

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

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*on behalf of the*



Beta-blockers in Heart Failure Collaborative Group

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# Beta-blockers in Heart Failure Collaborative Group



Group members
  Invited experts
  In memoriam
  Pharma collaborators

*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.  
Unrelated: Bayer advisory board; Atricure speaker fees.

## **Other Personal Funding:**

National Institute for Health Research - Career Development Fellowship.  
British Heart Foundation – Project Grant.  
EU Innovative Medicines Initiative – BigData@Heart Consortium.

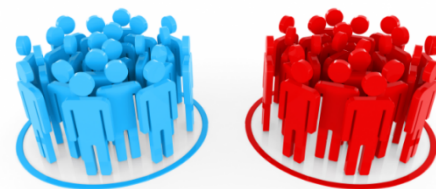
# Background



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

Renal dysfunction is common in heart failure patients and associated with worse outcomes

Randomised trials typically exclude patients with significant renal impairment



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

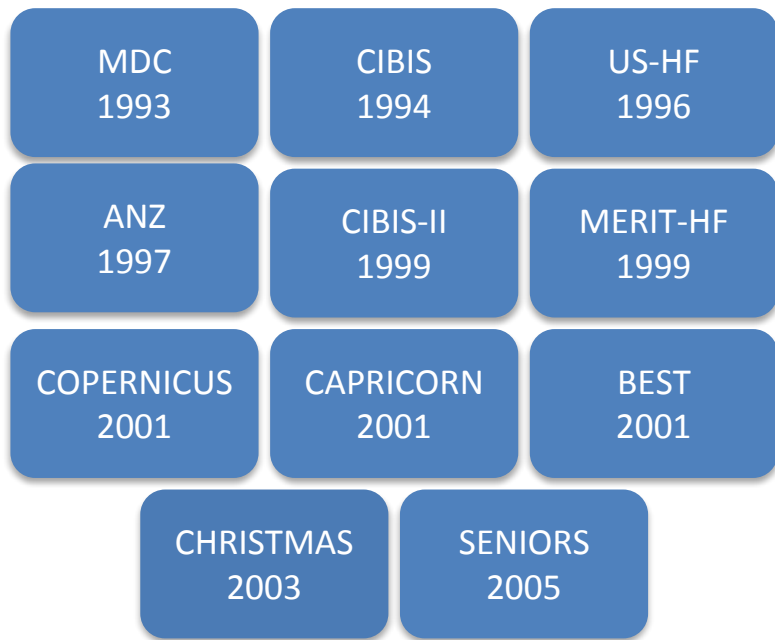
**This has implications for clinicians and the assumed effectiveness of treatment, impacting on prescription of guideline-recommended therapy, dosage given and the maintenance of drugs**

