Anti-thrombotic therapy in atrial fibrillation: difficult decisions

11:00-12:30, Monday 30 August, 2010
ESC Congress 2010

After successful cardioversion: for how long?

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Presenter Disclosure Information related to this presentation

- The presenter has participated in advisory boards related to antithrombotic treatment organized by Boehringer Ingelheim Hellas and Sanofi Hellas

- The presenter has received honoraria for lectures in satellite symposia from Boehringer Ingelheim Hellas, Sanofi Hellas, Bayer Hellas, Galenica SA, Pfizer Hellas, Astra-Zeneca Hellas and MSD Hellas
When AF lasts longer than 48 h

• Risk of stroke after cardioversion is high (6%-7%),

• Anticoagulation decreases this risk to less than 1%

Antithrombotic Therapy in Atrial Fibrillation
American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

Singer DE, et al. Chest 2008;133;546S-592S

2.1 Anticoagulation for Elective Cardioversion of AF

2.1.1. For patients with AF of ≥ 48 h or of unknown duration for whom pharmacologic or electrical cardioversion is planned, we recommend anticoagulation with an oral VKA, such as warfarin, at a target INR of 2.5 (range, 2.0 to 3.0) for 3 weeks before elective cardioversion and for at least 4 weeks after sinus rhythm has been maintained (Grade 1C).

ESC 2010 Guidelines for the Management of Patients With Atrial Fibrillation

AF for cardioversion

AF onset <48 h

Yes

Heparin

Cardioversion

SR

Risk factors

Yes

4 weeks anticoagulation*

No

No long-term OAC

No

Consider if long-term OAC indicated

Yes

Long-term OAC indicated

No LAA thrombus

Heparin

No

Conventional OAC or TOE

3 weeks therapeutic OAC

TOE strategy

LAA thrombus

Opt for rate control if LAA thrombus still present

Therapeutic OAC for 3 weeks

*Anticoagulation should normally be continued for 4 weeks after a cardioversion attempt except when AF is recent onset and no risk factors are present.

†Long-term OAC if stroke risk factors and/or risk of AF recurrence/presence of thrombus.
ESC 2010 Guidelines for the Management of Patients With Atrial Fibrillation

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1222 pts randomized to conventional or TEE guided CVA

- AF duration >2 days
- Anticoagulation for 3 weeks before and 4 weeks after CVA
- Thrombus detected in 13.8%
- 5 embolic events in the TEE group (0.8%) vs. 3 in the conventional treatment group (0.5%), P=0.50
MAJOR RISK FACTORS
Previous stroke-TIA
Age ≥ 75 years
### Table 9: Approach to thromboprophylaxis in patients with AF

<table>
<thead>
<tr>
<th>Risk category</th>
<th>CHA₂DS₂-VASc score</th>
<th>Recommended antithrombotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>One ‘major’ risk factor or ≥2 ‘clinically relevant non-major’ risk factors</td>
<td>≥ 2</td>
<td>OAC&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>One ‘clinically relevant non-major’ risk factor</td>
<td>1</td>
<td>Either OAC&lt;sup&gt;a&lt;/sup&gt; or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin.</td>
</tr>
<tr>
<td>No risk factors</td>
<td>0</td>
<td>Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.</td>
</tr>
</tbody>
</table>
Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation?

Robby Nieuwlaat, Trang Dinh, S. Bertil Olsson, A. John Camm, Alessandro Capucci, Robert G. Tieleman, Gregory Y.H. Lip, and Harry J.G.M. Crijns on behalf of the Euro Heart Survey Investigators

“...AF duration and frequency play a subordinate role for predicting stroke”

Figure 3: Multivariable effect of atrial fibrillation subtype on outcomes. Results are reported as odds ratio with 95% confidence interval for persistent and permanent atrial fibrillation, compared with the reference group with paroxysmal atrial fibrillation (odds ratio = 1). An odds ratio < 1 indicates a lower likelihood and odds ratio > 1 a higher likelihood for occurrence of the outcome event.
Increased variance of P wave duration on the electrocardiogram distinguishes patients with idiopathic paroxysmal atrial fibrillation.

