



Venice Arrhythmias 2015
Venice (Italy), October 16-18 2015
Fondazione Giorgio Cini



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.



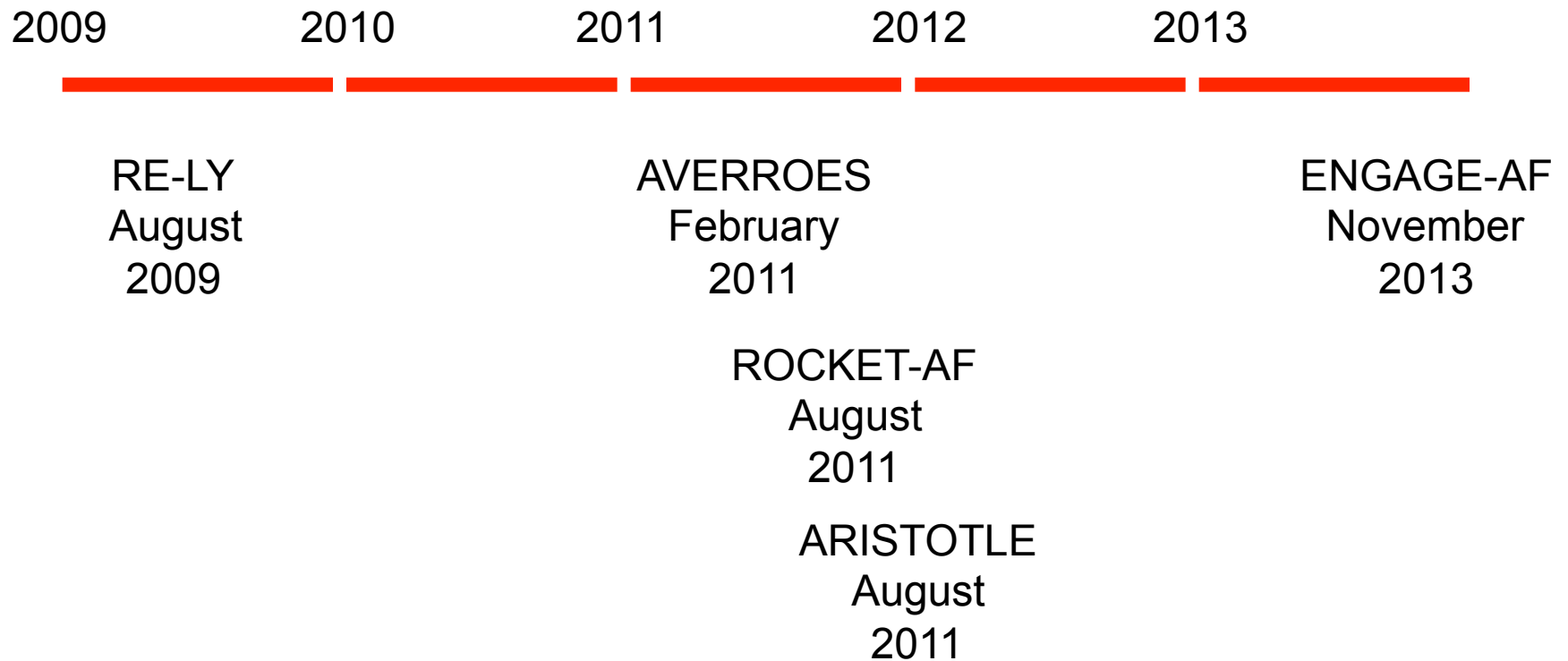
October 16 - 18
14th EDITION **2015**

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



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 AF¹

| ESC Guideline Recommendations ³ | Class | Level |
|---|------------|----------|
| 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 | I | B |
| 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 | Ila | A |

- The PREFER in AF registry was designed to describe how patients with AF are currently managed in Europe^{2,3}

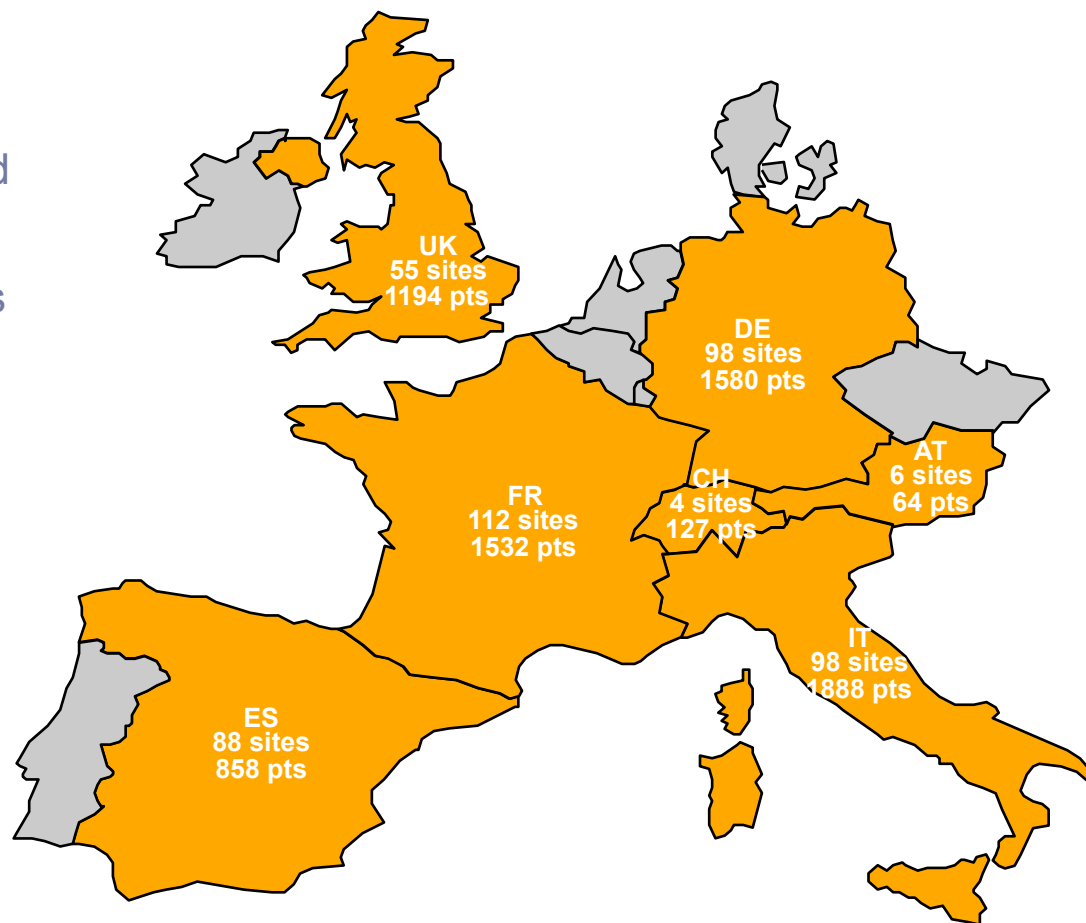
1. Camm et al. Europace 2010;12:1260–420;

