8th Annual Emirates Cardiac Society Conference

ACC Middle East Conference 2017

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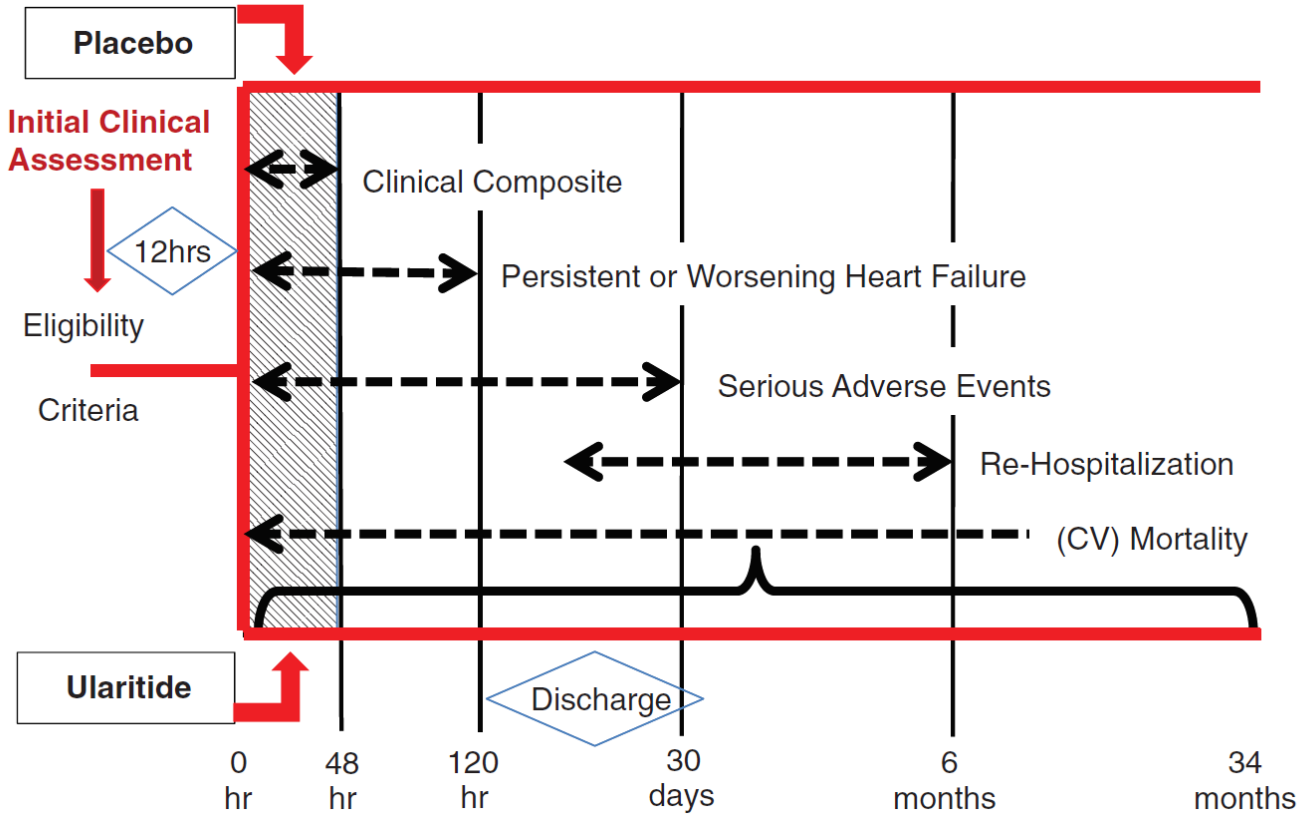
The LBCT of 2017 Heart Failure Trials

Prof.Dr.Mehmet Birhan YILMAZ, FESC, FACC, FHFA

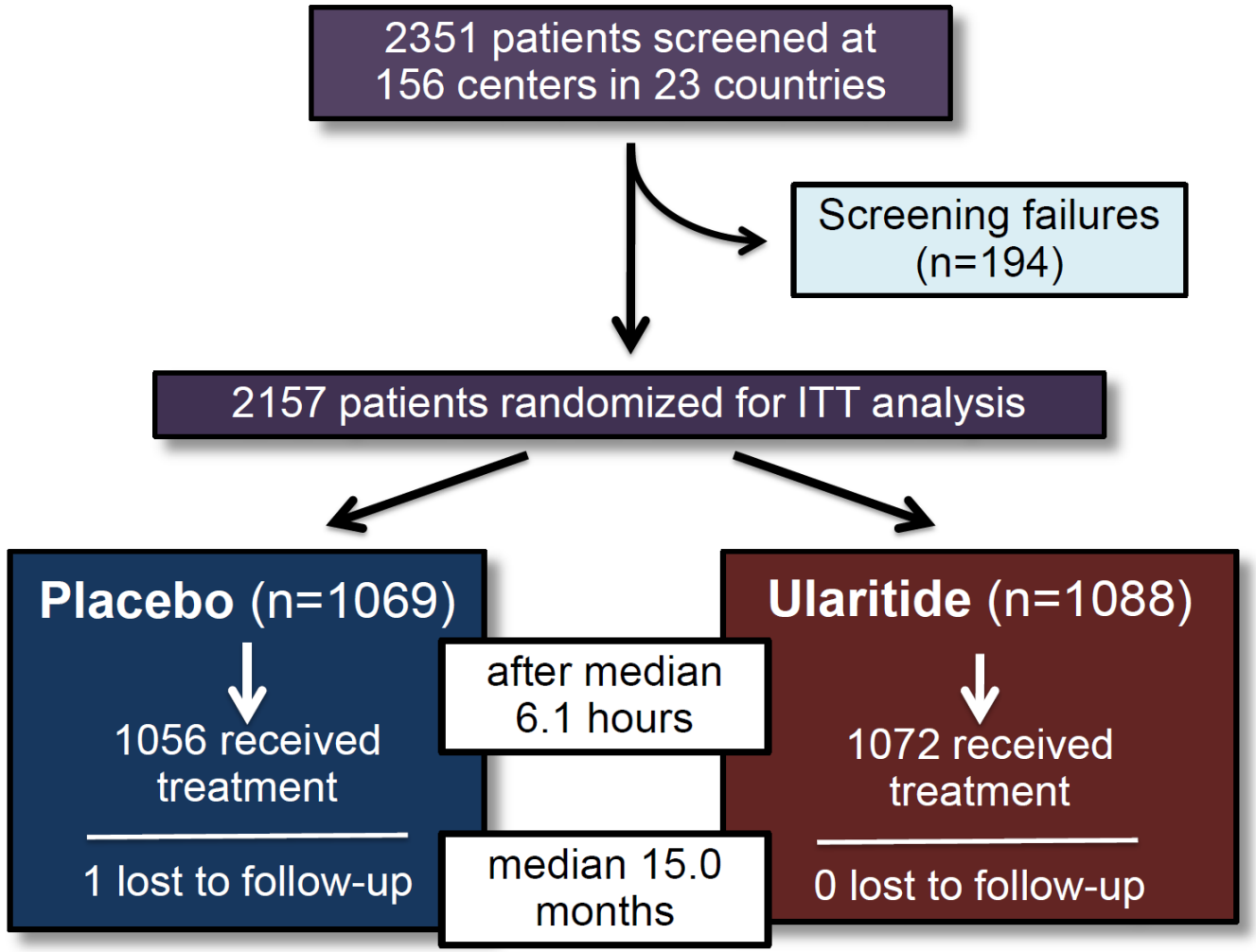
ACC Middle East Conference 2017

- TRUE-AHF
- RELAX-AHF-2
- Beta blockers in patients with HF with and without atrial fibrillation