Together with

ESC Congress Paris 2019

World Congress of Cardiology

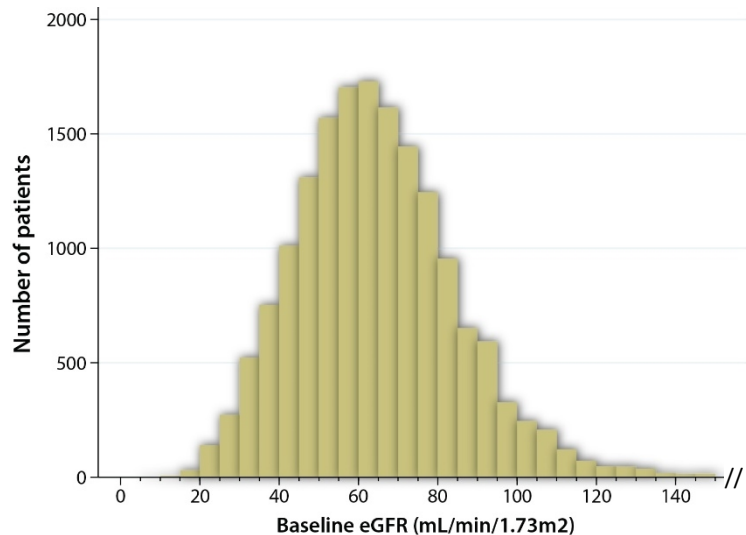
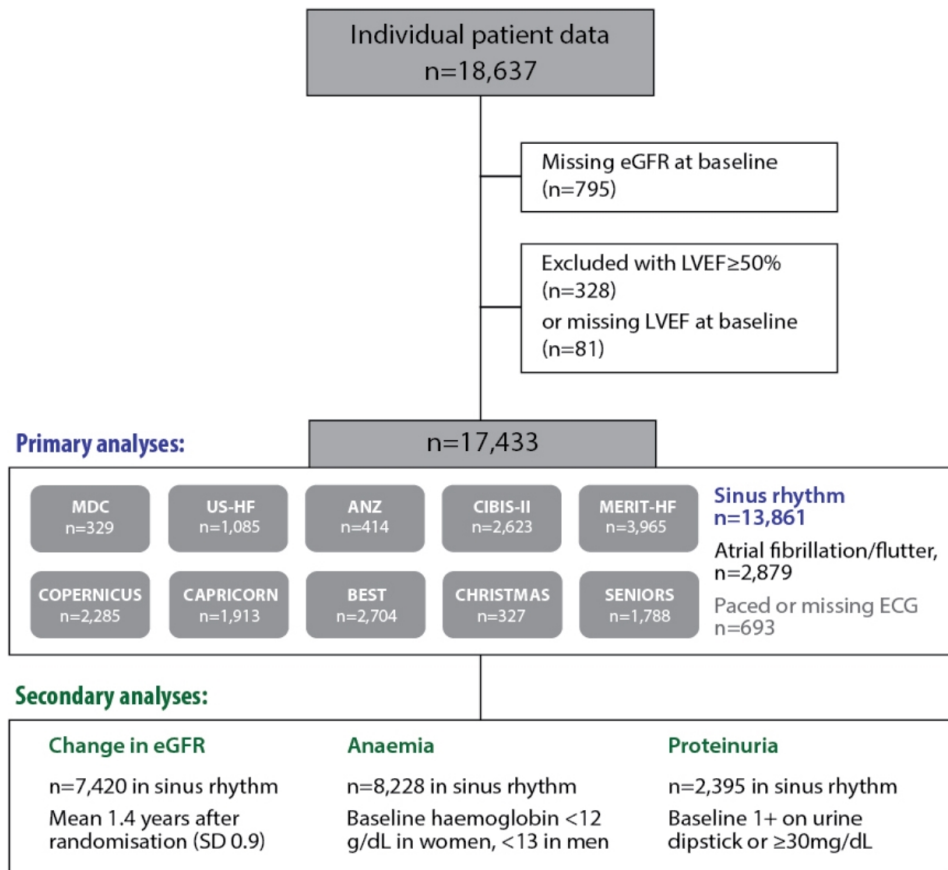
# Individual patient data meta-analysis



