Sinus rhythm: a “new” powerful anticoagulant

Prof. Fiorenzo Gaita
IN ITALY 816 DEATHS FOR YEAR BY MOTORCYCLE ACCIDENTS

HOW TO REDUCE?
IN ITALY 196,000 STROKES FOR YEAR

CAUSES OF ISCHEMIC STROKE

OTHER CAUSES:

- 30%-50% Atherosclerosis of major cerebral arteries (atherothrombotic stroke)
- 20% Small vessel occlusion (lacunar stroke)
- 5% Rare causes: dissection of epiaortic vessels, vasculitis, hematologic diseases …
- 15%-20% Unknown causes

HOW TO REDUCE?
Management cascade for patients with AF

Treatment

Acute rate and rhythm control

Precipitating factors:
lifestyle changes, treatment of underlying cardiovascular conditions

Assess stroke risk: oral anticoagulation if needed

Assess heart rate: rate control

Assess symptoms and comorbidities: rhythm control (antiarrhythmic drugs, cardioversion, TC ablation)

Desired outcome

Hemodynamic stability

Cardiovascular risk reduction

Stroke prevention

Symptoms improvement, LV function preservation

Symptoms improvement, comorbidities prevention

Patient benefit

Improved life expectancy

Improved quality of life, functional capacity

ESC 2016 AF guidelines
AFFIRM: Total Mortality (at 5 years)

Rate control vs Rhythm control

4060 pts,
Age 69.7 ± 9 years
528 pts (13%) > 80 y

-70.8% Hypertension
-38.2% Ischemic
-↓ EF 26%
-↑ Left atrium 64.7%

Mean FU: 3.5 y

AFFIRM: Circulation 2004; 109:1509

Covariates associated to survival:

<table>
<thead>
<tr>
<th>Covariate</th>
<th>p</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>&lt;0.0001</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Warfarin ↓ of about 50% risk of death
Management of anticoagulation therapy
Using CHADS Score

Congestive heart failure 1
Hypertension 1
Age > 75 years 1
Diabetes mellitus 1
Prior Stroke or TIA 2

Expected stroke rate \textit{per 100 pts/y} without antithrombotic therapy

<table>
<thead>
<tr>
<th>CHADS$_2$ score</th>
<th>Antithrombotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2</td>
<td>Oral Anticoagulation</td>
</tr>
<tr>
<td>1</td>
<td>Either OAC or aspirin 75-325 mg.</td>
</tr>
<tr>
<td>0</td>
<td>Aspirin 75-325 mg</td>
</tr>
</tbody>
</table>

Gage, JAMA 2001; 285:2864-2870

ACC/AHA/ESC AF Guidelines 2010
<table>
<thead>
<tr>
<th><strong>Drug interaction</strong></th>
<th><strong>P-gp competition</strong></th>
<th><strong>CYP3A4 inhibition</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DABIGATRAN</strong></td>
<td>150 bid or 110 bid</td>
<td></td>
</tr>
<tr>
<td><strong>APIXABAN</strong></td>
<td>5 bid or 2.5 bid</td>
<td></td>
</tr>
<tr>
<td><strong>RIVAROXABAN</strong></td>
<td>20 or 15 od</td>
<td></td>
</tr>
<tr>
<td><strong>EDOXABAN</strong></td>
<td>30 or 60 od</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Name</strong></th>
<th><strong>Pradaxa 2009</strong></th>
<th><strong>Eliquis 2012</strong></th>
<th><strong>Xarelto 2011</strong></th>
<th><strong>Lixiana 2015</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean CHADS</strong></td>
<td>2.1</td>
<td>2.1</td>
<td>3.5</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>7%</td>
<td>60%</td>
<td>60-80%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Half-life (T ½)</strong></td>
<td>12-17 h</td>
<td>12 h</td>
<td>5-9 h young</td>
<td>10-14</td>
</tr>
<tr>
<td><strong>T max h</strong></td>
<td>2-4 h</td>
<td>3-4 h</td>
<td>2-4 h</td>
<td>1-5 h</td>
</tr>
<tr>
<td><strong>Clearence</strong></td>
<td>80% renal</td>
<td>25% renal 75% biliary</td>
<td>60% renal 33% biliary</td>
<td>40% renal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Target</strong></th>
<th>Direct IIa inhibitor</th>
<th>Factor Xa inhibitor</th>
<th>Factor Xa inhibitor</th>
<th>Factor Xa inhibitor</th>
</tr>
</thead>
</table>

| **Mean CHADS** | 2.1 | 2.1 | 3.5 | 2.8 |
| **Bioavailability** | 7% | 60% | 60-80% | 40% |
| **Half-life (T ½)** | 12-17 h | 12 h | 5-9 h young | 10-14 |
| **T max h** | 2-4 h | 3-4 h | 2-4 h | 1-5 h |
| **Clearence** | 80% renal | 25% renal 75% biliary | 60% renal 33% biliary | 40% renal |

