Management of atrial fibrillation in heart failure

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Disclosures

- Grant support to the institution from Medtronic
- Grant support from the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation, CVON 2014-9: RACE V
The prevalence of AF in heart failure is:

- 10%: 0.96%
- 20-30%: 22.12%
- 30-50%: 61.54%
- >50%: 15.38%
Prevalence of AF in Biostat

Santema, Kloosterman, …, Voors submitted
Atrial fibrillation is not benign

Symptoms
- Dizziness
- Syncope
- Fatigue
- Palpitations
- Dyspnea
- Chest pain

Thromboembolism & stroke

Heart failure

Hospitalisations

Disability

Mortality
Incident AF analysis:
- 15203 observations
- Mean age 58
- Females 55%
- 403 had AF
- FU 8 yrs
- 215 HFrEF
- 272 HFpEF

Incidence rate of HFpEF and HFrEF higher in patients with AF

AF and HF – vicious twins

Patients with prevalent AF
Higher incidence of HF

No AF

Santhanakrishnan Framingham study Circulation 2016
AF and HF – vicious twins

Incident AF analysis:
- 14864 observations
- Mean age 58
- Females 55%
- 90 had HF

- FU 8 yrs
- 795 AF

Incidence rate of AF 10-fold higher in patients with HF

Patients with prevalent HF
Higher incidence of AF

Log rank P<0.0001
AF after HF – a bad combination!

Patients with prevalent HF
Higher incidence of AF

HFpEF
HFrEF
no HF

Mortality after new AF

Santhanakrishnan Framingham study Circulation 2016
NT-proBNP in RACE II

Median baseline NT-proBNP level: 1003 pg/ml

- N=543 / 614 (88.4%)
- Mean LVEF 54%
- IQR: 634-1632

Heart failure probably more often present

Mulder et al. For the RACE II Investigators submitted
Question 2

Beta-blockers in patients with AF and HFrEF are instituted for:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of mortality</td>
<td>37.62%</td>
</tr>
<tr>
<td>Rate control</td>
<td>57.43%</td>
</tr>
<tr>
<td>Reduction of stroke and myocardial infarction</td>
<td>4.95%</td>
</tr>
</tbody>
</table>
Beta-blockers do not reduce mortality

AF
OR 0.86 (0.66-1.13), p=0.28

SR
OR 0.63 (0.54-0.73, p<0.001

Rienstra et al J Am Coll Cardiol HF 2013
Rate control is instituted only after failure of rhythm control in patients with symptomatic AF and HF

Question 3

- yes: 47.92%
- no: 52.08%
Four reasons to consider rate control

- Background treatment in all patients with atrial fibrillation
- First choice treatment in patients with no or minor symptoms
- Treatment after failure of rhythm control
- Treatment when risks restoring sinus rhythm outweigh benefits
Background in nearly all AF patients

- Background treatment (‘adjunctive therapy’) in nearly all AF patients because during a relapse of AF well controlled heart rates are crucial
- Although not investigated it may also be instituted as a ‘pill in the pocket’ strategy in patients with infrequent AF paroxysms precluding long term drug treatment
First choice therapy in elderly asymptomatic patients who do not desire rhythm control because only oral anticoagulants have been associated with improved survival, not rhythm control therapies (awaiting EAST and CABANA results)

The only reason to institute rhythm control is to improve symptoms
Treatment after failure of rhythm control

- Treatment after failure of rhythm control
- But in every symptomatic patient AF ablation should be considered before accepting AF
Treatment when SR risks outweigh benefits

- Treatment when risks restoring sinus rhythm outweigh benefits
- Eg, in patients with the brady-tachy syndrome who do not need pacing when AF is present
Permanent AF $> 80$ bpm

- **lenient**
  - HR $< 110$ bpm (12 lead ECG)

- **strict**
  - HR $< 80$ bpm (12 lead ECG) and
  - HR $< 110$ bpm (at 25% duration of maximal exercise time)

After achieving rate control targets: Holter for safety

RACE II trial Van Gelder et al. New Engl J Med 2010
Cumulative incidence primary outcome

No. At Risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strict</td>
<td>303</td>
<td>282</td>
<td>273</td>
<td>262</td>
<td>246</td>
<td>212</td>
<td>131</td>
</tr>
<tr>
<td>Lenient</td>
<td>311</td>
<td>298</td>
<td>290</td>
<td>285</td>
<td>255</td>
<td>218</td>
<td>138</td>
</tr>
</tbody>
</table>

Cumulative Incidence (%)

- Strict: 14.9%
- Lenient: 12.9%

RACE II trial Van Gelder et al. New Engl J Med 2010
Rate control – how?