- 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.**

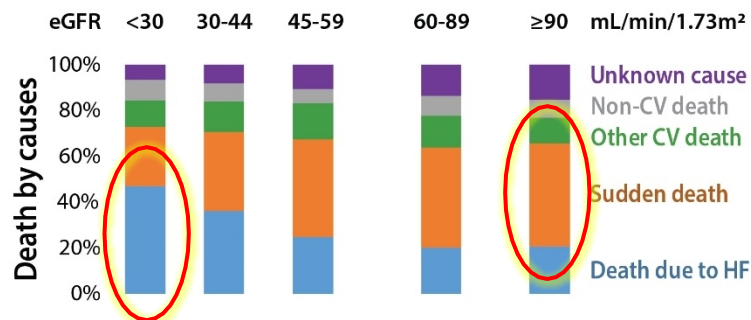
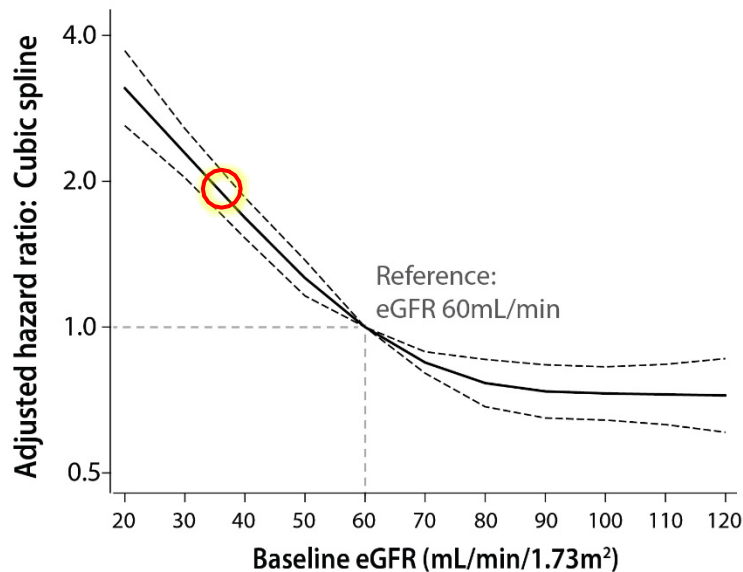
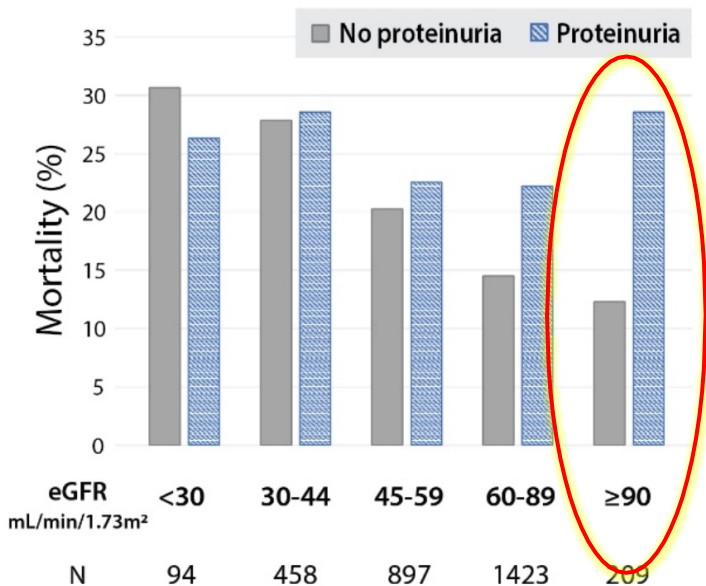
**Bisoprolol • Bucindolol • Carvedilol • Metoprolol XL • Nebivolol**



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

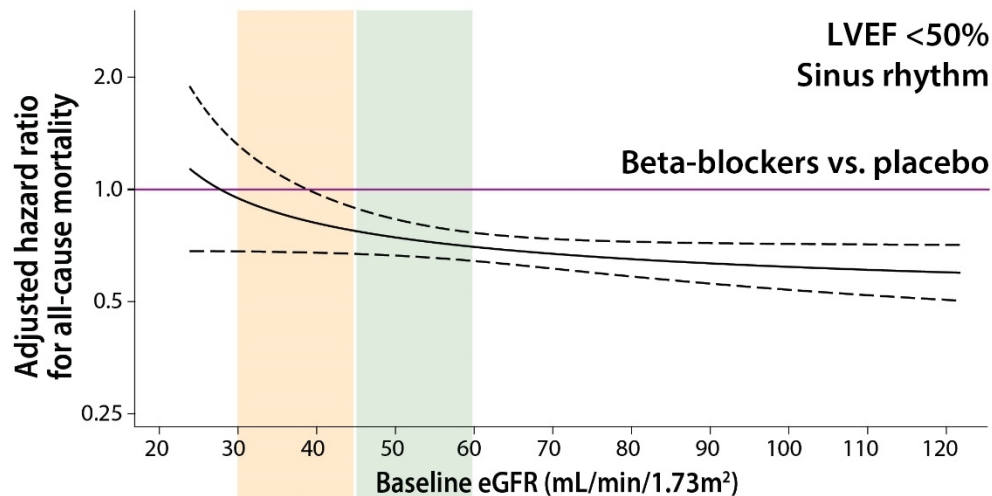
# Mortality associated with renal dysfunction