**Drug interaction**
- **P-gp competition**
  - Amiodarone (↑)
  - Quinidine (↑)
  - Verapamil (↑)
- **CYP3A4 inhibition**
  - Diltiazem (↑)
  - Ketoconazolo (↑)
  - Ritonavir (↑)
  - Ketokonazole (↑)
  - Quinidine (↑)
  - Verapamil (↑)
NON VALVULAR AF: ANNUAL THROMBOEMBOLIC RISK

Expected vs Warfarin vs New Oral Anticoagulants

- % Expected Stroke/y w/o therapy (data from 138691 AF pts)
- % Stroke/y in Warfarin
- % Stroke/y in New Oral Anticoag

<table>
<thead>
<tr>
<th>CHADS₂ score</th>
<th>Anticoagulant</th>
<th>Dose</th>
<th>Expected Stroke/y w/o therapy</th>
<th>Warfarin Stroke/y</th>
<th>New Oral Anticoag Stroke/y</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2</td>
<td>Dabigatran</td>
<td>150</td>
<td>4.1%</td>
<td>1.1%</td>
<td>2.1%</td>
</tr>
<tr>
<td>2.2</td>
<td>Dabigatran</td>
<td>110</td>
<td>4.1%</td>
<td>1.7%</td>
<td>2.4%</td>
</tr>
<tr>
<td>3.5</td>
<td>Rivaroxaban</td>
<td></td>
<td>8%</td>
<td>1.56%</td>
<td>2.1%</td>
</tr>
<tr>
<td>2.1</td>
<td>Apixaban</td>
<td></td>
<td>4.1%</td>
<td>1.6%</td>
<td>1.2%</td>
</tr>
<tr>
<td>2.8</td>
<td>Edoxaban 60</td>
<td></td>
<td>4.1%</td>
<td>1.5%</td>
<td>1.18%</td>
</tr>
<tr>
<td>2.8</td>
<td>Edoxaban 30</td>
<td></td>
<td>4.1%</td>
<td>1.5%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>
Direct Oral anticoagulation: **ANNUAL MAJOR BLEEDS RISK**

Warfarin vs **New Oral Anticoagulants**

- **Dabigatran 150** RELY: 3.36% Major bleeds /y in Warfarin
- **Dabigatran 110** RELY: 3.36% Major bleeds /y in New Oral Anticoag
- **Rivaroxaban** ROCKET-AF: 3.40% Major bleeds /y in Warfarin, 3.60% Major bleeds /y in New Oral Anticoag
- **Apixaban** ARISTOTLE: 3.09% Major bleeds /y in Warfarin, 2.13% Major bleeds /y in New Oral Anticoag
- **Edoxaban 60** ENGAGE: 3.43% Major bleeds /y in Warfarin, 2.75% Major bleeds /y in New Oral Anticoag
- **Edoxaban 30** ENGAGE: 3.43% Major bleeds /y in Warfarin, 1.61% Major bleeds /y in New Oral Anticoag

% Major bleeds /y in Warfarin

% Major bleeds /y in New Oral Anticoag
**ANNUAL INTRACRANIAL HEMORRAGE RISK**

Warfarin vs New Oral Anticoagulants

<table>
<thead>
<tr>
<th>CHADS₂</th>
<th>% ICH/y in Warfarin</th>
<th>% ICH/y in New Oral Anticoag</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2</td>
<td>0.75%</td>
<td>0.3%</td>
</tr>
<tr>
<td>2.2</td>
<td>0.75%</td>
<td>0.23%</td>
</tr>
<tr>
<td>3.4</td>
<td>0.7% 0.5%</td>
<td>0.33%</td>
</tr>
<tr>
<td>2.1</td>
<td>0.8% 0.33%</td>
<td>0.39%</td>
</tr>
<tr>
<td>2.8</td>
<td>0.85% 0.39%</td>
<td>0.26%</td>
</tr>
<tr>
<td>2.8</td>
<td>0.85% 0.39%</td>
<td>0.26%</td>
</tr>
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**RRA**: 0.4% ± 0.2%