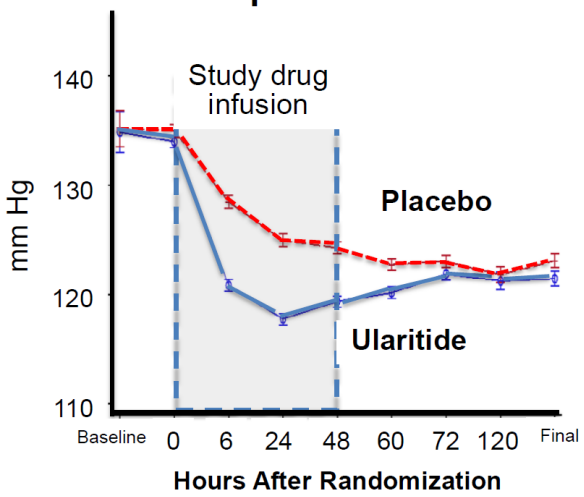
TRUE-AHF



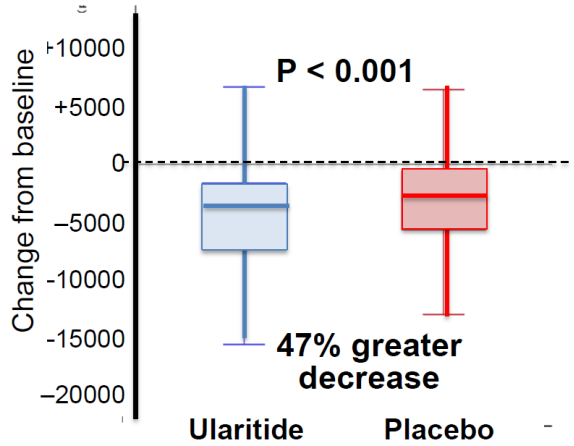
Cardiovascular Mortality ($\alpha = 0.04$)	Hierarchical Clinical Composite at 48 Hours ($\alpha = 0.01$)
No cardiovascular death	Moderate or marked improvement in symptoms at 6, 24 and 48 hours without in-hospital worsening heart failure or death
	Modest improvement or unchanged symptoms
Cardiovascular death (time-to-event)	Worsening of symptoms at 6, 24 or 48 hours
	Persistent or worsening heart failure (in-hospital) requiring IV or mechanical interventions during first 48 hours
	Death during first 48 hours

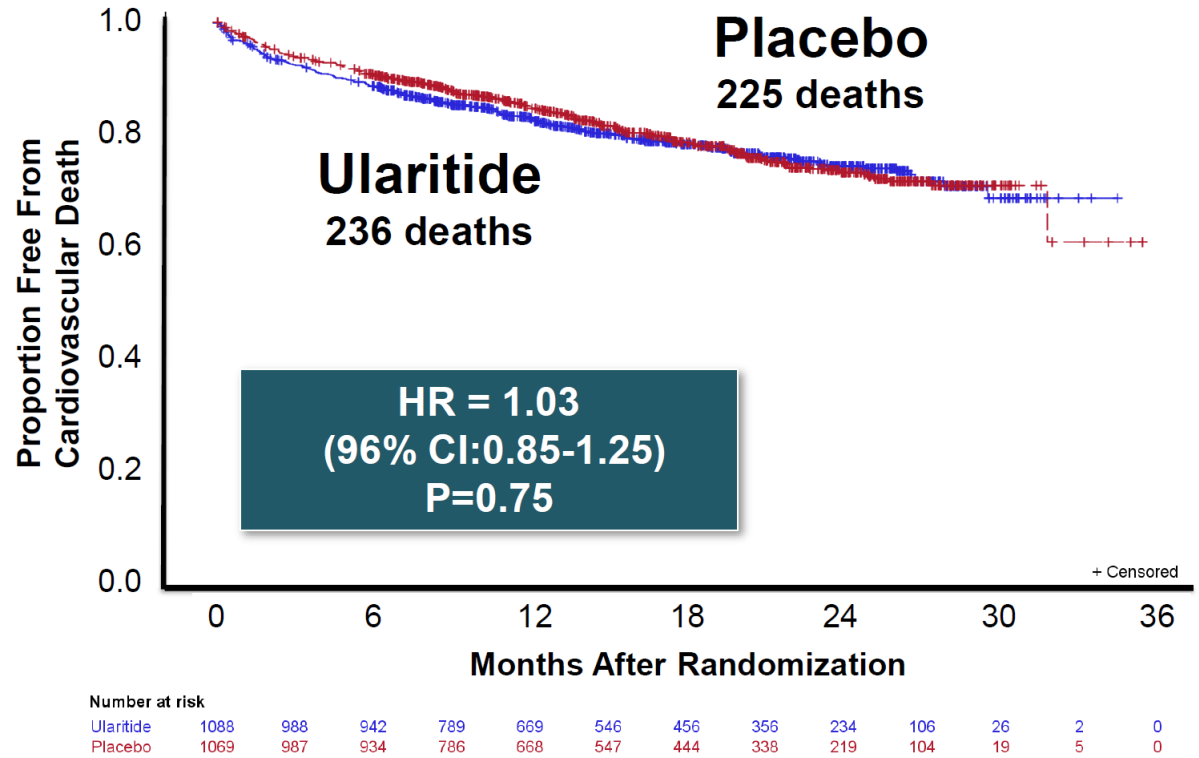

2351 patients screened at 156 centers in 23 countries
Screening failures (n=194)
2157 patients randomized for ITT analysis
Placebo (n=1069)
1056 received treatment
1 lost to follow-up
after median 6.1 hours
median 15.0 months
Ularitide (n=1088)
1072 received treatment
0 lost to follow-up

Systolic blood pressure



N-terminal pro BNP at 48 hours



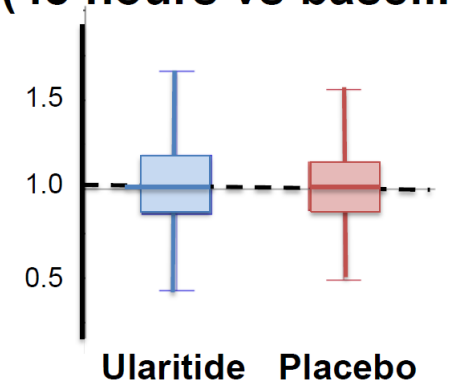


Number at risk

Ularitide	1088	988	942	789	669	546	456	356	234	106	26	2	0
Placebo	1069	987	934	786	668	547	444	338	219	104	19	5	0