In case of symptoms or detoriation of HF
Further reduction of heart rate

LVEF <40%  
Beta-blocker for RC
Consider early combination therapy
Add digoxin

LVEF ≥40%  
Digoxin: Careful institution Await DECISION
Add digoxin

Kirchhof et al. ESC guidelines Europace 2016
Rhythm control – how in HFpEF and HFrEF?
Rhythm control – how in HFpEF and HFrEF?

Initiation of long term rhythm control therapy to improve symptoms in AF

HFpEF
- No or minimal signs for structural heart disease
- Patient choice
- Dronedarone (IA), Flecaïnide (IA), Propafenone (IA), Sotalol (IA)
- Catheter ablation (IIa)ᵇ
- Dronedarone (IA), Sotalol (IA)ᵃ, Amiodarone (IA)ᵈ
- Catheter ablation (IIa)ᵇ

HFrEF
- Coronary artery disease, significant valvular heart disease, abnormal LVH
- Patient choice
- Amiodarone (IA)
- Catheter ablation (IIa)ᵇᶜ

Heart failure
- Patient choice

Kirchhof et al. ESC guidelines Europace 2016
AADs for rhythm control

Probability of Remaining in Sinus Rhythm

A vs S = 0.0001
A vs P = 0.0001
S vs P = 0.0001

No. Patients at Risk
Amiodarone: 206 131 98 60 38 18 10 8 0
Sotalol: 195 97 61 38 21 13 11 4 1
Placebo: 90 21 11 8 5 2 0

Amiodarone for RHC in AFFIRM and AF-CHF

Pooled analysis 3307 pts
1107 amiodarone treated
Freedom from AF at 5 yr 45%
No difference according to LVEF

Logrank P=0.63

Freedom from recurrent AF (%)

LVEF ≥50%
LVEF 30-49%
LVEF <30%

Number at risk
232 191 137 72 25
244 193 138 84 39
237 168 121 83 44

Time (months)
Failure rhythm control in AF-CHF

- Female sex: HR 1.68 (95% CI 1.16-2.44, p=0.007)
- High creatinine: HR 1.07 (per 10 µmol/L, 1.02-1.13, p=0.005)
- NYHA III/IV: HR 1.57 (1.11-2.24, p=0.01)
Is there still a role for AADs in AF and HF

- There is only a modest role
- Institution only for improving AF associated symptoms
  - Cave: symptoms always due to AF?
- Safety is a concern
- There are several niches – personalized medicine
  - Critically ill patients
  - Reduction of inappropriate ICD shocks
  - Hybrid therapy continuation after ablation – substrate modified
In patients with AF and HFrEF atrial ablation is effective, i.e. sinus rhythm at 1 year follow up, is maintained in:

- 10%: 26.32%
- 20-50%: 51.58%
- 50-70%: 20%
- 70-90%: 2.11%
# Atrial ablation versus amiodarone in HFrEF

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (Catheter Ablation, n=102)</th>
<th>Group 2 (Amiodarone, n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62±10</td>
<td>60±11</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>77 (75)</td>
<td>74 (73)</td>
</tr>
<tr>
<td>AF duration, mo</td>
<td>8.6±3.2</td>
<td>8.4±4.1</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30±8</td>
<td>29±4</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>46 (45)</td>
<td>48 (48)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>22 (22)</td>
<td>24 (24)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>63 (62)</td>
<td>66 (65)</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>47±4.2</td>
<td>48±4.9</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>29±5</td>
<td>30±8</td>
</tr>
<tr>
<td>6MWD, meters</td>
<td>348±111</td>
<td>350±130</td>
</tr>
<tr>
<td>MLHFQ Score</td>
<td>52±24</td>
<td>50±27</td>
</tr>
</tbody>
</table>
Atrial ablation versus amiodarone in HFrEF

Di Biase Circulation 2016
Catheter Ablation versus Standard conventional Treatment in patients with Left ventricular dysfunction and Atrial Fibrillation

The CASTLE-AF trial

Nassir F. Marrouche MD
on behalf the CASTLE AF Investigators
CASTLE-AF

Inclusion Criteria

- Symptomatic paroxysmal or persistent AF
- Failure or intolerance to ≥ 1 or unwillingness to take AAD
- LVEF ≤ 35%
- NYHA class ≥ II
- ICD/CRT-D with Home Monitoring capabilities already implanted due to primary or secondary prevention
Study Design— CASTLE-AF

