Heart failure in AF: How important is rate control with Beta-blockers?
Disclosures

Non-financial collaborations with GlaxoSmithKline, AstraZeneca, Merck Serono

Research grants: Menarini Farmaceutica

Lead for Beta-blockers in Heart Failure Collaborative Group

Chief Investigator for RAte control Therapy Evaluation in Atrial Fibrillation (RATE-AF) trial

European Society of Cardiology Guidelines Task Force for AF & ESC Education Committee
We have a problem…

Heart failure

30-41% 33-56%

AF

Loss of atrial systole
Decreased diastolic filling interval
Decreased cardiac output
Increased end-diastolic pressure
RAAS/neurohormonal activation

Tachycardia
Irregular conduction

Left atrial stretch
Increased atrial pressure
Increased atrial size
Atrial fibrosis

Increased focal triggers
Conduction slowing
Shortened atrial effective refractory period
Increased action potential duration heterogeneity

Cycle of interdependence between HF and AF

Kotecha & Piccini: Eur Heart J. 2015;36:3250-3257
HF / AF epidemiology and outcomes

**Prevalent HF in 88,038 patients in Sweden 2006-2010**

- Women: P=0.044
- Men: P=0.25

**Incident AF in 57,818 patients in UK 1998-2010**

- Prevalence: p<0.001
- Incidence: p=0.84
- Mortality: p<0.001

---


Lane / Kotecha; J Am Heart Assoc. 2017;6:e005155
Management of AF: 2016 ESC Guidelines

**Treatmet**

- Acute rate and rhythm control (e.g., β-blockers, cardioversion)
- Manage precipitating factors
- Assess stroke risk
- Assess heart rate
- Assess symptoms
- Lifestyle changes, treatment of underlying cardiovascular conditions
- Oral anticoagulation in patients at risk for stroke
- Rate control therapy
- Antiarrhythmic drugs, cardioversion, catheter ablation, AF surgery

**Desired outcome**

- Haemodynamic stability
- Cardiovascular risk reduction
- Stroke prevention
- Symptom improvement, preservation of LV function
- Symptom improvement

**Patient benefit**

- Improved life expectancy
- Improved quality of life, autonomy, social functioning

Evidence base for rate control

• Control of heart rate is not underpinned by a good evidence-base

• The choice of therapy mostly relies on local policies and physician/patient preference

Kotecha et al; BMJ Open 2017;7:e015099
AF-CHF trial:

- Impressive reduction in AF (70% vs 27% at 48m)
- But no difference in CV death with rate control (88% beta-blockers) compared to rhythm control (82% amiodarone; 59% electrical cardioversion)

? Beta-blockers versus placebo?

Rate control and mortality

Beta-blockers in Heart Failure Collaborative Group

- Randomised controlled trials
- Reporting mortality as a major trial endpoint
- Unconfounded head-to-head
- Planned >6m follow-up
- >300 patients
  (accounts for >95% of eligible RCT participants)

Pooling of individual data from 18,254 heart failure patients randomised to beta-blockers or placebo, according to a published extraction and analysis plan.†

† Kotecha et al: Syst Rev. 2013;2:7  * No AF patients
Rate control and mortality

All-cause mortality: Sinus rhythm

- Placebo
- Beta-blocker

HR 0.73 (95% CI 0.67-0.80); p<0.001

All-cause mortality: Atrial fibrillation

- Placebo
- Beta-blocker

HR 0.97 (95% CI 0.83-1.14); p=0.73

n=13,946 (sinus), n=3,066 (AF)

Kotecha et al; Lancet. 2014;384:2235-2243
Beta-blockers versus placebo in HFrEF:

- Consistently no benefit in patients with atrial fibrillation at baseline

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Sinus rhythm (n=13,946)</th>
<th>Atrial fibrillation (n=3,066)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years with HF diagnosis, median (IQR)</td>
<td>3.0 (1.0-6.0)</td>
<td>3.0 (1.0-7.0)</td>
</tr>
<tr>
<td>LVEF, median (IQR)</td>
<td>0.27 (0.21-0.33)</td>
<td>0.27 (0.22-0.33)</td>
</tr>
<tr>
<td>NYHA class III/IV</td>
<td>63%</td>
<td>72%</td>
</tr>
<tr>
<td>ACEi or ARB</td>
<td>95%</td>
<td>95%</td>
</tr>
</tbody>
</table>
### Subgroups of HFrEF-AF