2. Camm et al. Eur Heart J. 2012;33:2719–47;

3. Kirchhof et al. Europace 2014;16:6–14.

PREFER in AF: European Registry in Atrial Fibrillation

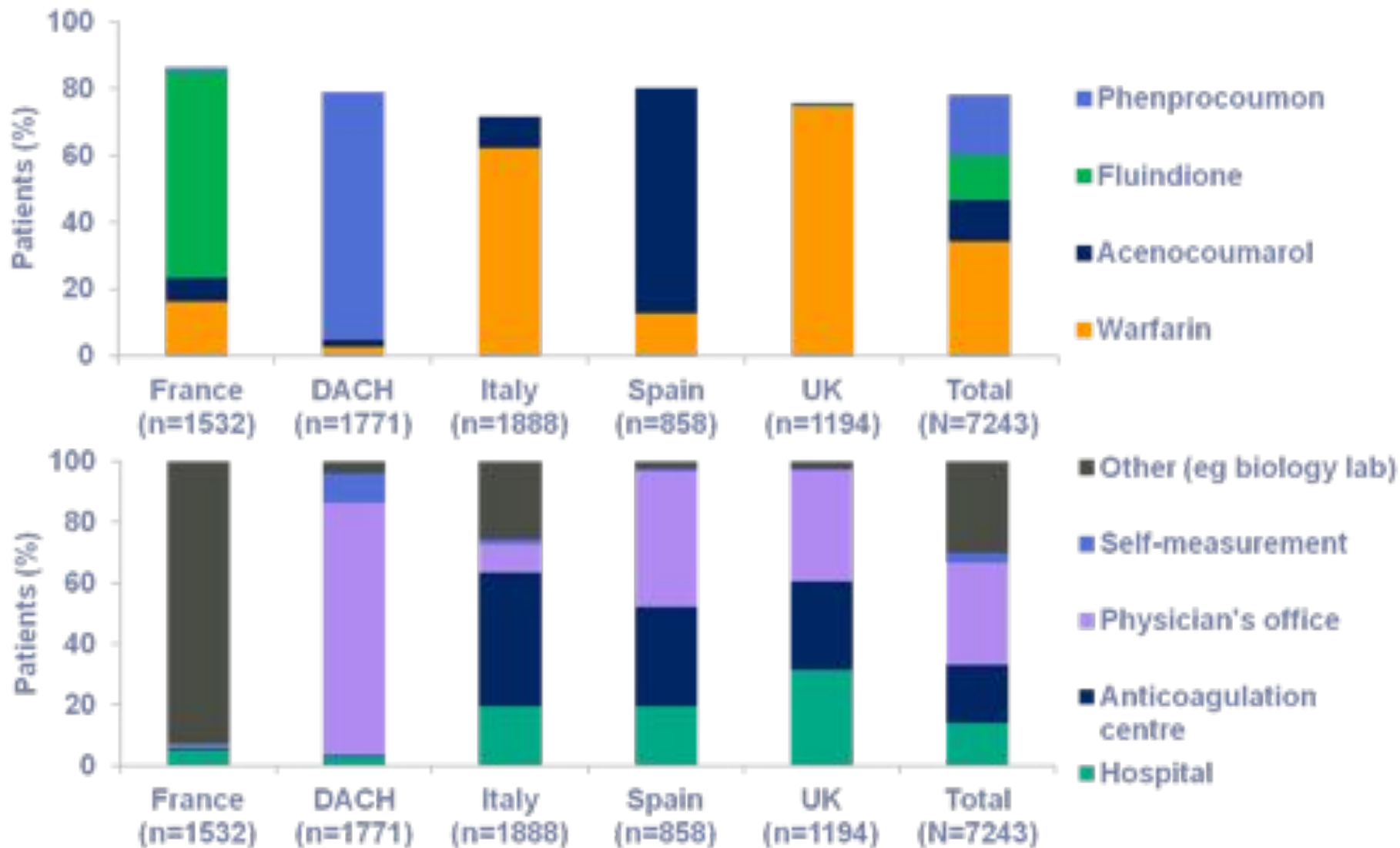
- PREFER in AF was a prospective, observational, multicentre study conducted in 7 EU countries
- Consecutive patients were enrolled from January 2012 to January 2013, with final N=7243 (≥ 18 years of age; provided written informed consent; history of AF)
- Patients were assessed at baseline and at a 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)

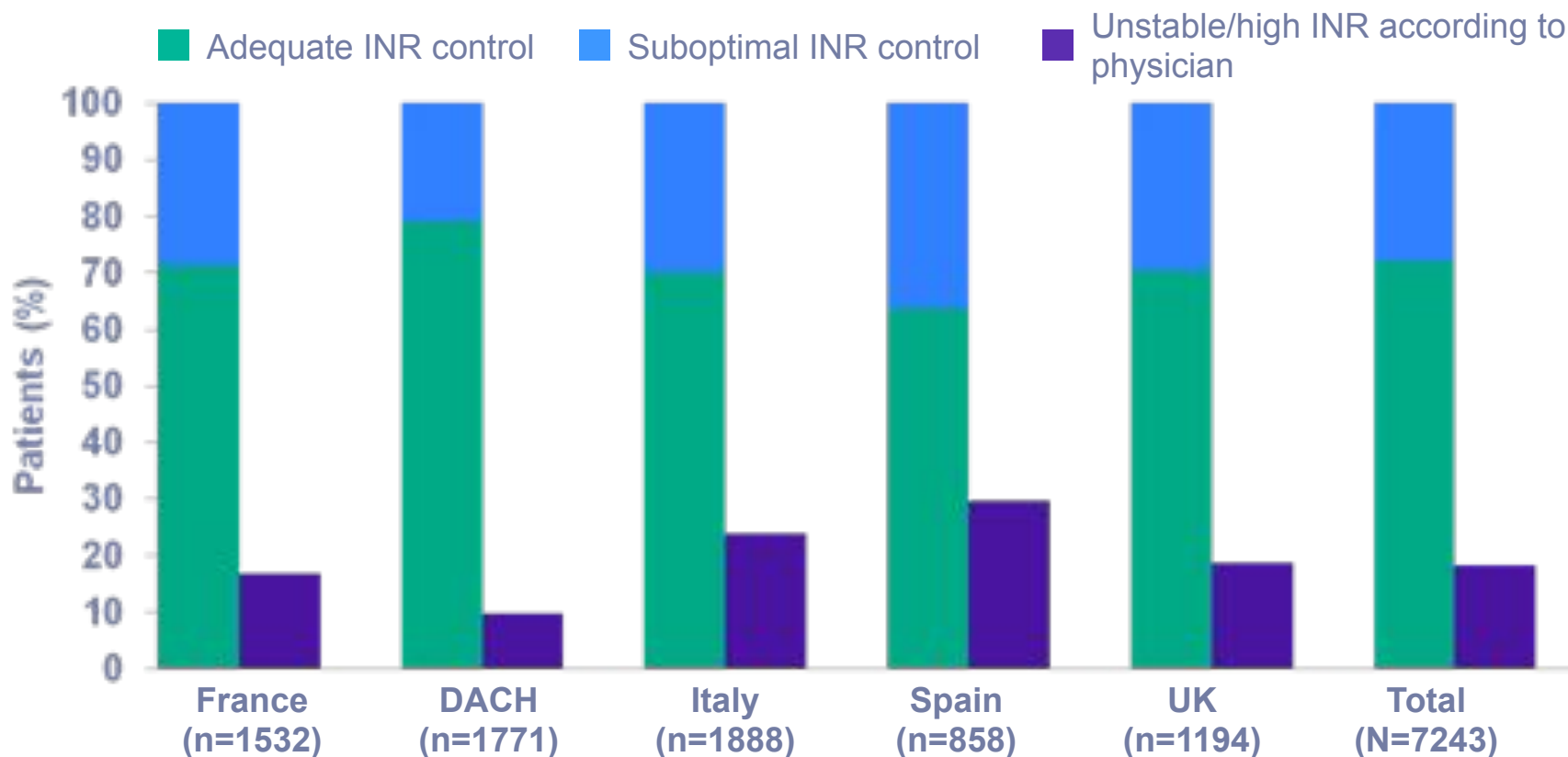
Kirchhof et al. Europace 2014;16:6–14;
Rincon et al. ESC Poster 2013;
Le Heuzey et al. Thromb Haemost 2014;111:833–41