- Investigator initiated, Prospective, Multicenter (31 sites, 9 countries), Randomized, Controlled

3013 pts

Eligibility Assessment

397 pts

Enrolled/Randomized

200 pts

Run-in 5 weeks

21 pts excluded

197 pts

Ablation

179 pts

153 pts (26 cross-overs)

Follow-up: 3, 6, 12, 24, 36, 48, 60 months

ICD/CRT-D check
Adverse event documentation
Echocardiography
6-minute walk test
Optimization of medication for HF
Home Monitoring programming
NYHA, weight, BP, QoL
Patients’ diary

Conventional

184 pts

165 pts (18 cross-overs)

13 pts excluded
Results-CASTLE AF

AF Burden Derived from Memory of Implanted Devices

![Graph showing AF Burden over time with Conventional and Ablation methods]
Results - CASTLE AF

Primary Composite Endpoint

Survival Probability

Follow-Up Time (Months)

Risk Reduction: 38%

HR, 0.62 (95% CI, 0.43-0.87); P=0.007
Log-rank test: P=0.006

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Ablation</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>179</td>
<td>184</td>
</tr>
<tr>
<td>12</td>
<td>141</td>
<td>145</td>
</tr>
<tr>
<td>24</td>
<td>114</td>
<td>111</td>
</tr>
<tr>
<td>36</td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td>48</td>
<td>58</td>
<td>48</td>
</tr>
<tr>
<td>60</td>
<td>22</td>
<td>12</td>
</tr>
</tbody>
</table>
EAST and CABANA change next guidelines

The EAST study: redefining the role of rhythm control therapy in atrial fibrillation

EAST, the Early treatment of Atrial fibrillation for Stroke prevention Trial

Pre-Study Screening

Patients at risk for cardiovascular events
(≥ CHA₂DS₂-VASc score ≥ 2)
and having
recent onset atrial fibrillation
(≤1 year duration or first documented by ECG)

*Detailed inclusion criteria:
One of the following: age > 75 years or prior stroke/TIA OR
Two of the following: age > 65 years; female sex; arterial hypertension; diabetes mellitus; previous myocardial infarction, CABG or PCI; stable heart failure (NYHA II or LVEF<50%); left ventricular hypertrophy (>15 mm wall thickness); chronic kidney disease (MDRD stage III-IV); peripheral artery disease.

Study Procedures

Early Rhythm Control
anticoagulation, rate control and either antiarrhythmic drug therapy or pulmonary vein isolation (PVI)
in case of recurrent AF:
Re-PVI, adaptation of antiarrhythmic drug therapy
ECG monitoring of therapy

Usual Care
anticoagulation, rate control, supplemented by rhythm control only in symptomatic patients on optimal rate control therapy

outpatient FU at 12, 24, 36 months (both study groups)
therapy of underlying heart disease (both study groups)
blind assessment of primary outcomes (both study groups)

EAST: NCT01288352
Cabana: NCT00911508

Haegeli et al for the EAST Investigators Eur Heart J 2015; Kirchhof Am Heart J 2014
In my hospital patients with AF and HF are seen at the outpatient department by:

- HF nurse: 47.31%
- AF nurse: 9.68%
- Cardiologist: 25.81%
- AF heart team: 17.2%
# Multidisciplinary teams - AF clinics

## Integrated AF management

<table>
<thead>
<tr>
<th>Patient involvement</th>
<th>Multidisciplinary teams</th>
<th>Technology tools</th>
<th>Access to all treatment options for AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central role in care process</td>
<td>Physicians (general physicians, cardiology and stroke AF specialists, surgeons) and allied health professionals work in a collaborative practice model</td>
<td>Information on AF</td>
<td>Structured support for lifestyle changes</td>
</tr>
<tr>
<td>Patient education</td>
<td>Efficient mix of communication skills, education, and experience</td>
<td>Clinical decision support</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>Encouragement and empowerment for self-management</td>
<td></td>
<td>Checklist and communication tools</td>
<td>Rate control</td>
</tr>
<tr>
<td>Advice and education on lifestyle and risk factor management</td>
<td></td>
<td>Used by healthcare professionals and patients</td>
<td>Antiarrhythmic drugs</td>
</tr>
<tr>
<td>Shared decision making</td>
<td></td>
<td>Monitoring of therapy adherence and effectiveness</td>
<td>Catheter and surgical interventions (ablation, LAA occluder, AF surgery, etc.)</td>
</tr>
</tbody>
</table>