<table>
<thead>
<tr>
<th>Sub-group of AF (deaths/number)</th>
<th>Log(hazard ratio) with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;70 years (279/1617)</td>
<td>-1.0</td>
</tr>
<tr>
<td>≥70 years (337/1446)</td>
<td>-0.5</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
</tr>
<tr>
<td>(114/593)</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td></td>
</tr>
<tr>
<td>(502/2470)</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Non-diabetic</strong></td>
<td></td>
</tr>
<tr>
<td>(413/2242)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Diabetic</strong></td>
<td></td>
</tr>
<tr>
<td>(161/674)</td>
<td>-1.0</td>
</tr>
<tr>
<td><strong>NYHA Class I/II</strong> (105/734)</td>
<td>-0.5</td>
</tr>
<tr>
<td><strong>NYHA Class III/IV</strong> (447/1898)</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;140/90 mmHg (566/2634)</td>
<td>-1.0</td>
</tr>
<tr>
<td>≥140/90 mmHg (50/429)</td>
<td>-0.5</td>
</tr>
<tr>
<td><strong>Estimated GFR ≥60 mL/min</strong></td>
<td></td>
</tr>
<tr>
<td>(249/1517)</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Estimated GFR&lt;60 mL/min</strong></td>
<td></td>
</tr>
<tr>
<td>(342/1447)</td>
<td>0.5</td>
</tr>
</tbody>
</table>


**Favours beta-blocker** ➔ **Favours placebo**

---

**Sub-group of AF (deaths/number)**

<table>
<thead>
<tr>
<th>Log(hazard ratio) with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF &gt;0.35 (83/510)</td>
</tr>
<tr>
<td>LVEF ≤0.35 (528/2537)</td>
</tr>
<tr>
<td>Heart rate ≥90 bpm (453/2231)</td>
</tr>
<tr>
<td>Heart rate &gt;90 bpm (163/831)</td>
</tr>
<tr>
<td>No digoxin (102/505)</td>
</tr>
<tr>
<td>Digoxin (514/2558)</td>
</tr>
<tr>
<td>No ACEi/ARB (37/167)</td>
</tr>
<tr>
<td>ACEi/ARB (579/2896)</td>
</tr>
<tr>
<td>No oral anticoagulant (488/2480)</td>
</tr>
<tr>
<td>Oral anticoagulant (105/500)</td>
</tr>
<tr>
<td>Overall crude (616/3063)</td>
</tr>
<tr>
<td>Overall adjusted (611/3046)</td>
</tr>
</tbody>
</table>

---

Discordant with observational data

AF +

Prevalent heart failure

Free from heart failure

Probability of Survival

Time since baseline (days)

Nielsen; Circ Heart Fail. 2016;9:e002597
Reverse association with digoxin

Digoxin versus control: Summary of all-cause mortality

Observational studies:
- Unadjusted (n=33) RR 1.76 (95% CI 1.57-1.97)
- Adjusted (n=8) RR 1.61 (95% CI 1.31-1.97)
- Adjusted (n=14) HR 1.17 (95% CI 1.07-1.29)
- Propensity-matched (n=6) RR 1.18 (95% CI 1.09-1.26)
- Propensity-matched (n=7) HR 1.07 (95% CI 0.96-1.19)
- Randomised controlled trials (n=7) RR 0.99 (95% CI 0.93-1.05)

Combined n=999,994 across 75 study analyses

Risk ratio (RR) / Hazard ratio (HR)

→ More deaths with digoxin
RACE II:

- One of only a few high quality RCTs of rate control (majority BB).
- No difference in outcomes or symptoms with strict versus lenient rate control.
- Similar results in subgroup analysis of 47% with HF.
Why no mortality benefit?

A HFrEF / Sinus rhythm

B HFrEF / Atrial fibrillation

Kotecha et al: J Am Coll Cardiol. 2017;69:2885-2896
Why no mortality benefit?

A Sinus rhythm

PLACEBO

BETA-BLOCKER

Log-rank trend
p<0.0001

Log-rank trend
p<0.0001

B Atrial fibrillation

PLACEBO

BETA-BLOCKER

Log-rank trend
p=0.99

Log-rank trend
p=0.18

Kaplan Meier survival curves censored from time of the interim visit (mean of 184 days from randomization). Includes a post-hoc analysis of heart rate that separates patients <60 beats/min in the beta-blocker arm.

Kotecha et al: J Am Coll Cardiol 69:2885-2896
Other reasons for beta-blockers?

If no apparent mortality benefit, are there other reasons for beta-blockers in AF and HF?

• Improve symptoms

• Improve cardiac function / prevent deterioration
Symptom improvement?

**RACE II:**

- Symptoms similar in strict and lenient groups.
- Subjective reduction with rate control.

N= 614 patients with permanent AF and baseline heart rate >80 bpm

Heart rate resting <80, exercise <110

Heart rate resting <110

--

Van Gelder; NEJM. 2010;362:1363-1373  
Groenveld; JACC. 2011;58:1795-1803  
Mulder; Eur J HF. 2013;15:1311-1318
**PIAF rate vs rhythm:**

- As with other RCTs, no difference in outcomes when adding rhythm control drugs ± cardioversion to rate control.

