicators) as the main reason

4. Many patients without indication appear to be treated (overtreatment)
Use of combination therapy at baseline

• Inappropriate use of dual or triple therapy was common at baseline
  • 95.3% of patients on dual OAC + AP therapy and 63.8% on OAC + ASA + clopidogrel triple therapy did not have an accepted indication

De Caterina et al. Heart 2014. DOI: 10.1136/heartjnl-2014-305486
Characteristics of patients treated with mono, dual and triple therapy at baseline

- Compared with patients only prescribed an OAC, those on combination treatment had:
  - Significantly more frequent diabetes, dyslipidaemia, coronary heart disease and peripheral arterial disease (p<0.05 for all)
  - Higher mean CHA₂DS₂-VASc (3.7 vs. 3.4) and HAS-BLED (2.7 vs. 1.9) scores

<table>
<thead>
<tr>
<th></th>
<th>OAC Monotherapy (n=5170)</th>
<th>OAC + AP Dual therapy (n=660)</th>
<th>OAC + ASA + clopidogrel Triple therapy (n=105)</th>
<th>p-value Dual vs. triple</th>
<th>p-value Mono vs. dual</th>
<th>p-value Mono vs. triple</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF thromboembolic risk (mean±SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHADS₂ score</td>
<td>2.0±1.29</td>
<td>2.1±1.29</td>
<td>2.3±1.13</td>
<td>0.1838</td>
<td>0.0807</td>
<td>0.0314</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score</td>
<td>3.4±1.71</td>
<td>3.7±1.75</td>
<td>4.3±1.55</td>
<td>0.0032</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bleeding risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAS-BLED score (mean)</td>
<td>1.9±1.1</td>
<td>2.7±1.15</td>
<td>3.0±1.05</td>
<td>0.0071</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anticoagulation control (mean±SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>2.43±0.511</td>
<td>2.38±0.623</td>
<td>2.14±0.683</td>
<td>0.0012</td>
<td>0.0737</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

De Caterina et al. Heart 2014. DOI: 10.1136/heartjnl-2014-305486
Frequent and possibly inappropriate use of combination therapy with an oral anticoagulant and antiplatelet agents in patients with atrial fibrillation in Europe

• Of the 660 patients on dual AP+OAC combination therapy, 629 (95.3%) did not have an accepted indication.

• Out of the 105 patients receiving triple combination therapy (aspirin, clopidogrel and a VKA in most cases), 67 (63.8%) did not have an accepted indication.

De Caterina et al. Heart 2014. DOI: 10.1136/heartjnl-2014-305486
Risk prediction score and bleeding events by treatment at 1-year follow-up

- Combined use of VKA + AP entailed the highest bleeding rates, as predicted by HAS-BLED score
Patient questionnaires: Satisfaction with and convenience of treatment

• Perception of Anticoagulant Treatment Questionnaire (PACT-Q)
  ▪ Patient expectations with treatment (PACT-Q1)
  ▪ Satisfaction with, and convenience of, treatment (PACT-Q2)

• In PREFER in AF, 5049 (69.7%) patients received any antithrombotic treatment and completed the PACT-Q2 questionnaire
Patient questionnaires: Overall treatment satisfaction

• In the anticoagulation treatment satisfaction dimension, the overall score was 63.4±15.9
  ▪ Score was higher with NOACs (66.1±16.6) than VKAs (63.2±15.9), AP (63.7±16.8) and VKA + AP (62.8±15.0)
• Scores with item D7 (Overall satisfaction) of the PACT-Q2 are illustrated below

![Patient satisfaction chart]

Brüggenjürgen et al. *ISPOR PCV140 2013*
Overall score in the convenience dimension was 82.9; score was higher with the NOACs (88.1) than VKAs (82.1), APs (87.0) and VKAs + APs (83.2)
Factors influencing switching from VKA to NOAC

- Treatment dissatisfaction and QoL factors may be related to and may influence the choice of switching from a VKA to a NOAC

<table>
<thead>
<tr>
<th></th>
<th>Stably treated with VKA ≥6 months (n=2102)</th>
<th>Switched from VKA to NOAC within past 12 months (n=213)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypertension (%)</td>
<td>76.2</td>
<td>68.1</td>
<td>0.0066</td>
</tr>
<tr>
<td>Concomitant AP use (%)</td>
<td>20.1</td>
<td>12.2</td>
<td>0.0055</td>
</tr>
<tr>
<td>Heart valve dysfunction (%)</td>
<td>39.7</td>
<td>30.0</td>
<td>0.0038</td>
</tr>
<tr>
<td>Mobility problems (%)</td>
<td>7.3</td>
<td>13.3</td>
<td>0.0025</td>
</tr>
<tr>
<td>Complained of severe difficulties in dose adjustments (%)</td>
<td>5.4</td>
<td>9.8</td>
<td>0.0116</td>
</tr>
<tr>
<td>Extreme discomfort about bruising or pain (%)</td>
<td>5.1</td>
<td>8.5</td>
<td>0.0429</td>
</tr>
<tr>
<td>Dissatisfied with previous treatment (%)</td>
<td>5.3</td>
<td>9.1</td>
<td>0.0266</td>
</tr>
<tr>
<td>Reported to be non-anxious or depressed (%)</td>
<td>85.9</td>
<td>77.2</td>
<td>0.009</td>
</tr>
</tbody>
</table>

QoL, quality of life

De Caterina et al. Presented at ESC 2014; Abstract 86285
Conclusions

1. Apparent decrease in the number of non-anticoagulated patients, and clear increase in number of patients treated with NOACs
2. Still many patients with AF eligible to anticoagulation do not receive it
3. Fear of bleeding (high HAS-BLED score and other indicators) as the main reason
4. Many patients without indication appear to be treated (overtreatment)
5. Large abuse of concomitant antithrombotic treatment
6. Treatment satisfaction and convenience may be factors for switching from a VKA to a NOAC
Thank you!