Andrikopoulos GK, Dilaveris PE, Richter DJ, Gialafos EJ, Synetos AG, Gialafos JE. Increased variance of P wave duration on the electrocardiogram distinguishes patients with idiopathic paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 2000;23(7):1127-32
Long-Term Risk of Recurrent Atrial Fibrillation as Documented by an Implantable Monitoring Device

- 110 pts, 19±11 months follow up
- class I indication for physiologic pacing
- history of AF

Carsten W. Israel, MD, Gerian Gronefeld, MD, Joachim R. Ehrlich, MD, Yi-Gang Li, MD, Stefan H. Hohnloser. JACC 2004;43:47–52

Figure 3. Prevalence of atrial fibrillation (AF) recurrences of various durations detected during follow-up.
Asymptomatic recurrences of atrial fibrillation after pulmonary vein isolation

80 pts with paroxysmal AF underwent PVI and were provided repeatedly with a portable Event Recorder (ER) upon discharge and every 3 months for a year.

- Asymptomatic AF was detected in 21.3%.
- In 9/80 patients (11.3%), who reported clinical AF recurrence, no AF could be shown by ER.

Asymptomatic atrial fibrillation: demographic features and prognostic information from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study

- 12% of AFFIRM patients were asymptomatic,
- Asymptomatic patients were more often men and had a lower incidence of coronary artery disease and congestive heart failure, but had more cerebrovascular events.

Mortality and major events were similar after correction for baseline differences

## Relationships Between Sinus Rhythm, Treatment, and Survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study

<table>
<thead>
<tr>
<th>Covariate</th>
<th>p</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment*</td>
<td>0.0001</td>
<td>1.06</td>
<td>1.05 - 1.08</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.0001</td>
<td>1.56</td>
<td>1.20 - 2.04</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.0001</td>
<td>1.57</td>
<td>1.18 - 2.09</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.0001</td>
<td>1.56</td>
<td>1.17 - 2.07</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>0.0001</td>
<td>1.70</td>
<td>1.24 - 2.33</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.0001</td>
<td>1.78</td>
<td>1.25 - 2.53</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>0.0065</td>
<td>1.36</td>
<td>1.02 - 1.81</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>0.0043</td>
<td>1.36</td>
<td>1.03 - 1.80</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>0.0001</td>
<td>0.53</td>
<td>0.39 - 0.72</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>0.0001</td>
<td>0.50</td>
<td>0.37 - 0.69</td>
</tr>
<tr>
<td>Digoxin use</td>
<td>0.0007</td>
<td>1.42</td>
<td>1.09 - 1.86</td>
</tr>
<tr>
<td>Rhythm-control drug use</td>
<td>0.0005</td>
<td>1.49</td>
<td>1.11 - 2.01</td>
</tr>
</tbody>
</table>

The AFFIRM study

Comment on the role of symptoms and ECG monitoring in the evaluation of thromboembolic risk

57% of strokes in the rhythm control arm occurred in patients who had their anticoagulation stopped

We all know but we tend to forget that........

**Cardioversion** resulting from electric shock, AAD therapy, pacing, or ablation, as well as spontaneous cardioversion, can result in transient atrial stunning or loss of atrial contraction.


(adopted from the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation)
We all know but we tend to forget that………

This stunning after cardioversion may persist for days or weeks. Stunning may promote atrial blood stasis and thrombus formation, which, in turn, can lead to stroke.


(adopted from the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation)
Changes in Left Atrial Structure and Function After Catheter Ablation and Electrical Cardioversion for Atrial Fibrillation

63 pts followed for 3 months after successful restoration of SR

“... because LA function was lower in the ABL group than in the ECV group and did not recover to the baseline levels until 3 months after ABL, a meticulous anticoagulation program should be considered”

Prevalence and clinical impact of left atrial thrombus and dense spontaneous echo contrast in patients with atrial fibrillation and low CHADS2 score (0/1)

295 consecutive patients with non-valvular AF and a CHADS2 score of 0 or 1 who underwent transoesophageal echocardiography before cardioversion and were followed for 5 years.

LA thrombus was present in 3% and dense SEC in 8% of patients. In anticoagulated patients, thrombus and dense SEC were not independently associated with an increased risk for stroke or death.

Differences in the management of patients with Paroxysmal AF vs Cardioverted patients 4 weeks after CV at intermediate or high risk (CHADS2 ≥ 1)

**In favor of OAC for PAF pts**

- Risk of stroke is high and comparable to permanent AF
- Stroke risk significantly reduced by OAC
- Rhythm control strategies often fail to eliminate AF
- True burden of AF cannot be reliably estimated for the vast majority of PAF pts

**In favor of OAC for cardioverted pts**

- Risk of stroke is high and comparable to permanent AF
- Stroke risk significantly reduced by OAC
- AF relapse likely
- Inability to estimate the true burden of AF
- Cardioversion per se promotes local thrombin activation in the atria
- Atrial stunning may last for >3 months especially after CV during ablation
Post Cardioversion Algorithm

(No thrombus in TEE – NO CV during ablation)

(NOT valid for pts with a single episode of AF due to reversible causes)

Low Risk pt (CHADS2=0)

Intermediate/High Risk pt (CHADS2 ≥ 1)

4 weeks OAC*

May STOP OAC or
OAC for 1 yr (1)

OAC beyond 4 weeks or
Lifelong?

