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. Hillege, Raymond Tukkie, Dirk J. Van Veldhuisen, Harry J.G.M. Crijns, Isabelle C. Van Gelder, for the RACE 3 Investigators
Declaration of interest

- Research contracts (Medtronic to the institute)
Financial support of RACE 3

This work was supported by the Netherlands Heart Foundation (Grant 2008B035), and the Netherlands Heart Institute.

Further, this trial was funded by unrestricted grants from AstraZeneca, Bayer, Biotronik, Boehringer-Ingelheim, Boston Scientific, Medtronic, Sanofi-Aventis, St-Jude-Medical paid to the Netherlands Heart Institute.
Background

- Maintenance of sinus rhythm improves AF-related symptoms

- However, sinus rhythm maintenance is cumbersome due to atrial remodelling, caused by risk factors and diseases underlying AF, and AF itself

- Recognition of the consequences of atrial remodelling has led to the notion that early intervening may prevent progression of AF

- Risk factor driven upstream therapy refers to interventions that aim to modify the atrial substrate, and at the same time has a favourable effect on risk factors and diseases underlying AF
Hypothesis and trial design

- **Hypothesis:**
  Risk factor driven upstream therapy is superior to conventional therapy for maintenance of sinus rhythm in patients with early persistent AF and HF

- **RACE 3 trial design:**
  - Prospective, randomized, open label, superiority trial
  - Investigator-initiated
  - Multicenter: 14 sites in The Netherlands and 3 in United Kingdom
  - Enrolment between 2009 and 2015
  - 1 year follow-up
Causal treatment of AF and HF

Risk factor driven upstream

Conventional

ECV after 3 weeks

On top of that in the upstream group:
1. Mineralocorticoid receptor antagonists
2. Statins
3. ACE-inhibitors and/or angiotensin-receptor blockers
4. Cardiac rehabilitation:
   - physical activity
   - dietary restrictions
   - counselling

In both groups rhythm control and HF therapy according to guidelines
Flowchart

Patients with early persistent AF and HF

Causal treatment of AF and HF

Risk factor driven upstream

- 1. Mineralocorticoid receptor antagonists
- 2. Statins
- 3. ACE-inhibitors and/or angiotensin-receptor blockers
- 4. Cardiac rehabilitation:
  - physical activity
  - dietary restrictions
  - counselling

Conventional

ECV after 3 weeks

In both groups rhythm control and HF therapy according to guidelines

7-day Holter at 1-year
Primary endpoint

Presence of sinus rhythm, defined as sinus rhythm during at least $6/7^{th}$ of assessable time, at the 7-day Holter* at 1-year

*All 7-day Holters were analysed by central core lab blinded for randomised therapy
## Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Upstream</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>n=119</td>
<td>n=126</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64±9</td>
<td>65±9</td>
</tr>
<tr>
<td>Male sex</td>
<td>79%</td>
<td>79%</td>
</tr>
<tr>
<td>Total history of AF (months)</td>
<td>3 (2-7)</td>
<td>3 (2-5)</td>
</tr>
<tr>
<td>Total persistent AF (months)</td>
<td>2 (1-4)</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>Duration of HF (months)</td>
<td>2 (1-4)</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>LVEF &lt;45%</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>1057 (694-1636)</td>
<td>1039 (717-1755)</td>
</tr>
</tbody>
</table>
Primary endpoint

Sinus rhythm at 1-year

<table>
<thead>
<tr>
<th>% of patients</th>
<th>Upstream</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75%</td>
<td>63%</td>
</tr>
</tbody>
</table>

Odds ratio: 1.765
Lower 95% confidence limit: 1.115
Superiority hypothesis is proven: p=0.021
Changes in secondary endpoints

% change between baseline and 1-year

RRsyst  RRdiast  NT-proBNP  LVEF  LDL  BMI  LA volume

* P<0.05 upstream versus conventional group
Conclusion and implication

- The RACE 3 study shows that risk factor driven upstream therapy, including treatment of risk factors and change of lifestyle, is effective and feasible to improve maintenance of sinus rhythm in patients with early persistent AF and HF.
- The effect of upstream therapy on reduction of risk factors, instead of its effect on atrial remodelling, is favourable.
- RACE 3 may contribute to the shift to focus on risk factor modification to improve outcomes in AF patients.
RACE 3 study organisation

Steering committee
I.C. Van Gelder
H.J.G.M. Crijns
M. Alings
M. Rienstra
J.G.P. Tijssen
M.D. Smit
J. Brügemann
R.G. Tieleman
H.L. Hillege
R. Tukkie
D.J. Van Veldhuisen

Trial and data management
W.J.M. Mol, O. Eriks

Central Holter core lab
J. Haaksma

Secondary end point adjudication committee
R.A. Tio, J.P. Van Melle

Statistical analysis committee
M. Rienstra, B. Geelhoed, H.L. Hillege, J.G.P. Tijssen, I.C. Van Gelder

Data Safety and Monitoring Board
H.J.J. Wellens, A.M. Wilde, Y.M. Pinto

Supported by:
Netherlands Heart Foundation
Netherlands Heart Institute
RACE 3 investigators

The Netherlands:
University Medical Center Groningen, Groningen - I.C. Van Gelder
Amphia Hospital, Breda - M. Alings
Martini Hospital, Groningen - R.G. Tieleman
Admiraal De Ruyter Hospital, Goes - I. Aksoy
Ziekenhuisgroep Twente Location Almelo, Almelo, - G.C.M. Linssen
Rijnstate Hospital, Arnhem - H.A. Bosker
Spaarne Hospital, Haarlem - G.J.E. Verdel
Radboud University Nijmegen Medical Center, Nijmegen - E. Cramer
Maastricht University Medical Center, Maastricht - H.J.G.M. Crijns
Tergooi Hospital, Blaricum - R.H.J. Peters
Deventer Hospital, Deventer - Y.S. Tuininga
Ommelander Hospital Group, Winschoten/Delfzijl, - A. Van Der Galiën/V. Hagens
Onze Lieve Vrouwe Gasthuis, Amsterdam - G.S. De Ruiter

United Kingdom:
Birmingham City Hospital, Birmingham - G.Y.H. Lip
Leeds General Infirmary, Leeds - M. Tayebjee
Poole Hospital, Poole - C. Boos