- Both groups had similar symptom improvement.

Hohnloser; Lancet. 2000;356:1789-1794
Grönefeld; Eur Heart J. 2003;24:1430-1436
**Symptom improvement?**

**Beta-blockers vs CCB:**

- Diltiazem/verapamil reduced BNP and improved symptoms
- Beta-blockers reduced VO$_2$, increased BNP and had a lesser effect on symptoms
- 60 patient crossover RCT of permanent AF without clinical HF or reduced LVEF (n=563 screened)

* p<0.05 compared to baseline

Ulimoen: Eur Heart J. 2014;35:517-524  
Improve cardiac function?

- Cardiac cycle length is strongly related to stroke volume
- RR interval affects LVEF in AF patients, more so than in sinus rhythm
- Beat-to-beat variability in stroke volume increases as heart rate increases in AF patients
- Tachycardiomyopathy can also occur in some patients

Improve cardiac function?

- Small RCT of digoxin and blinded use of beta-blocker
- N=47 with persistent AF and HFrEF
- Combination therapy improved LVEF from baseline (borderline significant, p=0.05)
Improve cardiac function?

Observed change in left ventricular ejection fraction (LVEF) from baseline in patients who survived to follow-up (median 1.0 years).

Cleland / Kotecha; Eur Heart J. 2017 (in press)
**Acute heart rate control of AF**

- **LVEF <40% or signs of congestive heart failure**
  - Smallest dose of beta blocker to achieve rate control
    - Amiodarone is an option in patients with haemodynamic instability or severely reduced LVEF
    - Initial resting heart rate target <110 bpm
  - Add digoxin
    - Initial resting heart rate target <110 bpm

- **LVEF ≥40%**
  - Beta blocker or diltiazem or verapamil
    - Check previous drug history to avoid concomitant administration
    - Initial resting heart rate target <110 bpm
  - Add digoxin
    - Initial resting heart rate target <110 bpm

- Avoid bradycardia
  - Perform echocardiogram to determine further management/choice of maintenance therapy
  - Consider need for anticoagulation
Adverse outcomes with CCB

Diltiazem / Verapamil

- Potential for increase in HF in patients with LVEF <40%.
- Subgroup data only from post-MI trials.

Adapted from Goldstein; Circulation 1991;83:52-60
Long-term heart rate control of AF

Perform echocardiogram (IC)
Choose initial rate control therapy (IB) and combination therapy if required (IIaC)
Target initial resting heart rate <110 bpm (IIaB), avoiding bradycardia

LVEF <40%
- Beta-blocker
- Digoxin
  - Consider early low-dose combination therapy
    - Add digoxin
    - Add beta-blocker

LVEF ≥40%
- Diltiazem/verapamil
- Beta-blocker
- Digoxin
  - Add therapy to achieve target heart rate or if ongoing symptoms
    - Add digoxin
    - Add digoxin
    - Add diltiazem, verapamil or beta-blocker
Management of AF and HF

- **Cardioversion** if signs of haemodynamic compromise
- **Anticoagulation** unless absolute contraindication
- **Normalise fluid balance** diuretics to control signs and symptoms of failure
- **Target initial heart rate <110 bpm** consider stricter control if persistent symptoms
- **Renin-angiotensin-aldosterone system** ACEi/ARB/mineralocorticoid receptor antagonists
- **Early consideration of rhythm control** amiodarone/cardioversion and ablation
- **Advanced heart failure therapies** resynchronization/defibrillator/mechanical support
- **Treatment of other CV disease** control of ischaemia and hypertension

**Patient-centred approach**
- Diagnosis/management of non-CV comorbidities, including diabetes, renal dysfunction, anaemia and airways disease
- Education and support

Kotecha & Piccini: Eur Heart J. 2015;36:3250-3257
Heart failure in AF: How important is rate control with Beta-blockers?

- One of only 2 agents available if LVEF <40% and safe
- Provides effective heart rate control (which may improve symptoms and cardiac function)
- Can prevent AF from developing in HFrEF (33% ↓)
- No evidence as yet in concomitant HF and AF for mortality benefit or reduction in hospital admissions
- Further comparative randomised studies urgently needed *

* Kotecha et al; BMJ Open 2017;7:e015099
ESC / CATCH ME apps for atrial fibrillation

Download now for free!

Search for “My AF” (patient app)

“AF Manager” (healthcare app)

Kotecha & Kirchhof; Eur Heart J. 2017;38:2643-2645    Kotecha et al; Europace. 2017; in press