Types of VKAs and sites of INR measurement across Europe

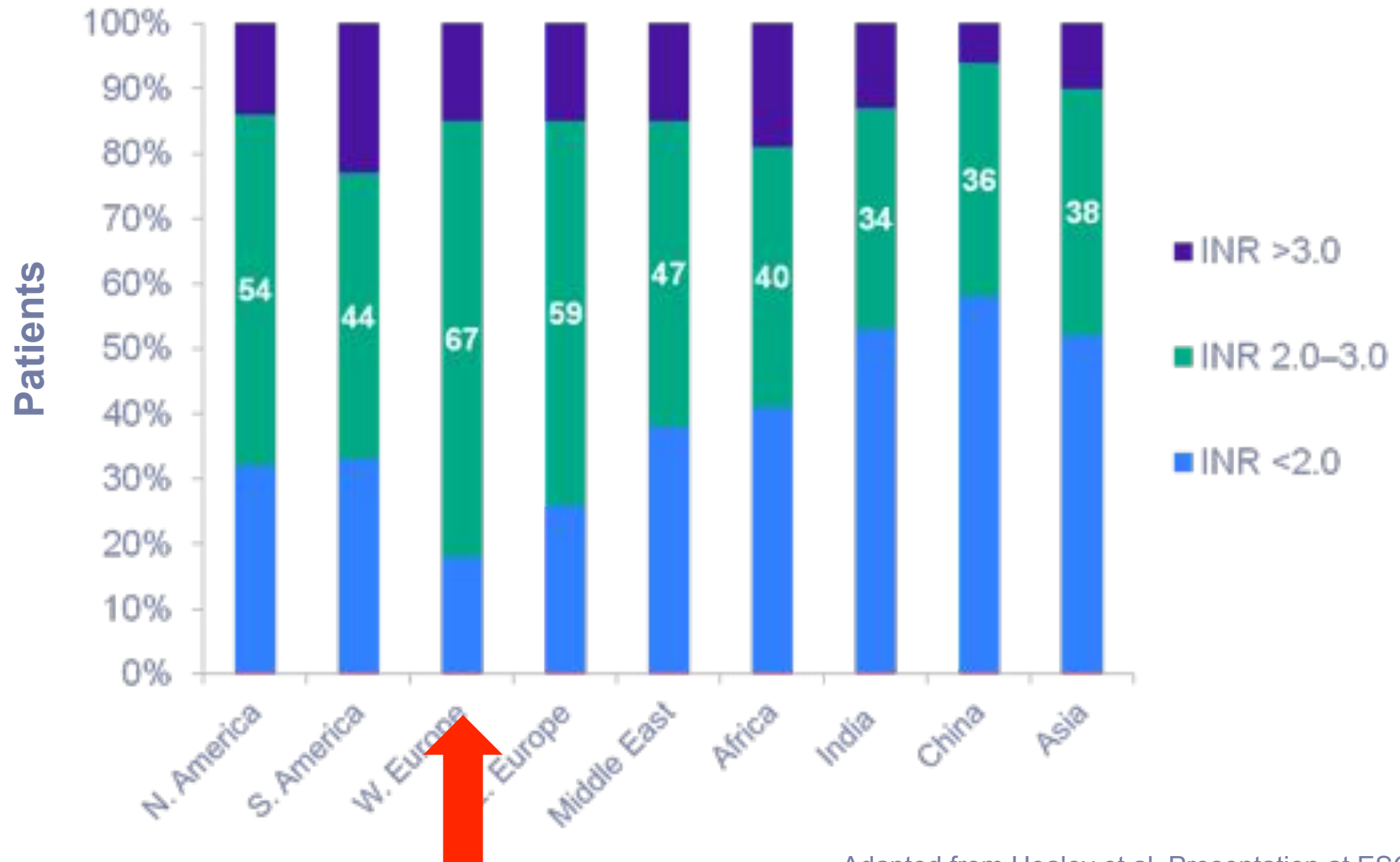


Adequacy of INR control

- 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



Patient demographics

- In PREFER in AF, patient characteristics
 - Were comparable across the different countries and to other registries¹⁻⁴
 - At baseline, **30.0% of patients had paroxysmal AF, 24.0% had persistent AF, 7.2% had long-standing persistent AF and 38.8% had permanent AF²**

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

DACH, Germany, Austria and Switzerland

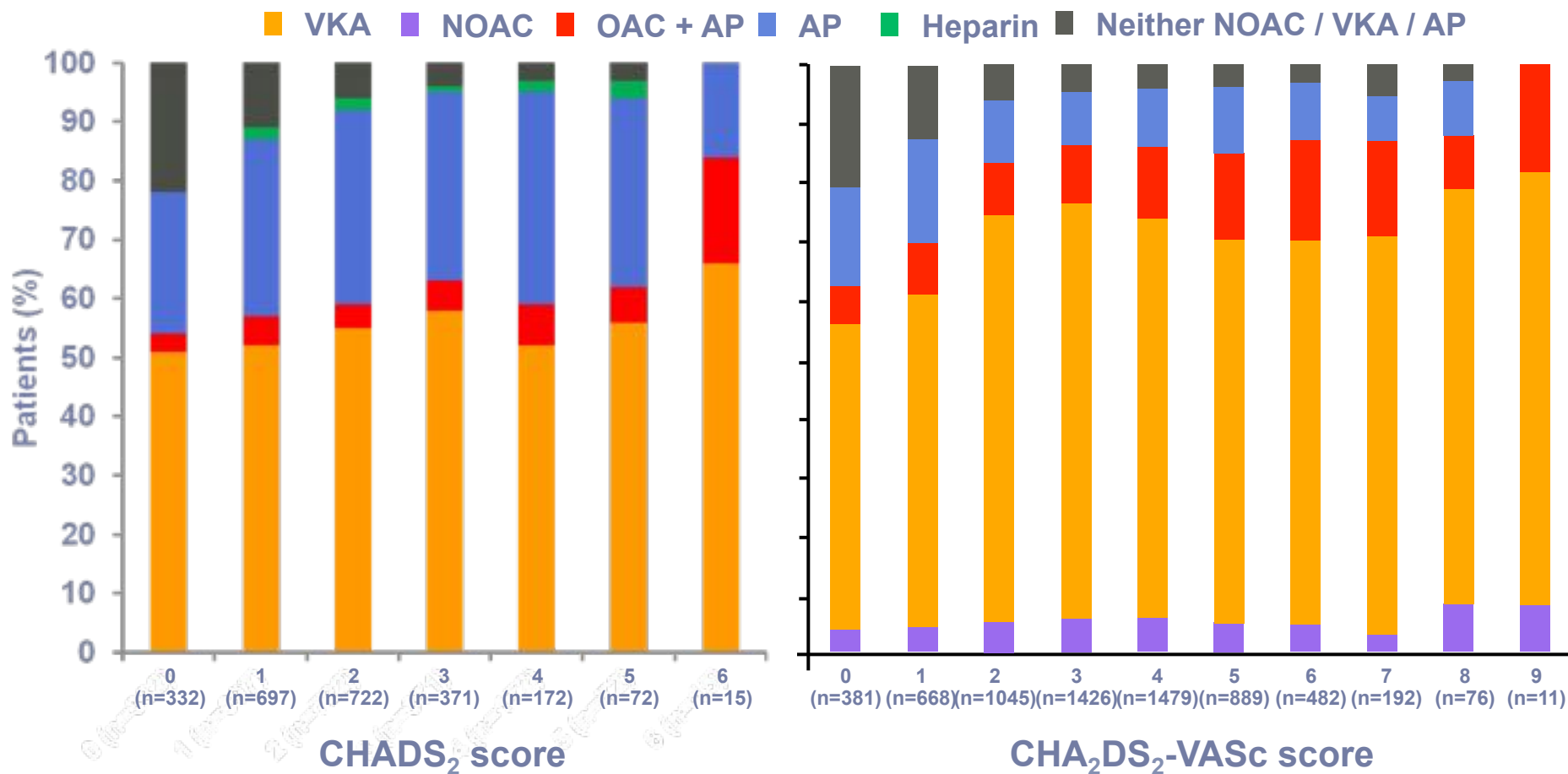
Similar stroke and bleeding risks at baseline across European countries^a

| | France (n=1532) | DACH (n=1771) | Italy (n=1888) | Spain (n=858) | UK (n=1194) | Total (N=7243) |
|--|----------------------------|--------------------------|---------------------------|--------------------------|------------------------|---------------------------|
| CHA ₂ DS ₂ VASc score (mean) | 3.3 | 3.7 | 3.3 | 3.3 | 3.2 | 3.4 |
| Score =1 (%) | 9.2 | 7.1 | 11.3 | 11.7 | 12.8 | 10.1 |
| Score ≥2 (%) | 83.0 | 89.6 | 83.4 | 81.8 | 80.2 | 84.1 |
| HAS-BLED score (mean) | 1.9 | 2.1 | 2.1 | 2.0 | 2.0 | 2.0 |

^a Risk factors reported in correlation with CHA₂DS₂-VASc score
DACH, Germany, Austria and Switzerland; TIA, transient ischaemic attack