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

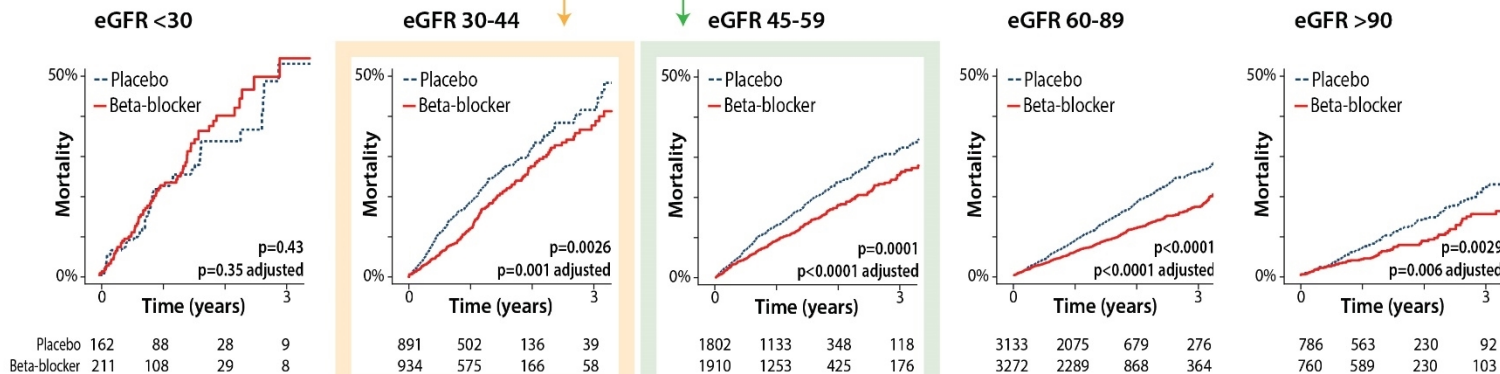


# Efficacy of beta-blockers

## Sinus rhythm



Interaction p=0.021

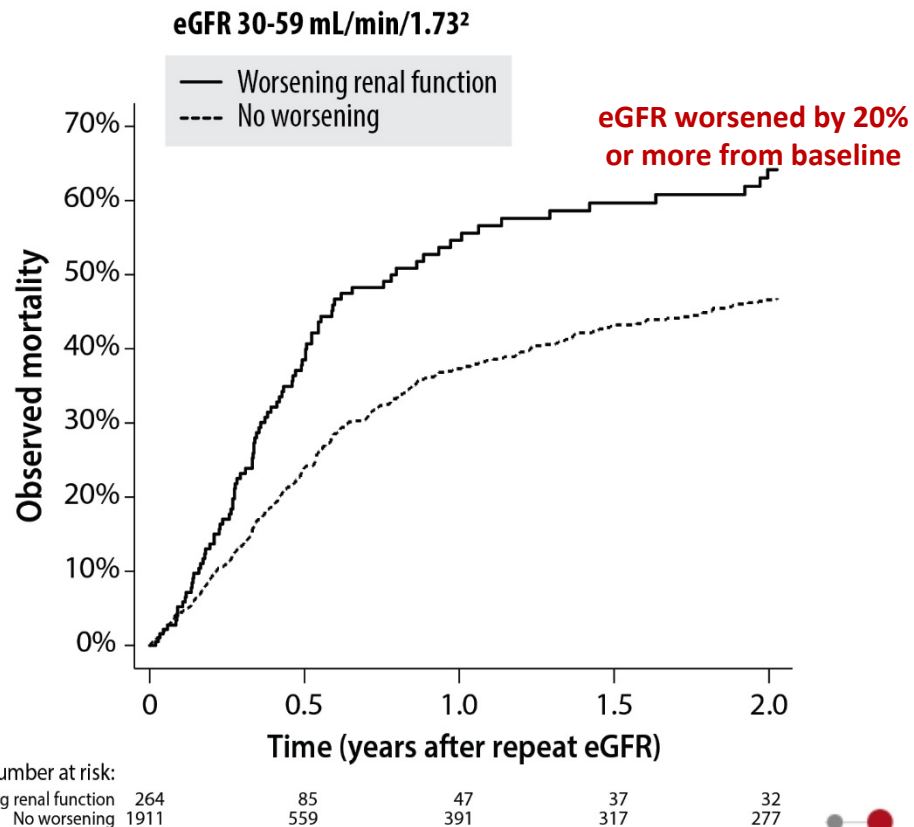
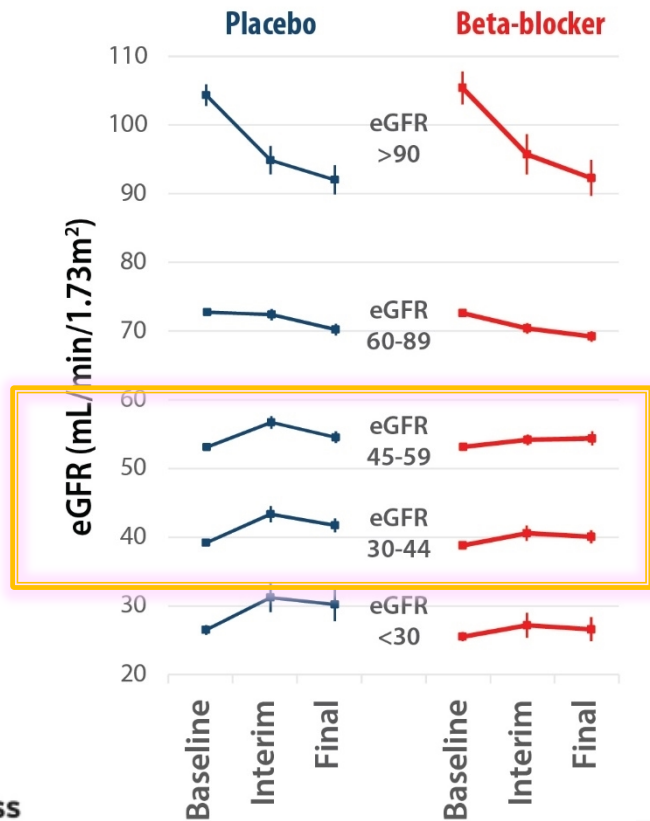