	Placebo (n=1069)	Ularitide (n=1088)	P Value
Length of stay (hr) in intensive care during first 120 hours,	69.8 (50.3, 94.3)	68.0 (49.3, 93.6)	0.24
Length of stay (hr) in the hospital during first 30 days,	148.2 (94.0, 216.8)	160.8 (96.0, 228.9)	0.16
Episodes of in-hospital worsening HF during first 120 hr	126	115	0.63
Proportion with in-hospital worsening HF during first 120 hr	94 (8.8%)	90 (8.3%)	0.70
Rehospitalization for HF within 30 days of hospital discharge	74 (7.0%)	75 (7.1%)	1.00
Duration (hours) of IV therapy for HF during index admission,	68.9 (44.6, 115.5)	70.5 (42.7, 115.4)	0.53
All-cause mortality or CV hospitalization at 6 months	398 (37.2%)	443 (40.7%)	0.10

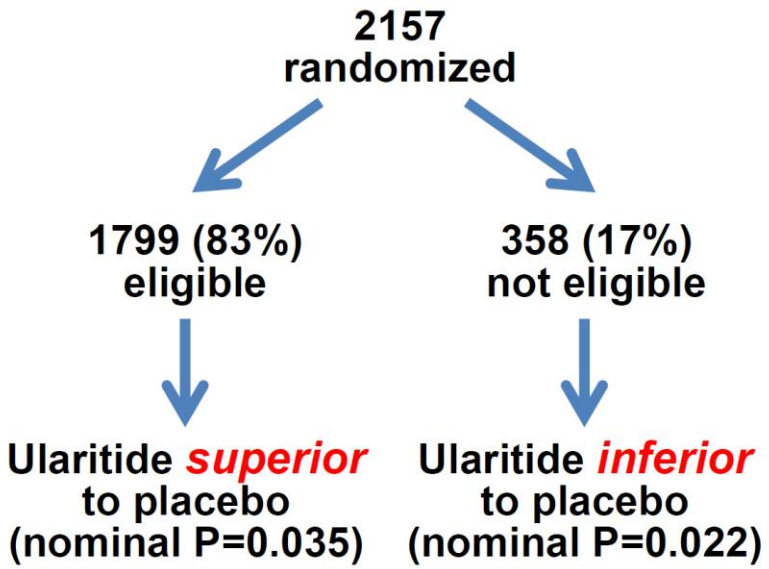
Ratio of high sensitivity cardiac troponin T (48 hours vs baseline)



P=0.70

Additional Analysis from TRUE-AHF

Heart Failure 2017
and 4th World Congress on Acute Heart Failure
29 April - 2 May



Before the database was locked and the blind was broken, the eligibility criteria for all patients were reviewed, and 358 patients (17%) were prospectively identified as not having met one or more of the protocol's prespecified conditions that needed to be fulfilled before the patient was to be randomized

RELAX-AHF-1

Serelaxin in AHF: Dyspnea relief (VAS AUC composite)

Teerlink JR, *et al. Lancet* 2013; 381:29-39.

1,161 patients hospitalized for AHF, randomized to:

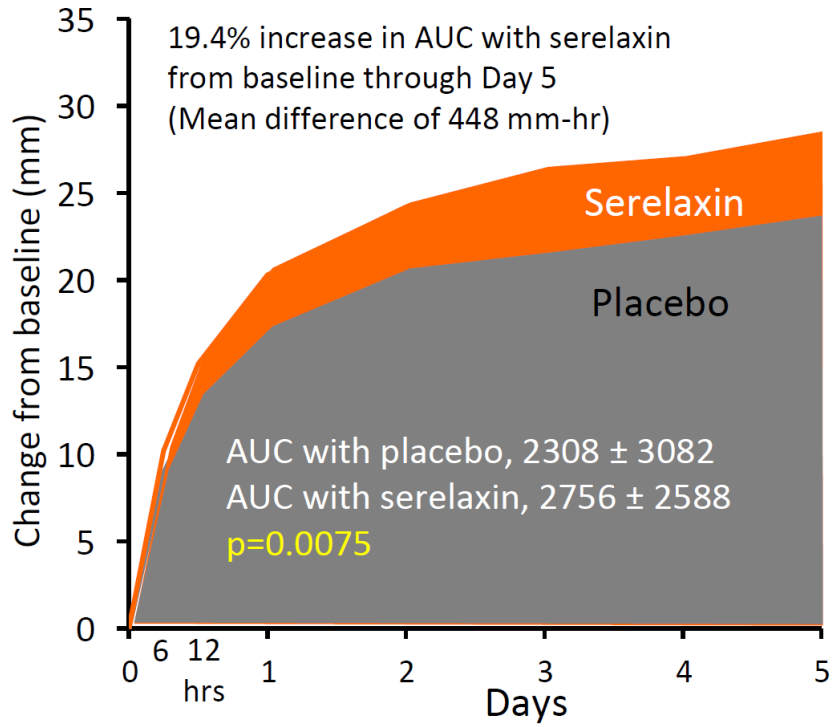
- Placebo (n=580)
- Serelaxin 30 µg/kg/d (n=581)

Entry Criteria:

- Dyspnea, congestion on CXR
- Elevated BNP/NT-proBNP
- SBP >125 mmHg
- eGFR 30–75 mL/min 1.73m^2
- ≥40 mg i.v. furosemide