EuroHeart and PREFER in AF: Improved anticoagulation by CHADS₂/CHA₂DS₂-VASc over time

EuroHeart (pre 2010) PREFER in AF (post 2010)



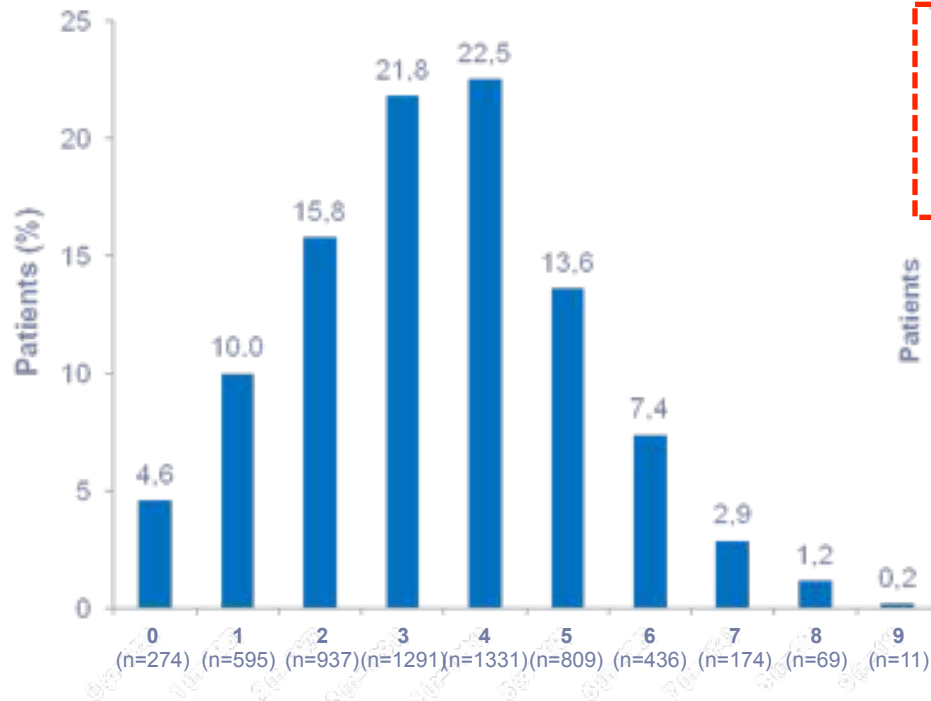
AP, antiplatelet

Nieuwlaet et al. *Eur Heart J* 2006;27:3018–26; Kirchhof et al. *Europace* 2014;16:6–14

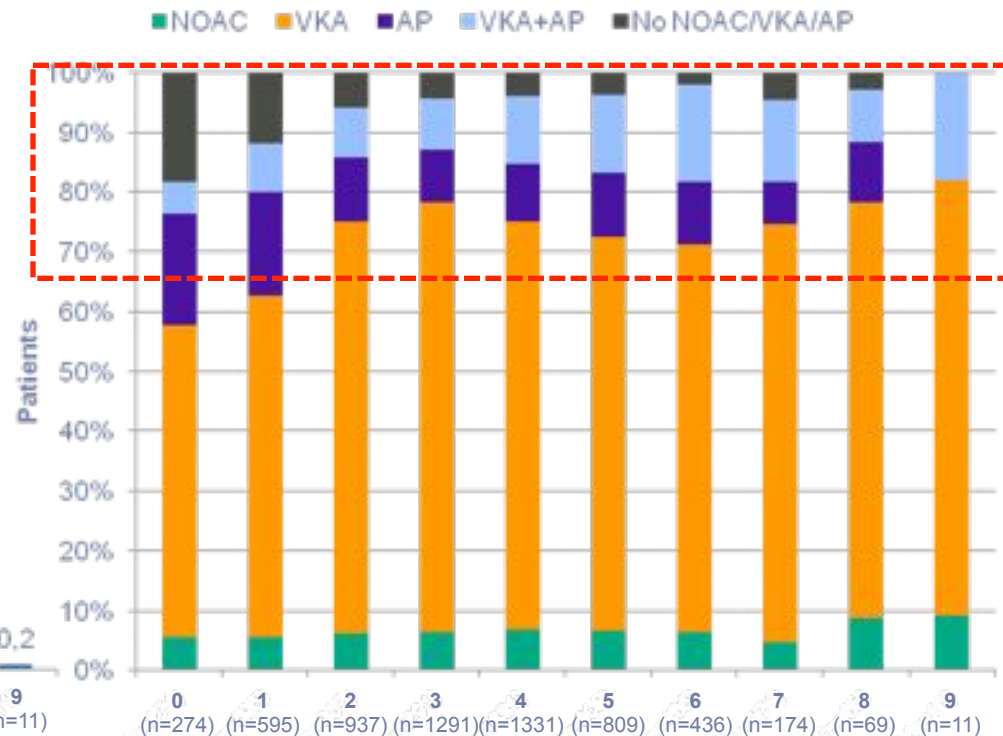
Stroke risk and treatment at baseline

- With increasing CHA₂DS₂-VASc score, more patients received a VKA and VKA + AP
- Still, a large proportion of patients received no anticoagulation despite a high thromboembolic risk

CHA₂DS₂-VASc score



Treatment by CHA₂DS₂-VASc score



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 $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ was 85.6% and 70.1% in those with $\text{CHA}_2\text{DS}_2\text{-VASc} = 1$
- From baseline to follow up, there was a significant reduction in the use of VKAs while NOAC use rose

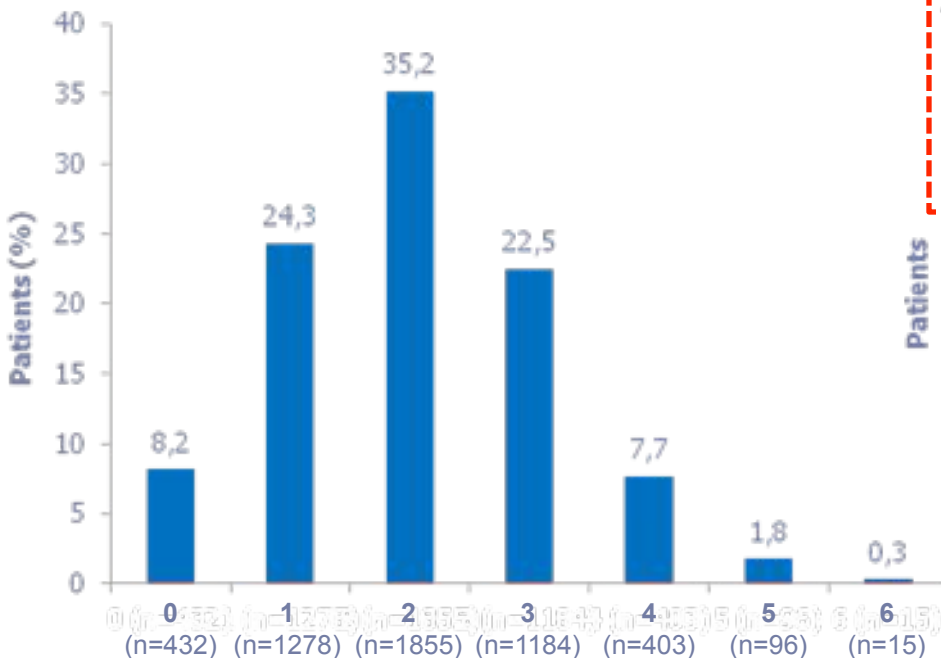
| | Baseline | 1-year follow-up |
|--|----------|------------------|
| Overall anticoagulation (%) | 82.3 | 80.0 |
| VKA alone (%) | 66.3 | 61.8 |
| NOAC (%) | 6.1 | 12.6 |
| Direct FXa inhibitor ^a | 1.9 | 6.0 |
| Direct thrombin inhibitor ^b | 4.0 | 6.5 |
| Long-term VKA + AP (%) | 9.9 | 5.7 |
| AP alone (%) | 11.2 | 8.0 |

