

Association between Beta-blocker Use and Mortality/Morbidity in Elderly Patients with Heart Failure with Reduced Ejection Fraction:

A prospective propensity score-matched cohort study

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Declaration of interest

- Research contracts (MSD, Boehringer Ingelheim, AstraZeneca, Vifor, Novartis)
- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Roche, AstraZeneca, Vifor, Societá Probiotici Italiana, Genesis, Servier)



Octogenarians constitute an important HF subpopulation: *HF incidence increases with aging*

European Heart Journal (2004) 25, 1614–1619



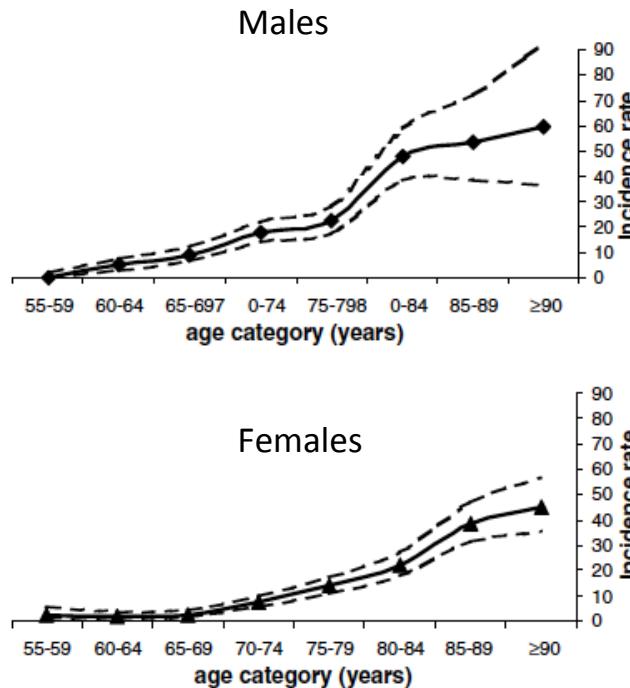
Clinical research

Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure

The Rotterdam Study

Gysèle S. Bleumink^{a,b}, Anneke M. Knetsch^{a,c}, Miriam C.J.M. Sturkenboom^{a,d},
Sabine M.J.M. Straus^a, Albert Hofman^a, Jaap W. Deckers^{a,c},
Jacqueline C.M. Witteman^a, Bruno H.Ch. Stricker^{a,b,*}

Age	HF incidence (*1000 pt-yrs)
80–84	30.1 (25.8–35.0)
85–89	41.9 (35.3–49.4)
≥90	47.4 (38.6–58.2)



Octogenarians constitute an important HF subpopulation



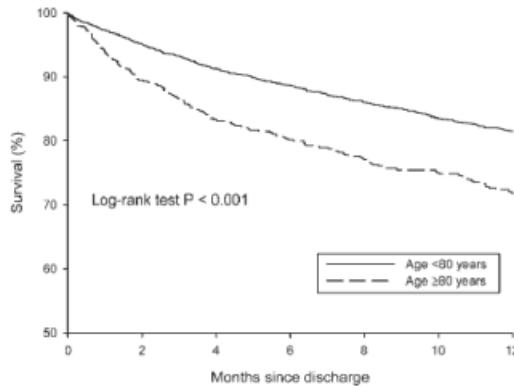
European Heart Journal (2009) 30, 478–486
doi:10.1093/eurheartj/ehn519

CLINICAL RESEARCH
Heart failure/cardiomyopathy

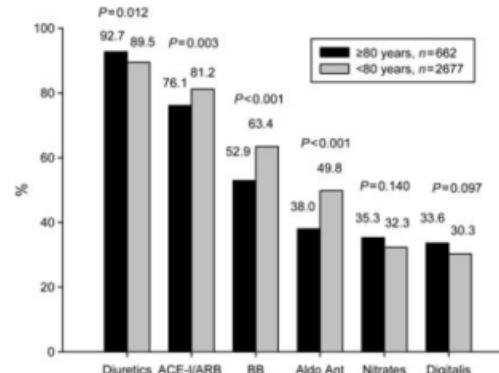
Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II

Michel Komajda^{1*}, Olivier Hanon², Matthias Hochadel³, Jose Luis Lopez-Sendon⁴, Ferenc Follath⁵, Piotr Ponikowski⁶, Veli-Pekka Harjola⁷, Helmut Drexler⁸, Kenneth Dickstein⁹, Luigi Tavazzi^{8,10}, and Markku Nieminen⁷