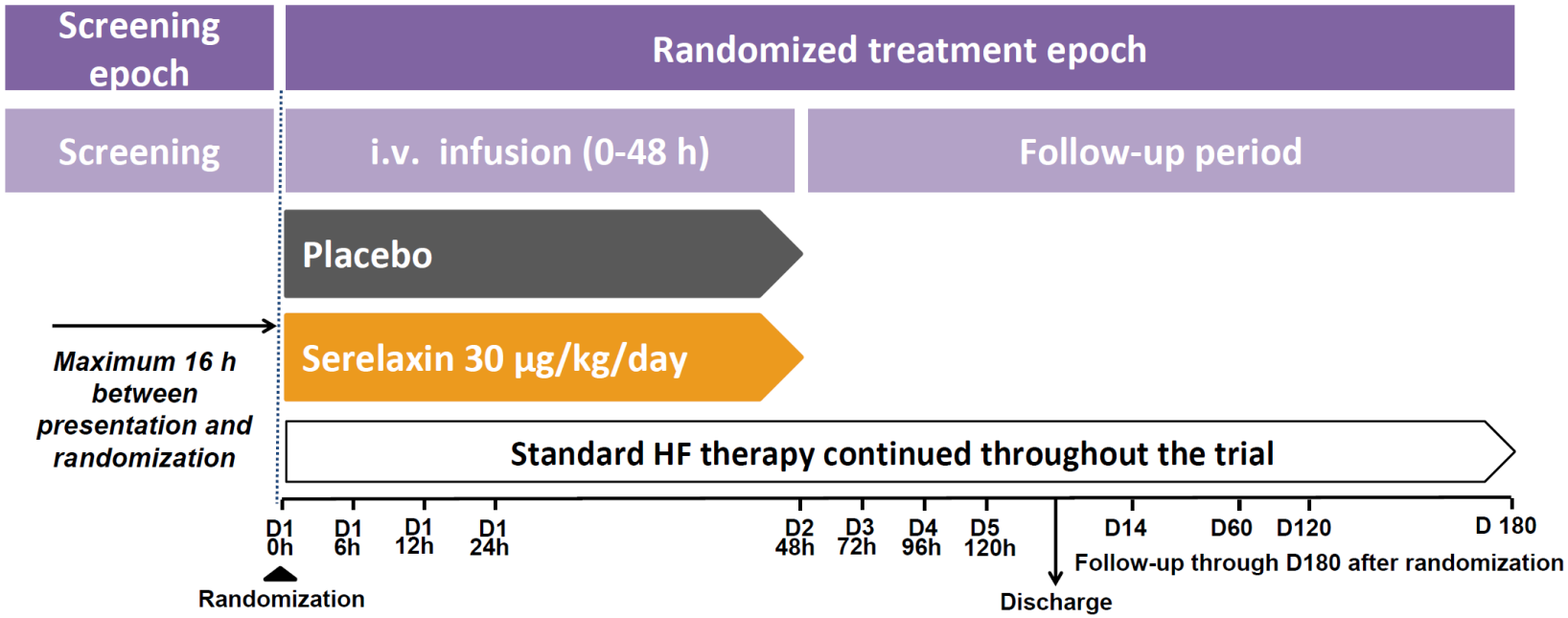
Excluded:

- Acute Coronary Syndrome
- High dose nitrates



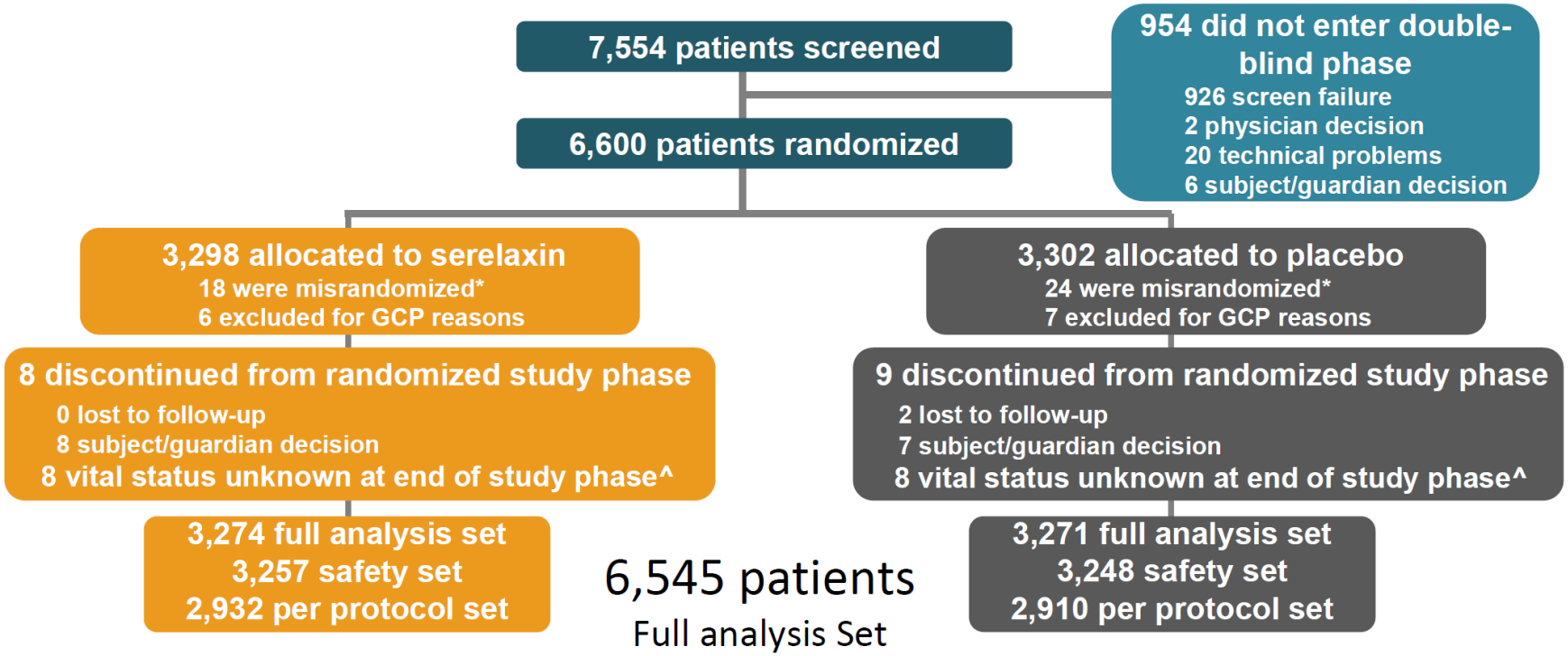
Study design

Teerlink JR, *et al. Eur J Heart Fail* 2017;*doi:*10.1002/ejhf.830.