^aRivaroxaban, apixaban; ^bdabigatran

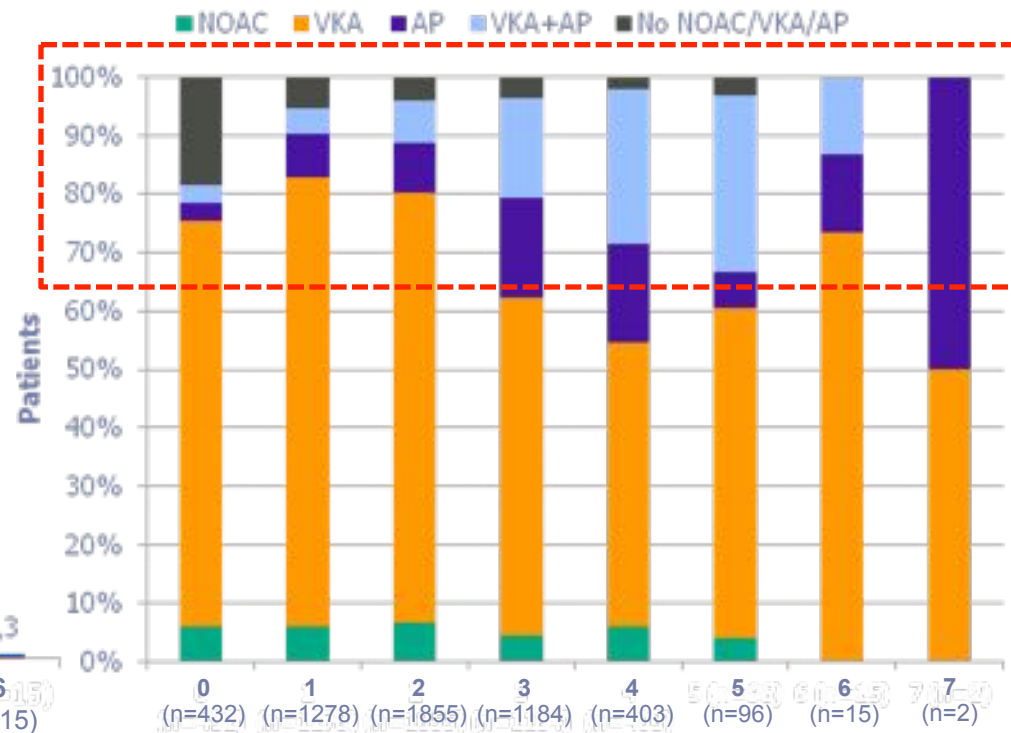
Bleeding risk and treatment at baseline

- With increasing HAS-BLED score, fewer patients received VKAs and an increasing proportion received a VKA + AP or AP alone

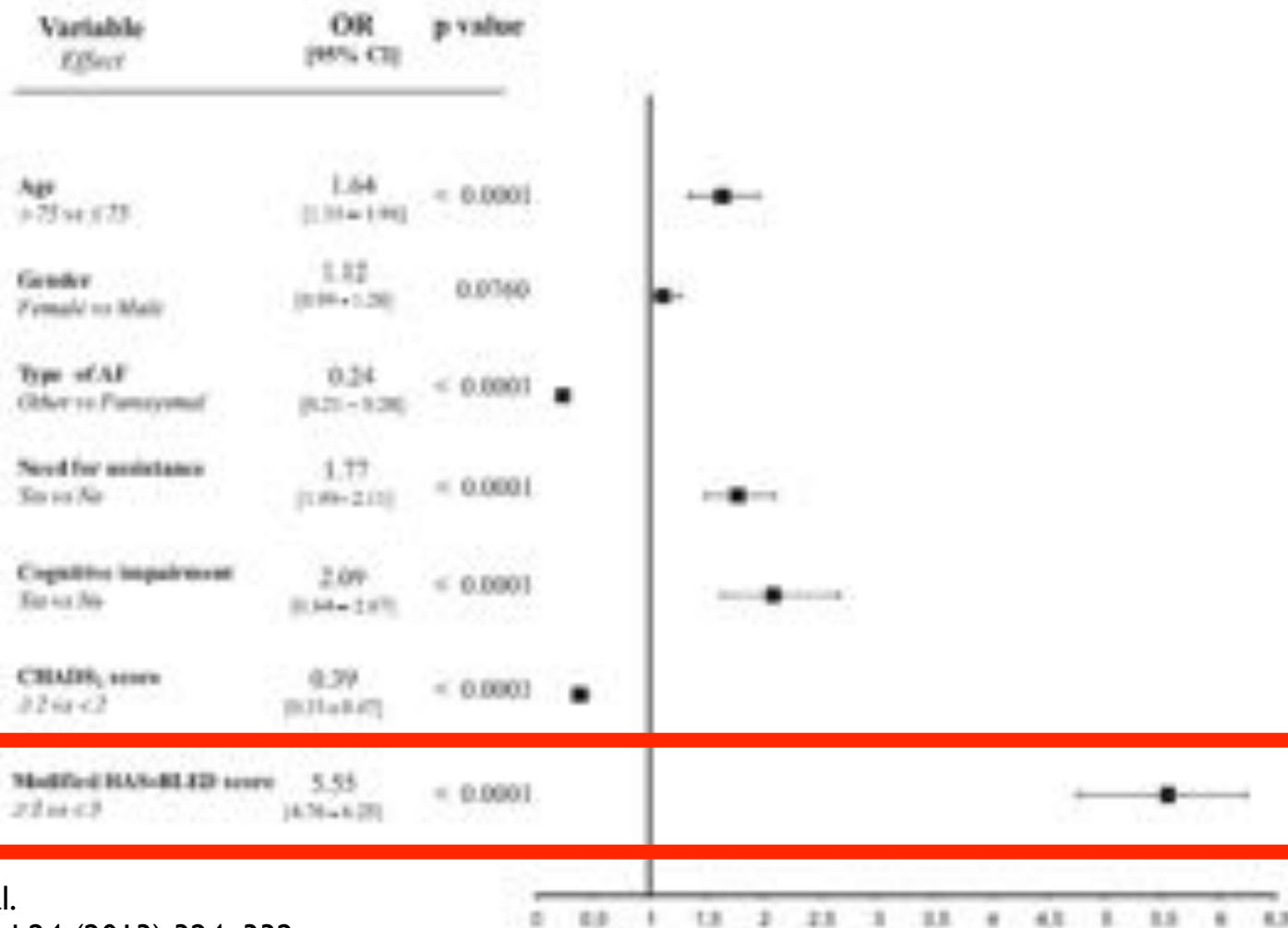
HAS-BLED score



Treatment by HAS-BLED score



Multivariable analysis for factors predicting the non-prescription of VKAs in non-valvular AF



Conclusions

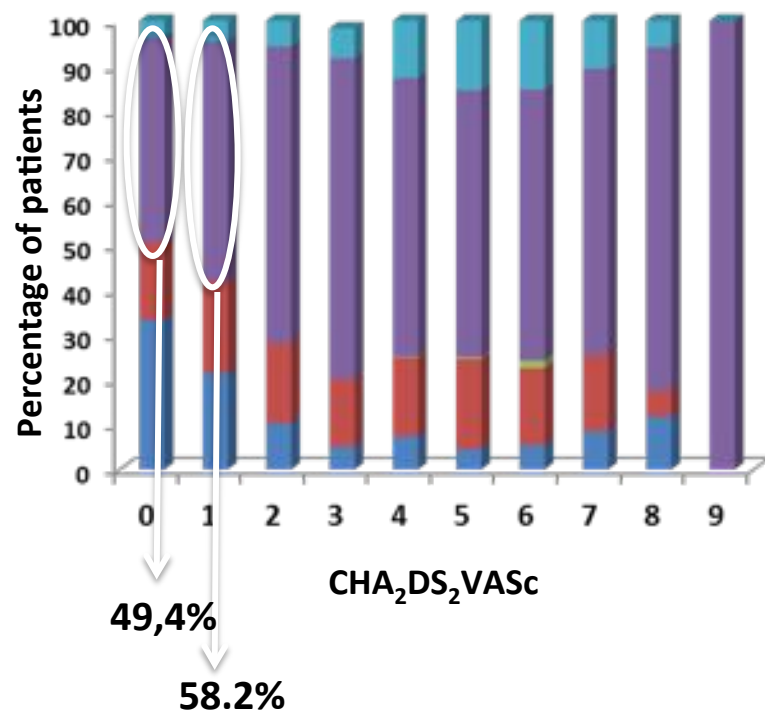
1. Apparent decrease in the number of non-anticoagulated patients, and clear increase in number of patients treated with NOACs
2. Still many patients with AF eligible to anticoagulation do not receive it
3. Fear of bleeding (high HAS-BLED score and other indicators) as the main reason