- **Informed, involved, empowered patient**
- **Working together in a multidisciplinary chronic AF care team**
- **Navigation system to support decision making in treatment team**
- **Complex management decisions underpinned by an AF Heart Team**

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2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>An integrated approach with structured organization of care and follow-up should be considered in all patients with AF, aiming to improve guidelines adherence and to reduce hospitalizations and mortality.</td>
<td>II(^a)</td>
<td>B</td>
</tr>
<tr>
<td>Placing patients in a central role in decision-making should be considered in order to tailor management to patient preferences and improve adherence to long-term therapy.</td>
<td>II(^a)</td>
<td>C</td>
</tr>
</tbody>
</table>
RACE 3

Risk Factor Driven Upstream Therapy in Early Persistent Atrial Fibrillation

The Routine versus Aggressive upstream rhythm Control for prevention of Early persistent atrial fibrillation in heart failure study

Michiel Rienstra, Anne H. Hobbelt, Marco Alings, Jan G.P. Tijssen, Marcelle D. Smit, Johan Brügemann, Bastiaan Geelhoed, Robert G. Tieleman, Hans L. Hilleges, Raymond Tukkie, Dirk J. Van Veldhuisen, Harry J.G.M. Crijns, Isabelle C. Van Gelder,

for the RACE 3 Investigators
Causal treatment of AF and HF

Risk factor driven upstream

Conventional

ECV after 3 weeks

Guideline-recommended rhythm and rate control

In the upstream group, on top of that

RACE 3 Investigators Hotline ESC 2017
Risk factor driven upstream therapy

- Four upstream therapies, intended to affect the atrial substrate and reduce risk factors, were started:
  1) Mineralocorticoid receptor antagonist (MRA)
  2) Statins
  3) ACE-inhibitors (ACE-I) and/or angiotensin-receptor blockers (ARB)
  4) Cardiac rehabilitation
Risk factor driven upstream therapy

- Four upstream therapies, intended to affect the atrial substrate and reduce risk factors, were started:
  1) Mineralocorticoid receptor antagonist (MRA)
  2) Statins
  3) ACE-inhibitors (ACE-I) and/or angiotensin-receptor blockers (ARB)
  4) Cardiac rehabilitation

- MRAs, ACE-Is, ARBs were dosed aiming to the highest tolerated dose
- Blood pressure target was < 120/80 mmHg
- Statins were prescribed at the recommended dosages
Primary endpoint

Presence of sinus rhythm at the 7-day Holter* at 1-year

*All 7-day Holters were analysed by central core lab blinded for randomised therapy
Changes in secondary endpoints

% change between baseline and 1-year

RRsyst  RRdiast

* P<0.05 upstream versus conventional group
Changes in secondary endpoints

Upstream
Conventional

% change between baseline and 1-year

RRsyst  RRdiast  NT-proBNP  LVEF

* P<0.05 upstream versus conventional group
Changes in secondary endpoints

% change between baseline and 1-year

RRsyst  RRdiast  NT-proBNP  LVEF  LDL

* P<0.05 upstream versus conventional group
Primary endpoint
Sinus rhythm at 1-year

<table>
<thead>
<tr>
<th></th>
<th>Upstream</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients</td>
<td>75%</td>
<td>63%</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.765</td>
<td></td>
</tr>
<tr>
<td>Lower 95% conf. limit</td>
<td>1.115</td>
<td></td>
</tr>
</tbody>
</table>

Superiority hypothesis was proven (p=0.021)

RACE 3 Investigators Hotline ESC 2017
Conclusion

The RACE 3 study demonstrates that risk factor driven upstream therapy is effective and feasible to improve maintenance of sinus rhythm in patients with early persistent AF and HF.
Clinical implication

The effect of upstream therapy on reduction of risk factors and cardiovascular diseases was favourable. Therefore, RACE 3 may contribute to the shift to focus on EARLY risk factor modification to improve AF outcomes.
Take home messages

- Look always for AF in HF and for HF in AF
- Rate control always needed in HF patients with AF
- Beta-blocker instituted only for rate control in AF
- Digoxin should be instituted carefully
- Rhythm control in case of symptoms or HF deterioration
- Still very difficult to maintain long term SR
- Multidisciplinary approach needed
- Because optimal therapy of risk factors is essential!
Thank you for your attention

AF and HF specialists

Let’s work together!