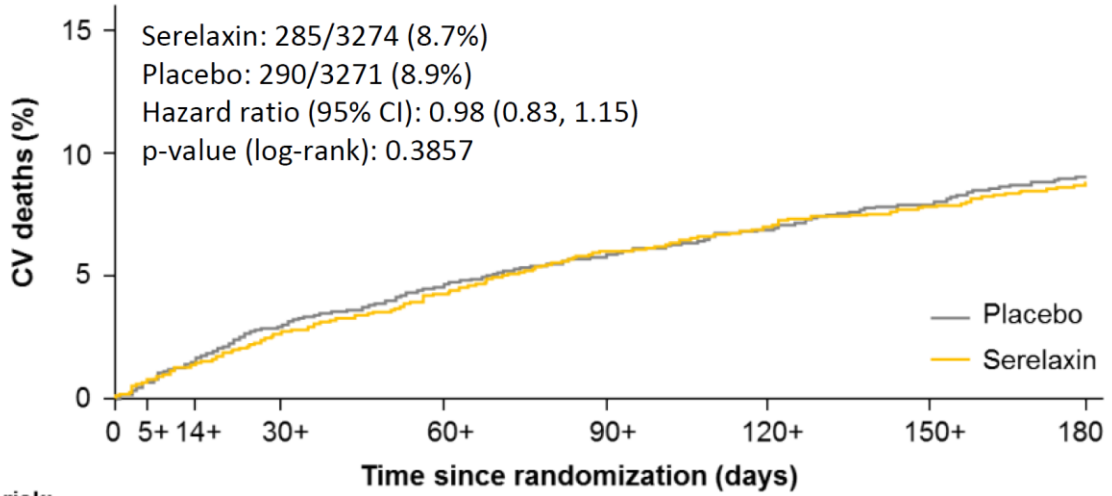


RELAX-AHF-2
Outcomes of seRELAXin in AHF

Patient disposition



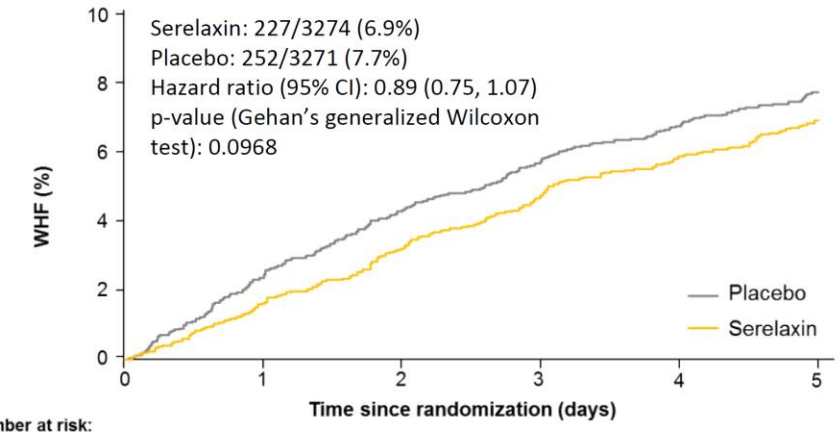
Primary endpoint: CV mortality through Day 180



Number at risk:

Placebo	3271	3244	3210	3149	3080	3018	2962	2912	2545
Serelaxin	3274	3247	3218	3165	3100	3032	2988	2949	2548

Primary endpoint: WHF through Day 5



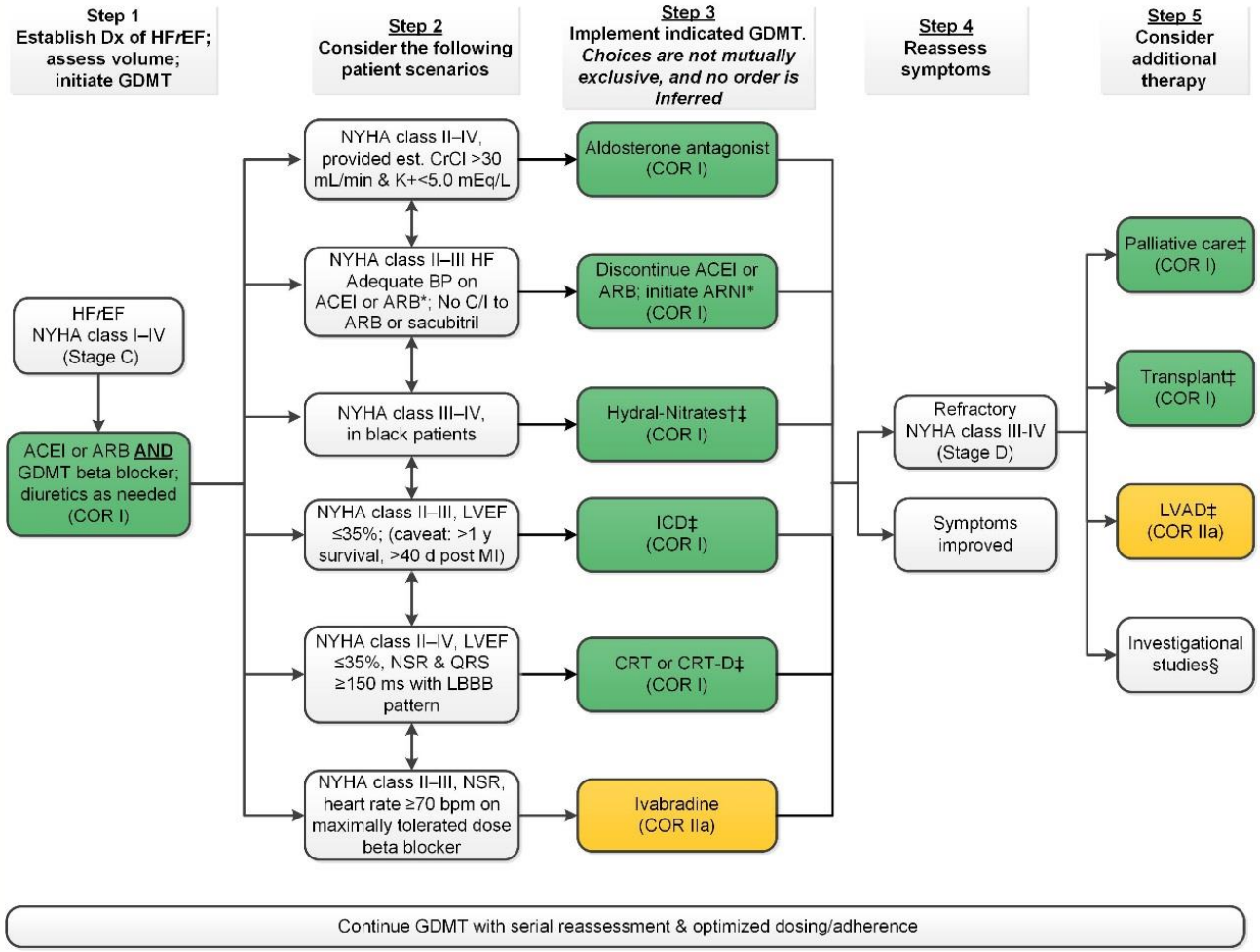
Number at risk:

Placebo	3271	3190	3128	3081	3047	3016
Serelaxin	3274	3219	3166	3117	3078	3043

- WHF includes in-hospital WHF, adjudicated rehospitalization due to HF and death through Day 5

Conclusions from Both Vasodilator Trials in AHF

- Short term infusion of an vasodilator agent (either serelaxin or ularitide) does not seem to translate into improved long term CV outcomes.
- Short term infusion of vasodilator agents might improve some soft outcomes (inhospital worsening etc) and they were usually safe (but much more expensive than nitrates)
- AHF trials are hard to conduct and patient selection criteria is utmost importance. Problems in patient selection (suitcase patients, low BP etc) might dilute potential positive outcome.
- One size does not fit all, particularly if AHF is concerned.