OAC or ... alternative Rx

(1) Berry C, McMurray J. Anticoagulation for patients with atrial fibrillation. Warfarin should be given for up to one year after successful cardioversion. BMJ. 2000 May 6;320(7244):1219-20.

* OAC denotes Oral Anticoagulation treatment

The HAS-BLED bleeding risk score*

<table>
<thead>
<tr>
<th>Letter</th>
<th>Description</th>
<th>Score</th>
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<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (one point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (age &gt;65)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or alcohol (one point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>
Post Cardioversion Algorithm
(Thrombus detected in TEE or CV during ablation)
(NOT valid for pts with a single episode of AF due to reversible causes)

At least 3 months OAC
Repeat TEE

Low Risk pt (CHADS2=0)
intermediate/High Risk pt (CHADS2 ≥ 1)

HAS-BLED<3
OAC >3 months
OAC strongly suggested or alternative Rx

HAS-BLED≥3
OAC Lifelong
Lifelong OAC if thrombus in TEE

* OAC denotes Oral Anticoagulation treatment
Cumulative risk of stroke, myocardial infarction, systemic embolism, or vascular death for patients treated at centers with a TTR below or above the study median (65%)

“A target threshold TTR exists (estimated between 58% and 65%) below which there appears to be little benefit of OAC over antiplatelet therapy (clopidogrel+aspirin)”

Patient satisfaction with AF treatments. Physicians’ estimates and perceptions of their patients’ satisfaction with AF treatments compared with patients’ own satisfaction ratings for AF treatments.

An international survey of physician and patient understanding, perception, and attitudes to atrial fibrillation and its contribution to cardiovascular disease morbidity and mortality

Etienne Aliot, Günter Breithardt, Josep Brugada, John Camm, Gregory Y.H. Lip, Panos E. Vardas, and Markus Wagner for the Atrial Fibrillation AWAreness And Risk Education (AF AWARE) group [comprising the Atrial Fibrillation Association (AFA), the European Heart Rhythm Association (EHRA), Stroke Alliance for Europe (SAFE), and the World Heart Federation (WHF)].

Europace 2010;12:626–633
Primary Outcome

Dabigatran 110 vs. Warfarin

- Non-inferiority p-value: <0.001
- Superiority p-value: 0.34

Dabigatran 150 vs. Warfarin

- Non-inferiority p-value: <0.001
- Superiority p-value: <0.001

Margin = 1.46

Connolly J, et al. NEJM 2009
ROCKET AF study
Rivaroxaban Once daily, oral, direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation

Preliminary patient demographics

Enrolment is now complete; a total of 14,269 patients have been randomized at over 1,100 sites in 45 countries
✓ The median age is 73 years, (40% females)
✓ Approximately 35% of patients were naïve to VKA therapy at the time of randomization
✓ Over 90% of patients have hypertension, 63% have heart failure, and 40% have diabetes
✓ Over 50% of patients have a history of stroke, transient ischaemic attack, or non-CNS systemic embolism
✓ 20% of patients are receiving concomitant acetylsalicylic acid therapy

Keith Fox1, Richard Becker2, Scott Berkowitz3, Gunther Breithardt4, Werner Hacke5, Jonathan Halperin6, Graeme Hankey7, Kenneth Mahaffey2, Christopher Nessel8, Manesh Patel2, Daniel Singer9, Robert Califf2, on behalf of the ROCKET AF Study Investigators
Radiofrequency catheter ablation has become an established treatment option for the management of patients with atrial fibrillation (AF). Although the concept of a rhythm control strategy devoid of the adverse events related to antiarrhythmic treatment seems highly attractive, further steps are needed in order to improve our understanding and increase our therapeutic efficacy. Furthermore, the increased cost of this invasive treatment mandates the evaluation of this invasive treatment against the existing evidence pertaining to cost-effectiveness of AF catheter ablation in such a cost-to-benefit analysis.

**Figure 1** The cost-effectiveness plane.
RCTs are not always available or even applicable

Common sense vs Evidence-based practice
“Experience is the name we give to our mistakes”

Oscar Wilde