**RRR**: 50%
Expected stroke rate per 100 pt/y without antithrombotic therapy

FROM CHADS₂

TO CHA₂DS₂VASC

Gage, JAMA 2001

ESC GL for AF 2010
Risk Categorization for CHADS$_2$ Score and CHA$_2$DS$_2$ - VASc Score: Euro Heart Survey pts who did not receive OAC at baseline

CHADS$_2$ Score
- High Risk (score ≥ 2): 17.7%
- Intermediate Risk (score 1): 61.9%
- Low Risk (score 0): 20.4%

CHA$_2$DS$_2$ - VASc Score
- High Risk (score ≥ 2): 75.7%
- Intermediate Risk (score 1): 15.1%
- Low Risk (score 0): 9.2%

CHEST 2010; 137(2):263–272
Mechanical heart valve, moderate/sever mitral stenosis?

NO

CHA\textsubscript{2}DS\textsubscript{2}VASC

0

no treatment (IIIB)

1

OAC should be considered (IIaB)

≥2

Oral anticoagulation indicated

Direct oral anticoagulants (IA)

Vitamin K Antagonist (IA)

yes

ESC 2016

ESC AF Guidelines 2016
AHA/ACC/HRS Guidelines for the Management of patients with AF

Mechanical heart valve, moderate/severe mitral stenosis?

NO

CHA2DS2VASC

0

No treatment (IIaB)

1

No treatment or ASPIRIN or OAC (IIbC)

≥2

Oral anticoagulation indicated

Direct Oral Anticoagulants (IB)

Vitamin K Antagonist (IA)

Circulation 2014
HOW TO REDUCE EVEN MORE THE RISK?

ATRIAL FIBRILLATION

ANTICOAGULANT THERAPY

SINUS RHYTHM: DRUGS OR AF ABLATION
Covariates associated to survival:

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<thead>
<tr>
<th>Covariate</th>
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<tbody>
<tr>
<td>Warfarin</td>
<td>&lt;0.0001</td>
<td>0.50</td>
</tr>
<tr>
<td>Sinus Rhythm</td>
<td>&lt;0.0001</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Warfarin ↓of about 50% risk of death

Sinus rhythm ↓of about 50% risk of death

RS or Warfarin ↓of about 50% risk of death; if both of them a risk ↓of 73%
ROCKET AF Trial patients enrollment – 14264 pts

Physician’s choice of rhythm control

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation
Physician’s choice of rhythm control

Out of 14,264 ROCKET-AF pts

Paroxysmal AF
2802 (20%)

Rhythm control
176 pts (6.3%)
(cardioversion or ablation)

Persistent AF
11,462 (80%)

Rhythm control
154 pts (1.3%)
(cardioversion or ablation)

Piccini JP; J Am Coll Cardiol 2013
Rhythm Versus Rate Control Therapy and Subsequent Stroke or Transient Ischemic Attack in Patients With Atrial Fibrillation

Meytal Avgil Tsadok, Cynthia A. Jackevicius, Vidal Essebag, Mark J. Eisenberg, Elham Rahme, Karin H. Humphries, Jack V. Tu, Hassan Behlouli and Louise Pilote

Circulation 2012;126:2680-87

57518 AF Quebec pts, aged > 65 y, mean CHADS₂ 2 (1999-2007)

Less incidence of stroke/TIA in rhythm control

41193 pts
(Rate control tx
(OAT 59 %, beta blockers 57 %)

16325 pts
(Rhythm control tx. Only AADs
(OAT 59 %, class III 82%, Ic 15 %)
Reduction of Stroke with antiarrhythmic drugs

Mean follow-up $21 \pm 5$ months

RRR: 34%
RRA: 0.6%

Placebo
70/2327 (1.8%)

Dronedarone
46/2301 (1.2%)

Pz a rischio
Placebo
2327 2275 2220 1598 618 6
Dronedarone
2301 2266 2223 1572 608 4

ATHENA. Circulation 2009;120:1174-1180
What is the thromboembolic risk after AF ablation?
Radiofrequency Ablation vs Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation (RAAFT-2)
A Randomized Trial