Recommendations	Class [a]	Level [b]	Ref [c]
An ACE-I[d] is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A	2, 163–165
A beta-blocker is recommended, in addition an ACE-I[d], for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A	167–173
An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I[d] and a beta-blocker, to reduce the risk of HF hospitalization and death.	I	A	174, 175

Beta blockers are strongly recommended in HFrEF

Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis

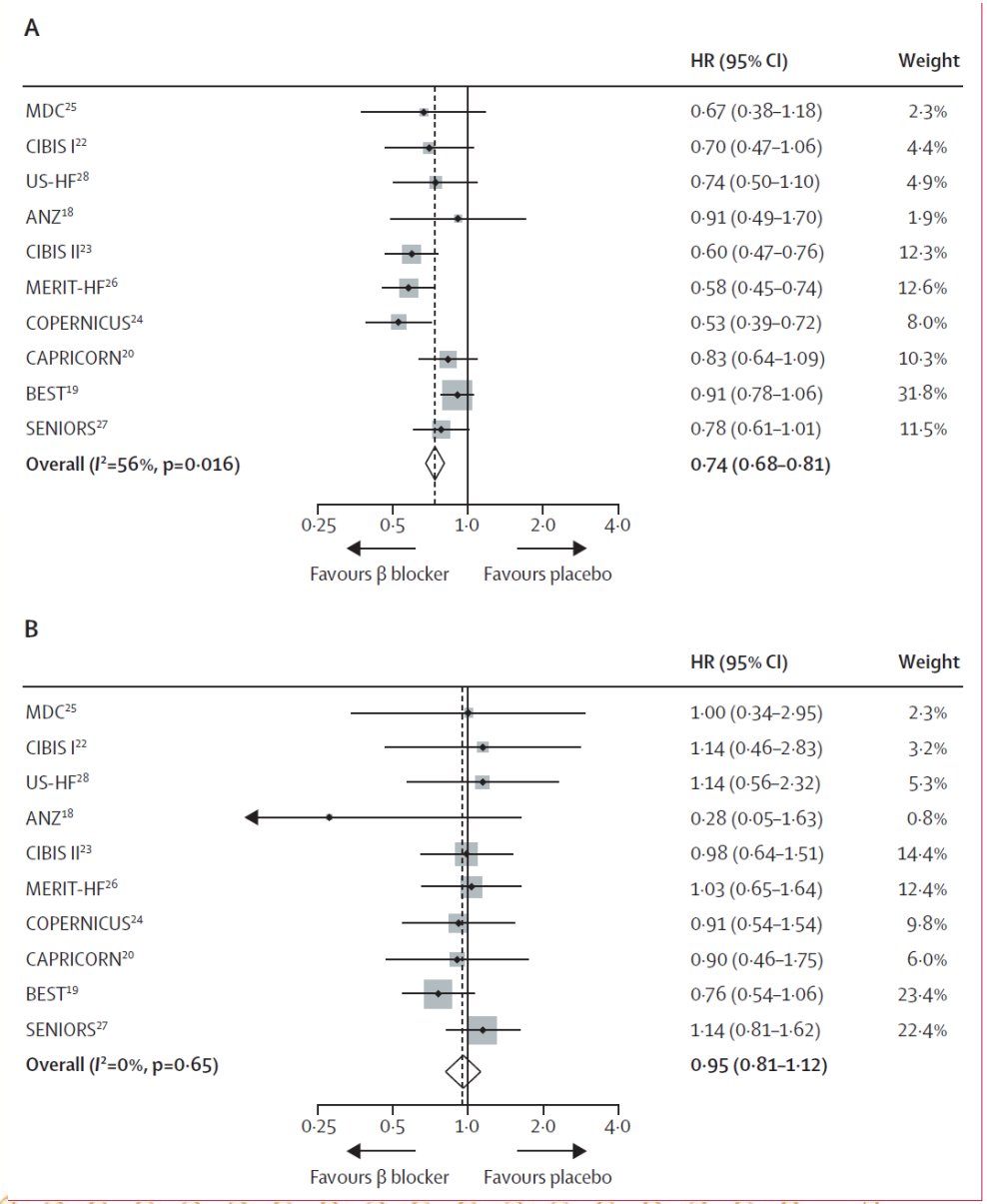
Dipak Kotecha, Jane Holmes, Henry Krum, Douglas G Altman, Luis Manzano, John G F Cleland, Gregory Y H Lip, Andrew J S Coats, Bert Andersson, Paulus Kirchhof, Thomas G von Lueder, Hans Wedel, Giuseppe Rosano, Marcelo C Shibata, Alan Rigby, Marcus D Flather, on behalf of the Beta-Blockers in Heart Failure Collaborative Group

Summary

Background Atrial fibrillation and heart failure often coexist, causing substantial cardiovascular morbidity and mortality. β blockers are indicated in patients with symptomatic heart failure with reduced ejection fraction; however, the efficacy of these drugs in patients with concomitant atrial fibrillation is uncertain. We therefore meta-analysed individual-patient data to assess the efficacy of β blockers in patients with heart failure and sinus rhythm compared with atrial fibrillation.

Lancet 2014; 384: 2235–43
Published Online
September 2, 2014
http://dx.doi.org/10.1016/S0140-6736(14)61373-8

- Individual-patient data from ten randomised controlled trials of the comparison of β blockers versus placebo in heart failure were extracted. The presence of sinus rhythm or atrial fibrillation was ascertained from the baseline ECG. The primary outcome was all-cause mortality. Analysis was by intention to treat. Outcome data were meta-analysed with an adjusted Cox proportional hazards regression.
- 18 254 patients were assessed, and of these 13 946 (76%) had sinus rhythm and 3066 (17%) had atrial fibrillation at baseline. Mortality rates over a mean follow-up of 1·5 years (SD 1·1) were 16% (2237 of 13 945) in patients with sinus rhythm and 21% (633 of 3064) in patients with atrial fibrillation. β-blocker therapy led to a significant reduction in all-cause mortality in patients with sinus rhythm (hazard ratio 0·73, 0·67–0·80; p<0·001), but not in patients with atrial fibrillation (0·97, 0·83–1·14; p=0·73), with a significant p value for interaction of baseline rhythm (p=0·002). The lack of effi cacy for the primary outcome was noted in all subgroups of atrial fibrillation, including age, sex, left ventricular ejection fraction, New York Heart Association class, heart rate, and baseline medical therapy.
- **β blockers should not be used preferentially over other rate-control medications and not regarded as standard therapy to improve prognosis in patients with concomitant heart failure and atrial fi brillation.**