Distribution of antithrombotic treatments as a function of thromboembolic risk – PREFER Italian cohort

■ Neither VKA, nor NOAC, nor AP ■ AP ■ NOAC ■ VKA ■ VKA+AP

Baseline

De Caterina et al.
G Ital Cardiol 2014;15(2):99-109

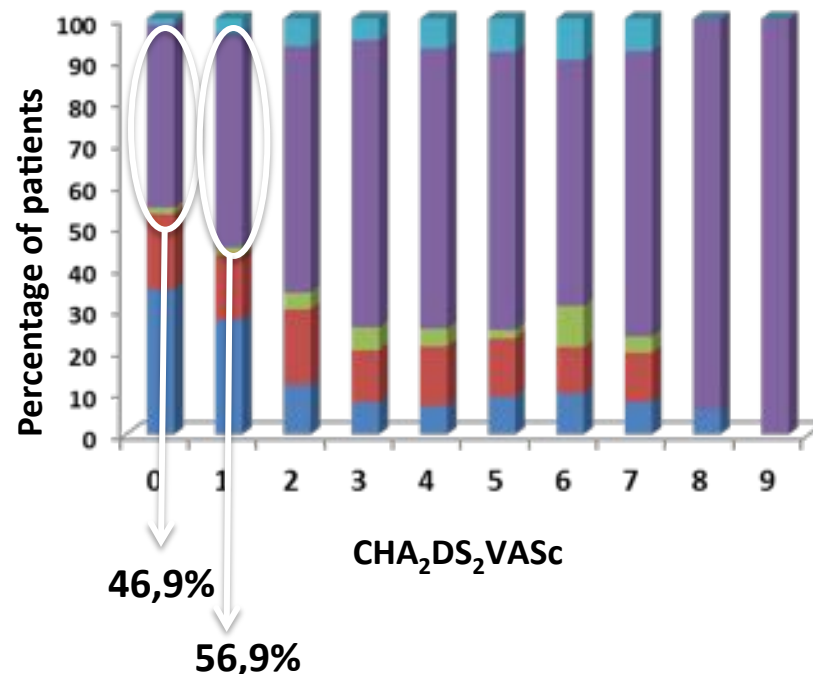


% Patients not on OAC:

CHA₂DS₂VASc ≥ 1 26%

CHA₂DS₂VASc ≥ 2 23,9%

Follow-Up

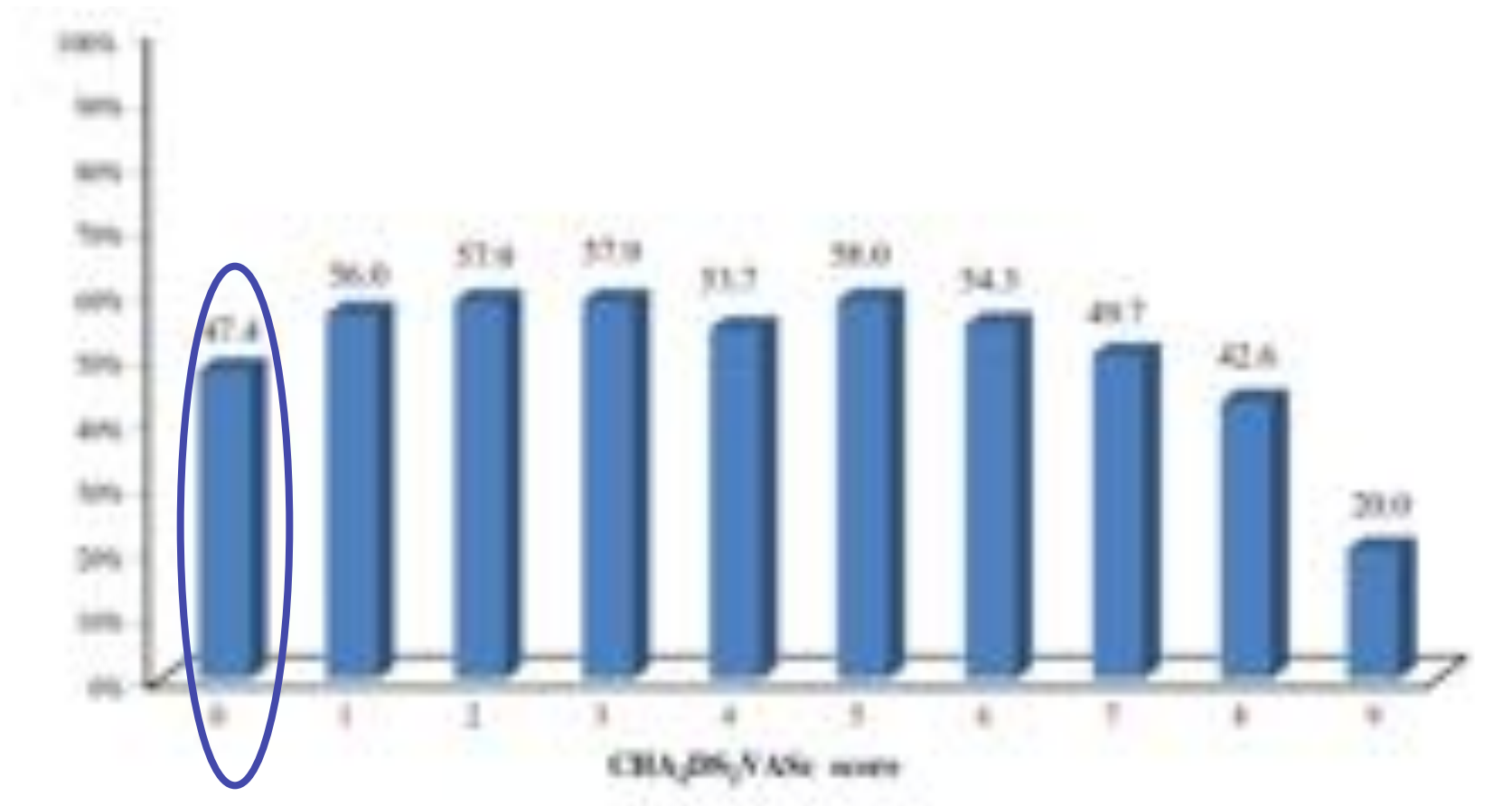


% Patients not on OAC:

CHA₂DS₂VASc ≥ 1 25,3%

CHA₂DS₂VASc ≥ 2 22,6%

Distribution of antithrombotic treatments as a function of thromboembolic risk – The Italian ATAF Registry