Carlos A. Morillo, MD, FRCPC; Atul Verma, MD, FRCPC; Stuart J. Connolly, MD, FRCPC; Karl H. Kuck, MD, FHRDS; Girish M. Nair, MBBS, FRCPC; Jean Champagne, MD, FRCPC; Laurence D. Sterns, MD, FRCPC; Heather Beresh, MSc; Jeffrey S. Healey, MD, MSc, FRCPC; Andrea Natale, MD; for the RAAFT-2 Investigators

Figure 2. Kaplan-Meier Curves of Time to First Recurrence of Any Atrial Tachyarrhythmias (A) and Time to First Recurrence of Symptomatic Atrial Tachyarrhythmias (B)

A Primary efficacy outcome

B Time to first recurrence of symptomatic atrial tachyarrhythmias

No. at risk
Antiarrhythmic drug
Radiofrequency catheter ablation
61 61 46 39 28 18 12
66 66 50 47 36 24 18

Tachyarrhythmias include atrial fibrillation, tachycardia, and flutter. HR indicates hazard ratio.
Thromboembolic and Haemorrhagic events in 1500 patients (5 years of follow up)

500 pts- Rate control + VKA \textit{FOR CHADS\textsubscript{2}VASC \geq 2}

500 pts- AF ablation + VKA \textit{FOR CHADS\textsubscript{2}VASC \geq 2}

500 pts- AF ablation \textit{FOR CHADS\textsubscript{2}VASC \leq 1}

Long-term events following atrial fibrillation rate control or transcatheter ablation: a multicenter observational study

Cristina Gallo\textsuperscript{a}, Alberto Battaglia\textsuperscript{a}, Matteo Anselmino\textsuperscript{a}, Francesca Bianchi\textsuperscript{c}, Stefano Grossi\textsuperscript{b}, Giulia Nangeroni\textsuperscript{a}, Elisabetta Toso\textsuperscript{a}, Luca Gaido\textsuperscript{a}, Marco Scaglione\textsuperscript{b}, Federico Ferraris\textsuperscript{a} and Fiorenzo Gaita\textsuperscript{a}

JCM, 2016
Thromboembolic events / 100 pts/ year

- Rate control+VKA
- Ablation+VKA
- Ablation

<table>
<thead>
<tr>
<th>CHADSVASC≥2</th>
<th>CHADSVASC≤1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.44%</td>
<td>0.20%</td>
</tr>
<tr>
<td>RRR 54 %</td>
<td>0.28%</td>
</tr>
</tbody>
</table>

Gallo et al JCM 2016; 17: 187
Thromboembolic and Haemorrhagic events/ 100 pts/ year

<table>
<thead>
<tr>
<th>CHADSVASC≥2</th>
<th>CHADSVASC≤1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate control+VKA</td>
<td>0.69%</td>
</tr>
<tr>
<td>Ablation+VKA</td>
<td>0.44%</td>
</tr>
<tr>
<td>Ablation</td>
<td>0.20%</td>
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</tbody>
</table>

RRR 35 %

Gallo et al JCM 2016; 17: 187
Catheter ablation for atrial fibrillation is associated with lower incidence of stroke and death: data from Swedish health registries

2496 ablated pts matched with 2496 non-ablated pts
Follow up 4.4 years

78 TE events (0.7 %pts/y) in ablated pts
112 TE events (1.01%pts/y) in non-ablated pts

Stroke reduction with ablation 31%

TE events in AF pts (metaanalysis)
warfarin vs. NOACs vs. AF Ablation

46 studies, **387379** AF pts, mean FU 2,4 y
MEAN CHADS 2

*Stroke rate/100 pts/year*

- **2.09%** for WARFARIN with RRR 41%
- **1.24%** for NOACs with RRR 52%
- **0.60%** for AF ABLATION

Gaita et al. Data submitted 2017
Conclusions

Oral anticoagulant therapy is the first therapeutical step in the TE risk prevention.

Synus rhythm maintenance by means of TC ablation reduce TE of about 50%.
Conclusions

In pts with CHADS$_2$ ≥ 2
the best therapy to reduce TE risk could be
AF ablation associated with OAT

In pts with CHADS$_2$ 0-1
the best therapy to reduce TE risk is
AF ablation without OAT
(haemorrhagic risk > TE risk)
Thank you for your attention!