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CLINICAL RESEARCH

Beta-Blockers and Outcome in Heart Failure and Atrial Fibrillation

A Meta-Analysis

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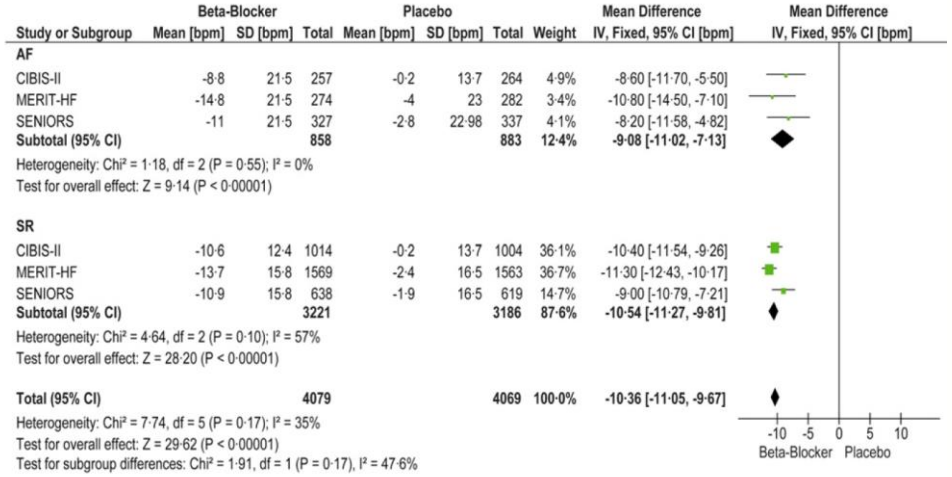
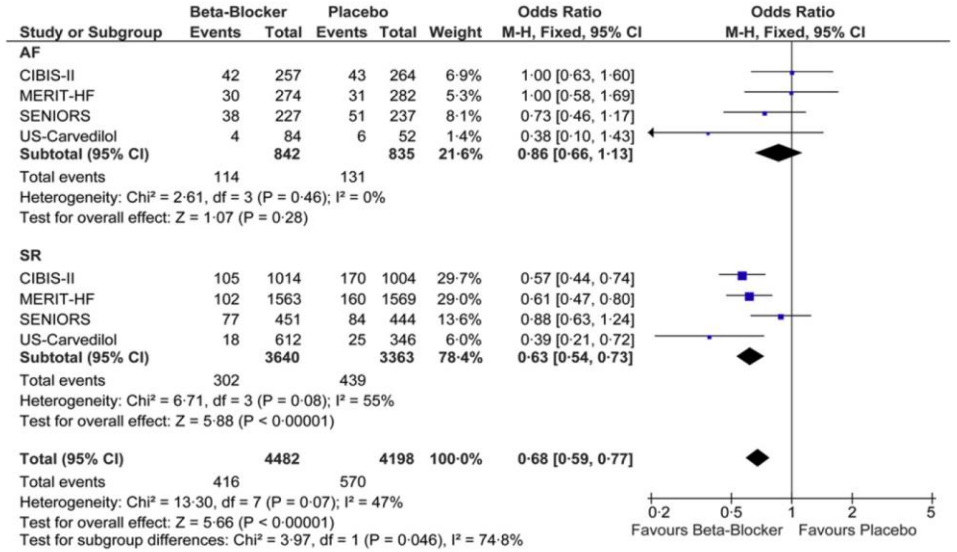
Isabelle C. Van Gelder, MD, PhD,* John J. V. McMurray, MD,† Dirk J. Van Veldhuisen, MD, PhD*

Groningen, the Netherlands; and Glasgow, United Kingdom

First Author Study (Ref. #)	BB	Year	Follow-Up	n (%)	Types of Patients	Endpoints	Major Exclusion Criteria
Joglar et al. U.S.-Carvedilol (13)	Carvedilol	2001	Maximum 400 days	AF: 136 (12%); SR: 958	HF; LVEF ≤35%	All-cause mortality	Unstable HF; heart rate <68 beats/min; Class I or III antiarrhythmic drugs
Lechat et al. CIBIS-II (14)	Bisoprolol	2001	Maximum 800 days	AF: 521 (21%) SR: 2,018	HF; LVEF ≤35%; NYHA III–IV	All-cause mortality; HF hospitalizations	Unstable HF; heart rate <60 beats/min; antiarrhythmic drugs other than amiodarone
Van Veldhuisen et al. MERIT-HF (15)	Metoprolol	2006	Mean F/U 1 yr	AF: 556 (14%); SR: 3,132	HF; LVEF <40%; NYHA II–IV	All-cause mortality; HF; hospitalizations	Unstable HF; heart rate <68 beats/min; CCB or amiodarone
Mulder et al. SENIORS (16)*	Nebivolol	2011	Mean F/U 21 months	AF: 464 (22%); SR: 895	≥70 yrs of age; HF admission <1 yr or LVEF ≤35%	All-cause mortality; HF; hospitalizations	Unstable HF; beta-blocker use

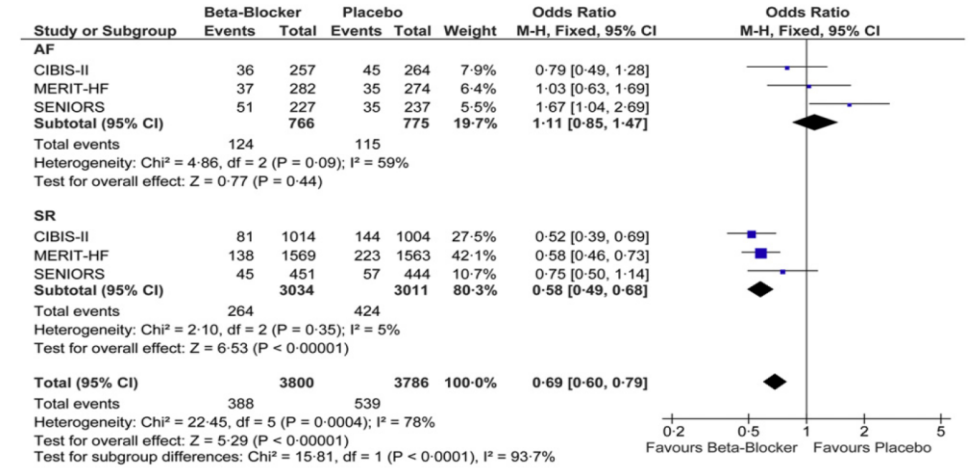


Heart Rate and Heart Rate Reduction



Combined All-Cause Mortality Risk

- **Effect of beta-blockers on outcome in HF patients with reduced systolic LVEF who have AF is less than in those who have sinus rhythm.**



Combined HF Hospitalization Risk

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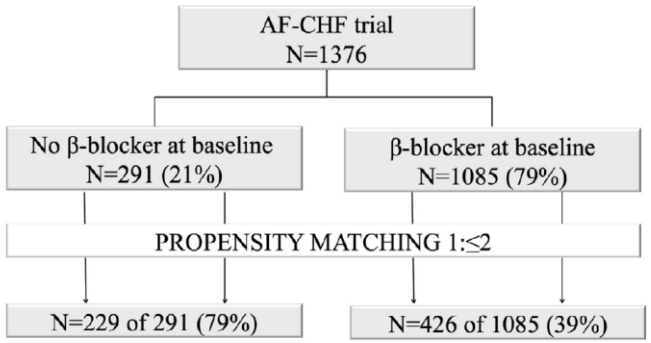
Decreased Mortality With Beta-Blockers in Patients With Heart Failure and Coexisting Atrial Fibrillation