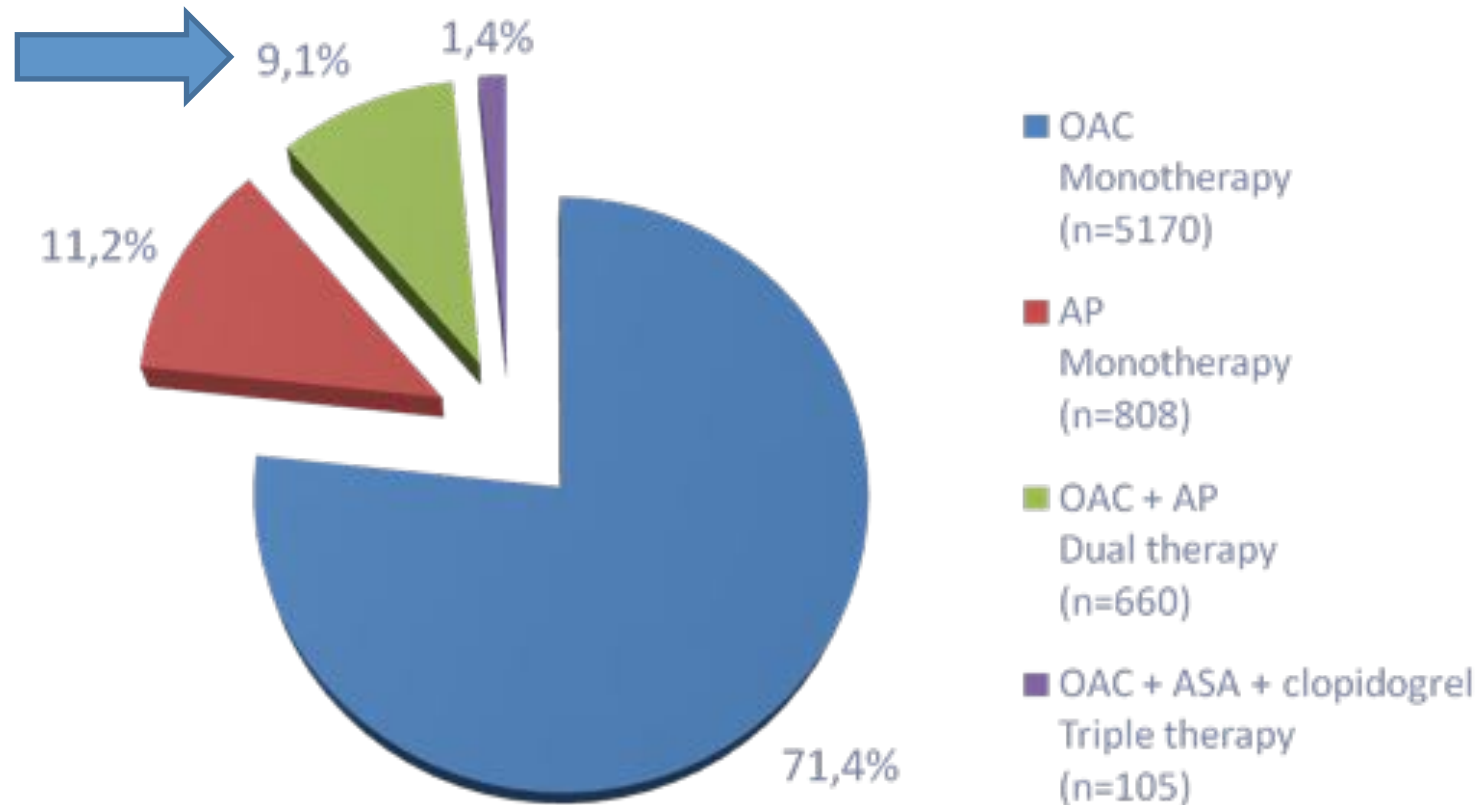


Conclusions

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



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

| | OAC Monotherapy (n=5170) | OAC + AP Dual therapy (n=660) | OAC + ASA + clopidogrel Triple therapy (n=105) | p-value Dual vs. triple | p-value Mono vs. dual | p-value Mono vs. triple |
|--|--------------------------------|-------------------------------------|---|----------------------------|--------------------------|----------------------------|
| AF thromboembolic risk (mean±SD) | | | | | | |
| CHADS ₂ score | 2.0±1.29 | 2.1±1.29 | 2.3±1.13 | 0.1838 | 0.0807 | 0.0314 |
| CHA ₂ DS ₂ -VASc score | 3.4±1.71 | 3.7±1.75 | 4.3±1.55 | 0.0032 | 0.0002 | <0.0001 |
| Bleeding risk | | | | | | |
| HAS-BLED score (mean) | 1.9±1.1 | 2.7±1.15 | 3.0±1.05 | 0.0071 | <0.0001 | <0.0001 |
| Anticoagulation control (mean±SD) | | | | | | |
| INR | 2.43±0.511 | 2.38±0.623 | 2.14±0.683 | 0.0012 | 0.0737 | 0.0002 |

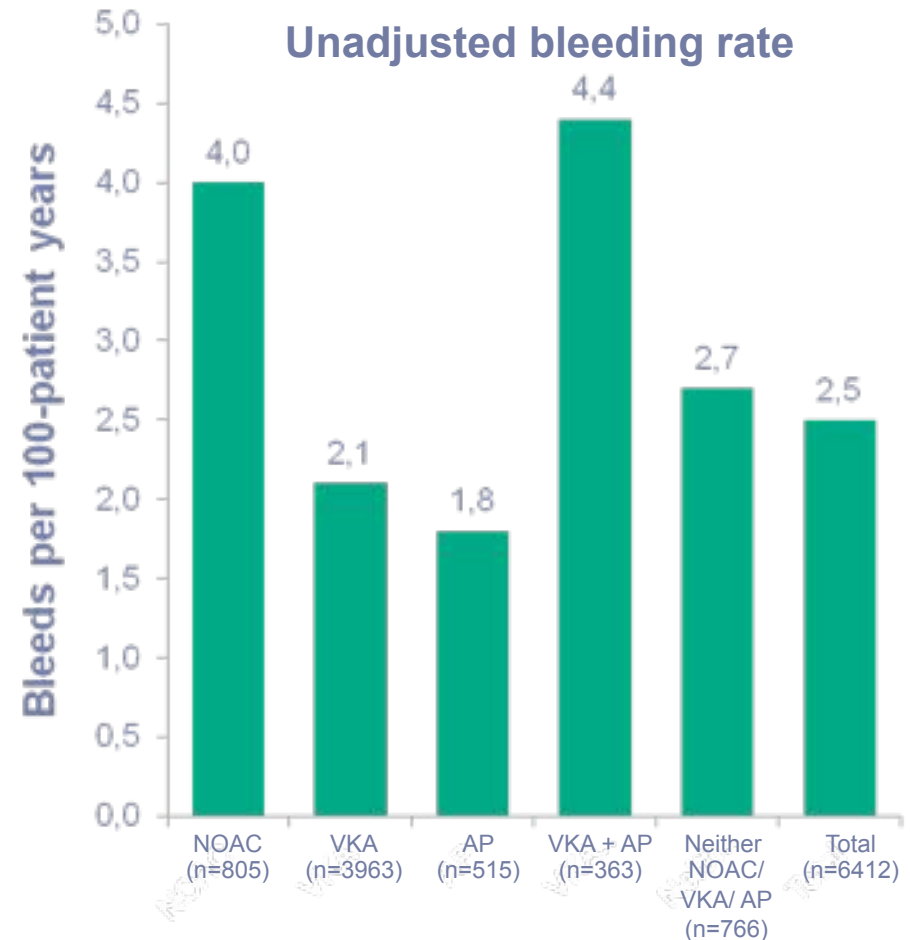
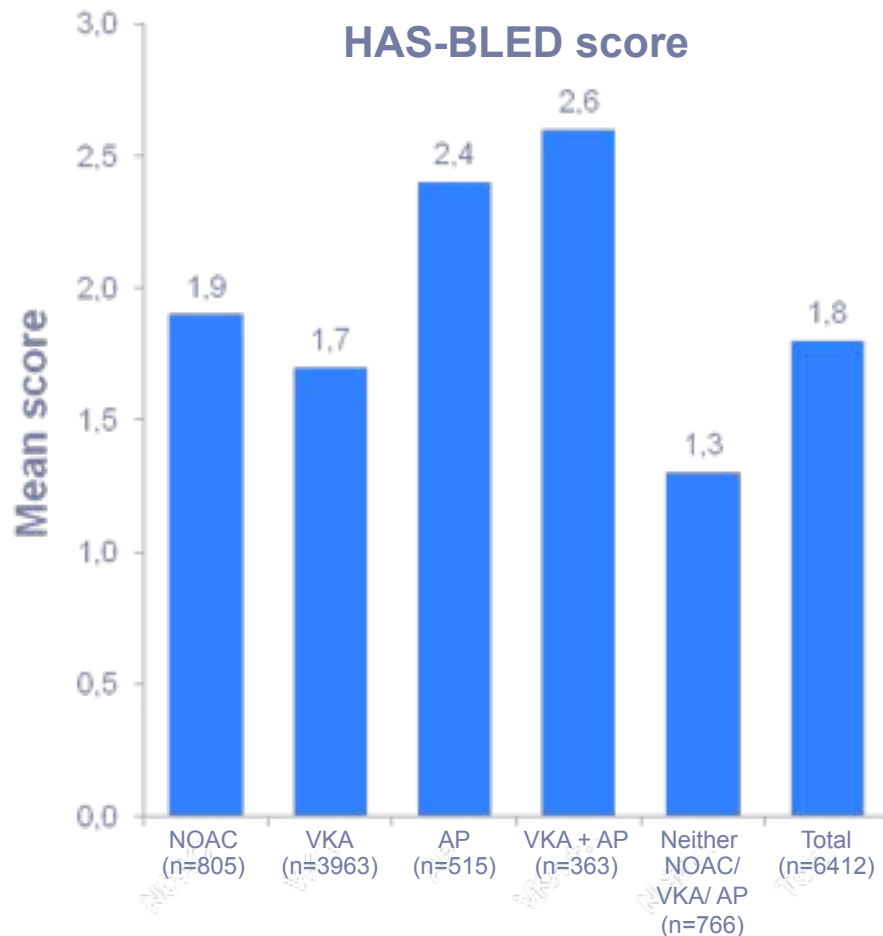
ORIGINAL ARTICLE