NNT 21.4

NNT 21.5

# Change in renal function

## Sinus rhythm



# Efficacy of beta-blockers

## Atrial fibrillation

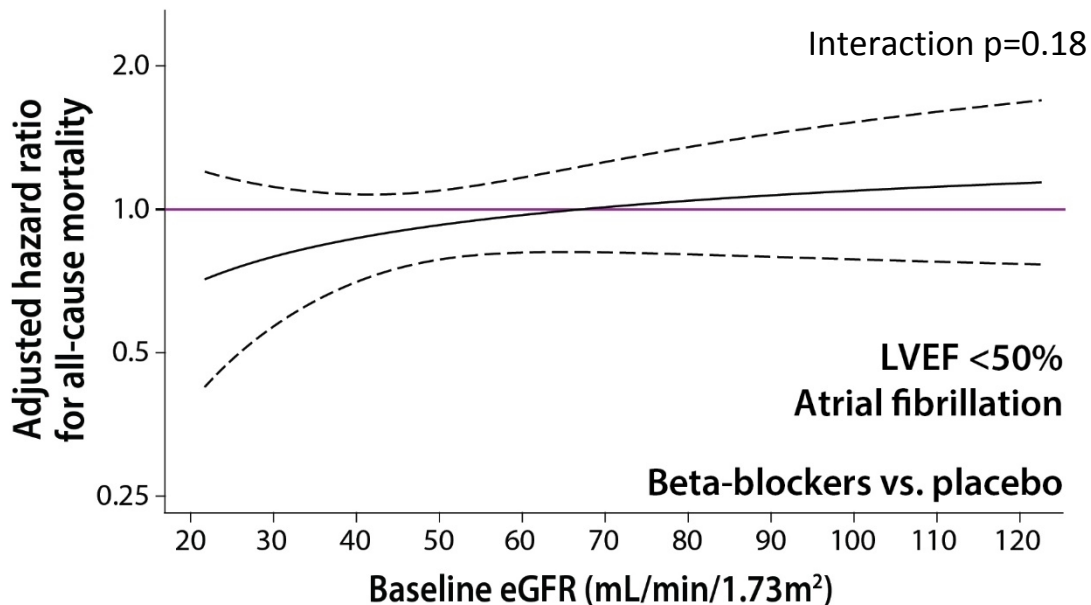
### Lower eGFR in patients with AF:

- 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:



# Adverse events

Discontinuation of study drug	eGFR 30-44 mL/min		eGFR 45-59 mL/min	
	Placebo	Beta-blocker	Placebo	Beta-blocker
Due to any adverse event	20.9%	19.4%	14.9%	14.8%

eGFR >90 mL/min	
Placebo	Beta-blocker
15.1%	11.0%

# Dose

Beta-blocker dose achieved	eGFR 30-44 mL/min		eGFR 45-59 mL/min	
		Beta-blocker		Beta-blocker
>50% of max target dose		76.3%		77.9%

eGFR >90 mL/min	
	Beta-blocker
	83.8%

# 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<sup>2</sup>).
- 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.**