Beta-blockers in high-risk heart failure patients with reduced ejection fraction and moderately-severe renal dysfunction

Dipak Kotecha, FESC
on behalf of the

Beta-blockers in Heart Failure Collaborative Group
In memory of the late Philip Poole Wilson, Henry Krum and Doug Altman
Disclosures

**Beta-blockers in Heart Failure Collaborative Group:**
The majority of the group have received speaker fees, honoraria or grant support from pharmaceutical companies involved in beta-blocker therapies.

**Personal:**
Grants to support administration from Menarini Farmaceutica; Data extraction support from GlaxoSmithKline; Collaborative research grant from IRCCS San Raffaele.
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**Other Personal Funding:**
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British Heart Foundation – Project Grant.
EU Innovative Medicines Initiative – BigData@Heart Consortium.
Previous studies based on sub-groups of trials have lacked sufficient patients to make any robust conclusions on those with moderate or moderately-severe renal dysfunction.

Renal dysfunction is common in heart failure patients and associated with worse outcomes. Randomised trials typically exclude patients with significant renal impairment.

“You’ve worked so hard on the kidney... very special... the kidney has a very special place... in the heart”

This has implications for clinicians and the assumed effectiveness of treatment, impacting on prescription of guideline-recommended therapy, dosage given and the maintenance of drugs.
Individual patient data meta-analysis

- 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 patient data from 18,637 heart failure patients in double-blind RCTs according to a published extraction and analysis plan.

Bisoprolol ● Bucindolol ● Carvedilol ● Metoprolol XL ● Nebivolol

Median age: 65 years (55-72)
Women: 23%
Median LVEF: 27% (21-33%)
ACE inhibitors: 95%
MRA: 9%
Mortality associated with renal dysfunction

12% increase in the hazard of death for every 10 mL/min lower eGFR (95% CI 10-15%; p<0.001).
Efficacy of beta-blockers

Sinus rhythm

Baseline eGFR (mL/min/1.73m²)

Adjusted hazard ratio for all-cause mortality

LVEF <50%

Sinus rhythm

Beta-blockers vs. placebo

Interaction p=0.021

eGFR <30

Mortality

Placebo 162 88 28 9
Beta-blocker 211 108 29 8

p=0.43
p=0.35 adjusted

NNT 21.4

eGFR 30-44

Mortality

Placebo 891 502 136 39
Beta-blocker 934 575 166 58

p=0.026
p=0.01 adjusted

NNT 21.4

eGFR 45-59

Mortality

Placebo 1802 1133 348 118
Beta-blocker 1910 1253 425 176

p<0.0001
p<0.001 adjusted

NNT 21.5

eGFR >90

Mortality

Placebo 3133 2075 679 276
Beta-blocker 3272 2289 868 364

p<0.0001
p<0.001 adjusted

NNT 21.5
Change in renal function

Sinus rhythm

- eGFR worsened by 20% or more from baseline
Efficacy of beta-blockers
Atrial fibrillation

Lower eGFR in patients with AF:
• Median 60 mL/min (compared to 64 in sinus)
• eGFR <60 in 48.9% (versus 42.9% in sinus)

Higher mortality in AF:
• 21% (versus 16% in sinus) during 1.3 years mean follow-up

No impact of beta-blockers:

Interaction $p=0.18$
### Adverse events

<table>
<thead>
<tr>
<th>Discontinuation of study drug</th>
<th>eGFR 30-44 mL/min</th>
<th>eGFR 45-59 mL/min</th>
<th>eGFR &gt;90 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Beta-blocker</td>
<td>Placebo</td>
</tr>
<tr>
<td>Due to any adverse event</td>
<td>20.9%</td>
<td>19.4%</td>
<td>14.9%</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>15.1%</td>
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</table>

### Dose

<table>
<thead>
<tr>
<th>Beta-blocker dose achieved</th>
<th>eGFR 30-44 mL/min</th>
<th>eGFR 45-59 mL/min</th>
<th>eGFR &gt;90 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta-blocker</td>
<td>Beta-blocker</td>
<td>Beta-blocker</td>
</tr>
<tr>
<td>&gt;50% of max target dose</td>
<td>76.3%</td>
<td>77.9%</td>
<td>83.8%</td>
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</tbody>
</table>
Take home messages

Renal impairment is often considered a barrier in clinical practice for the commencement and uptitration of guideline-recommended HFrEF therapy.

- We have demonstrated with sufficient sample size that beta-blockers are effective in reducing mortality in patients with HFrEF and sinus rhythm, even in those with moderately-severe renal dysfunction (as low as an eGFR of 30-44 mL/min/1.73m$^2$).
- Despite higher rates of comorbidities, the absolute benefit in this group was similar to patients with preserved renal function.
- Discontinuation due to adverse events was the same for both beta-blockers and placebo in these double-blind trials and renal function did not appear to worsen, even in those with kidney dysfunction at baseline.

These results suggest that renal impairment should not obstruct the prescription and maintenance of beta-blockers in patients with HFrEF.