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

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



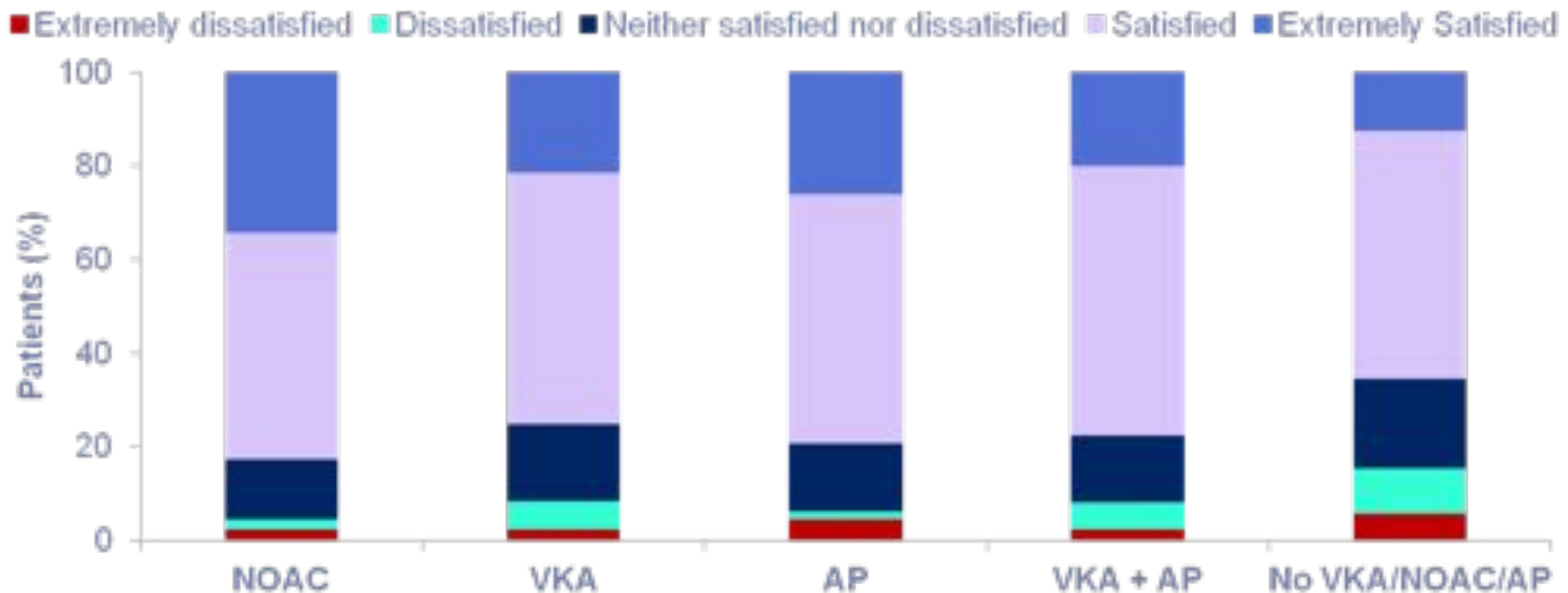
Patient questionnaires: Satisfaction with and convenience of treatment

- 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:

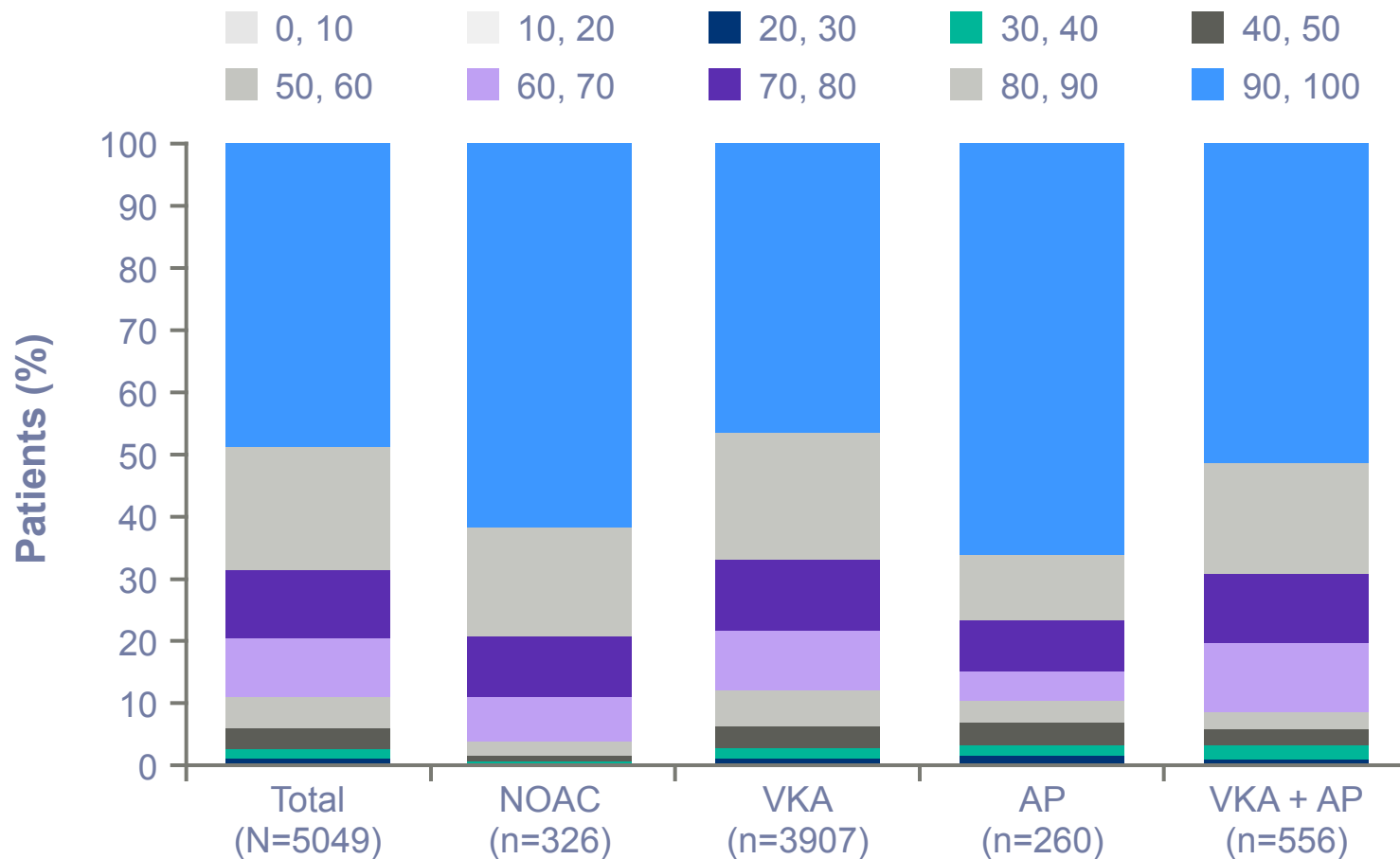
Overall treatment satisfaction

- 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 questionnaires: Convenience of current treatment

- 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

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

QoL, quality of life

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



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Thank you!