An AF-CHF Substudy

Julia Cadrin-Tourigny, MD,[a] Azadeh Shohoudi, PhD,[b] Denis Roy, MD,[a] Mario Talajic, MD,[a] Rafik Tadros, MD, PhD,[a] Blandine Mondésert, MD,[a] Katia Dyrda, MD,[a] Léna Rivard, MD,[a] Jason G. Andrade, MD,[a] Laurent Macle, MD,[a] Peter G. Guerra, MD,[a] Bernard Thibault, MD,[a] Marc Dubuc, MD,[a] Paul Khairy, MD, PhD[a,b]



	Events			
	No Beta-Blockers (n = 229)	Beta-Blockers (n = 426)	HR (95% CI)	p Value
Primary intention-to-treat analyses				
All-cause mortality	95 (41.5)	136 (31.2)	0.721 (0.549-0.945)	0.0180
Cardiovascular mortality	72 (31.4)	109 (25.6)	0.763 (0.562-1.037)	0.0838
All-cause hospitalization	149 (65.4)	271 (63.6)	0.886 (0.715-1.100)	0.2732
Cardiovascular hospitalization	119 (52.2)	219 (51.5)	0.914 (0.721-1.158)	0.4557
Hospitalization for worsening HF	62 (27.1)	105 (24.7)	0.894 (0.659-1.214)	0.4744
Sensitivity analyses (modeling beta-blockers as a time-dependent covariate)				
All-cause mortality	–	–	0.668 (0.511-0.874)	0.0032
Cardiovascular mortality	–	–	0.748 (0.539-1.039)	0.0832
All-cause hospitalization	–	–	0.814 (0.653-1.014)	0.0658
Cardiovascular hospitalization	–	–	0.929 (0.731-1.182)	0.5505
Hospitalization for worsening HF	–	–	0.876 (0.644-1.191)	0.3969

Values are n (%).
CI = confidence interval; HF = heart failure; HR = hazard ratio (estimated).

- The AF-CHF trial randomized 1,376 patients with AF and HFrEF from 123 centers to rhythm control treatment (n ¼ 694) versus rate (n ¼ 682) control treatment.
- In propensity-matched analyses, beta-blockers were associated with significantly lower mortality but not hospitalizations in patients with HFrEF and AF, irrespective of the pattern or burden of AF.

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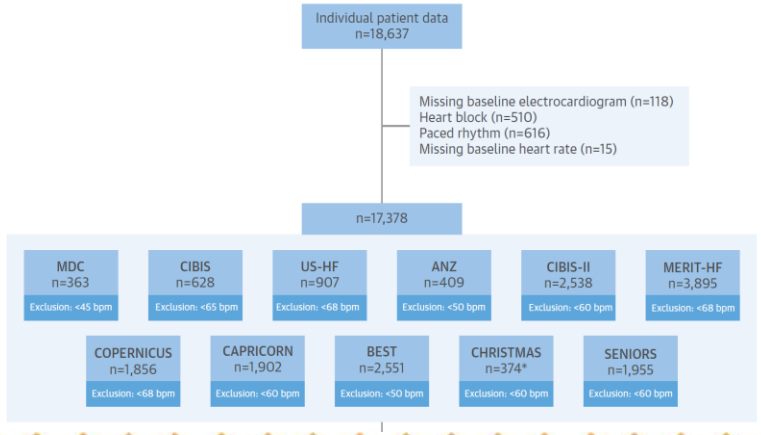
ORIGINAL INVESTIGATIONS

Heart Rate and Rhythm and the Benefit of Beta-Blockers in Patients With Heart Failure

Dipak Kotecha, MBBS, PHD,[a,b] Marcus D. Flather, MBBS,[c] Douglas G. Altman, DSC,[d] Jane Holmes, PHD,[d] Giuseppe Rosano, MD, PHD,[e,f] John Wikstrand, PHD,[g] Milton Packer, MD,[h] Andrew J.S. Coats, DSC,[i,j] Luis Manzano, MD,[k] Michael Böhm, MD,[l] Dirk J. van Veldhuisen, MD,[m] Bert Andersson, MD, PHD,[n] Hans Wedel, PHD,[o] Thomas G. von Lueder, PHD,[b,p] Alan S. Rigby, MSC,[q] Åke Hjalmarson, MD, PHD,[n] John Kjekshus, MD, PHD,[r] John G.F. Cleland, MD,[s] on behalf of the Beta-Blockers in Heart Failure Collaborative Group



BACKGROUND The relationship between mortality and heart rate remains unclear for patients with heart failure with reduced ejection fraction in either sinus rhythm or atrial fibrillation (AF).

OBJECTIVES This analysis explored the prognostic importance of heart rate in patients with heart failure with reduced ejection fraction in randomized controlled trials comparing beta-blockers and placebo.

METHODS The Beta-Blockers in Heart Failure Collaborative Group performed a meta-analysis of harmonized individual patient data from 11 double-blind randomized controlled trials. The primary outcome was all-cause mortality, analyzed with Cox proportional hazard ratios (HR) modeling heart rate measured at baseline and approximately 6 months post-randomization.

RESULTS A higher heart rate at baseline was associated with greater all-cause mortality for patients in sinus rhythm ($n = 14,166$; adjusted HR: 1.11 per 10 beats/min; 95% confidence interval [CI]: 1.07 to 1.15; $p < 0.0001$) but not in AF ($n = 3,034$; HR: 1.03 per 10 beats/min; 95% CI: 0.97 to 1.08; $p = 0.38$). Beta-blockers reduced ventricular rate by 12 beats/min in both sinus rhythm and AF. Mortality was lower for patients in sinus rhythm randomized to beta-blockers (HR: 0.73 vs. placebo; 95% CI: 0.67 to 0.79; $p < 0.001$), regardless of baseline heart rate (interaction $p = 0.35$). Beta-blockers had no effect on mortality in patients with AF (HR: 0.96, 95% CI: 0.81 to 1.12; $p = 0.58$) at any heart rate (interaction $p = 0.48$). A lower achieved resting heart rate, irrespective of treatment, was associated with better prognosis only for patients in sinus rhythm (HR: 1.16 per 10 beats/min increase, 95% CI: 1.11 to 1.22; $p < 0.0001$).

CONCLUSIONS Regardless of pre-treatment heart rate, beta-blockers reduce mortality in patients with heart failure with reduced ejection fraction in sinus rhythm. Achieving a lower heart rate is associated with better prognosis, but only for those in sinus rhythm. (J Am Coll Cardiol 2017;69:2885-96) © 2017 by the American College of Cardiology Foundation.

Conclusion for BB in HFrEF with/without AFib

- Beta blockers are strongly recommended in HF guidelines for the management of Stage C-D HFrEF irrespective of rhythm
- However, patients HFrEF with atrial fibrillation seems not to get similar benefit as it was observed in those with sinus rhythm in retrospective analyses of large trials (it was relatively known before)

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