- 21% aged ≥ 80
- 61% of these with LVEF $\leq 45\%$



Higher mortality in age ≥ 80



Less treatments in age ≥ 80

Together with

ESC Congress
Paris 2019

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of Cardiology

Octogenarians neglected in HFrEF trials

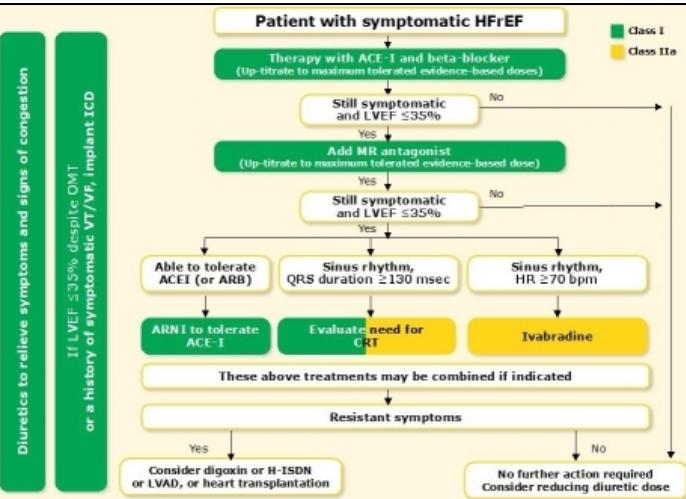


European Heart Journal (2016) 37, 2129–2200
doi:10.1093/euroheartj/ehw128

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)



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



European Journal of Heart Failure (2013) 15, 717–723
doi:10.1093/eurjhrt/hft028

REVIEW

Heart failure in elderly patients: distinctive features and unresolved issues

Valentina Lazzarini^{1,2*}, Robert J. Mentz^{1,3}, Mona Fiuzat^{1,3}, Marco Metra², and Christopher M. O'Connor^{1,3}

Trial	Year	Study treatment ^a	No. of patients	Age (years) ^b	Key age-related inclusion criteria
SOLVD	1991	Enalapril	2569	61	Age <80; EF ≤ 35%
DIG (main trial)	1997	Digoxin	6800	63 ± 11	EF ≤ 45%
RALES	1999	Spironolactone	1663	65 ± 12	EF ≤ 35%
CIBIS II	1999	Bisoprolol	2647	61 ± 11	Age 18–80; EF ≤ 35%
ATLAS	1999	Low-dose vs. high-dose lisinopril	3793	64 ± 10	EF ≤ 30%
COPERNICUS	2001	Carvedilol	2289	63 ± 12	EF ≤ 25%
BEST	2001	Bucindolol	2706	60 ± 12	EF ≤ 35%
EPHESUS	2001	Eplerenone	6632	64 ± 11	EF ≤ 40%
Val-HeFT	2002	Valsartan	5010	62 ± 11 ACB, 67 ± 10 no ACB	EF ≤ 40%
MADIT II	2002	ICD	1232	64 ± 10	EF ≤ 30%
COMET	2003	Carvedilol vs. metoprolol	3029	62 (11–4) ^c	EF ≤ 35%
CARE HF	2005	CRT vs. medical therapy alone	813	66 (59–72) no CRT, 67 (60–73) CRT ^c	EF ≤ 35%
MADIT-CRT	2009	CRT-D vs. ICD	1820	65 ± 11	EF ≤ 30%
SHIFT	2010	Ivabradine	6558	60 ± 11	EF ≤ 35%
EMPHASIS	2011	Eplerenone	2737	69 ± 8	EF ≤ 35%

BUT

Mean age: 61-69+8-12

Limited evidence on Beta-blockers in octogenarians from trials

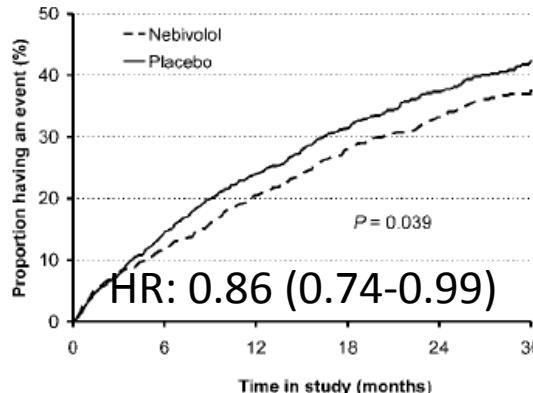
European Heart Journal (1995) 26, 215-225
doi:10.1093/euheartj/16.115



Clinical research

FASTTRACK Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS)

All-cause death or CV hospitalization

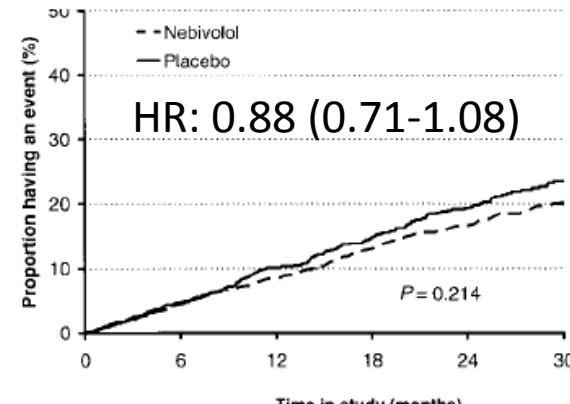


Number at risk

Nebivolol	1067	933	757	517	318	185
Placebo	1061	900	721	487	303	182

- Inclusion criterion: HF and age ≥ 70 years
- Mean age = 76.1 ± 4.6 years
- 36% had EF > 35%

All-cause death



Number at risk

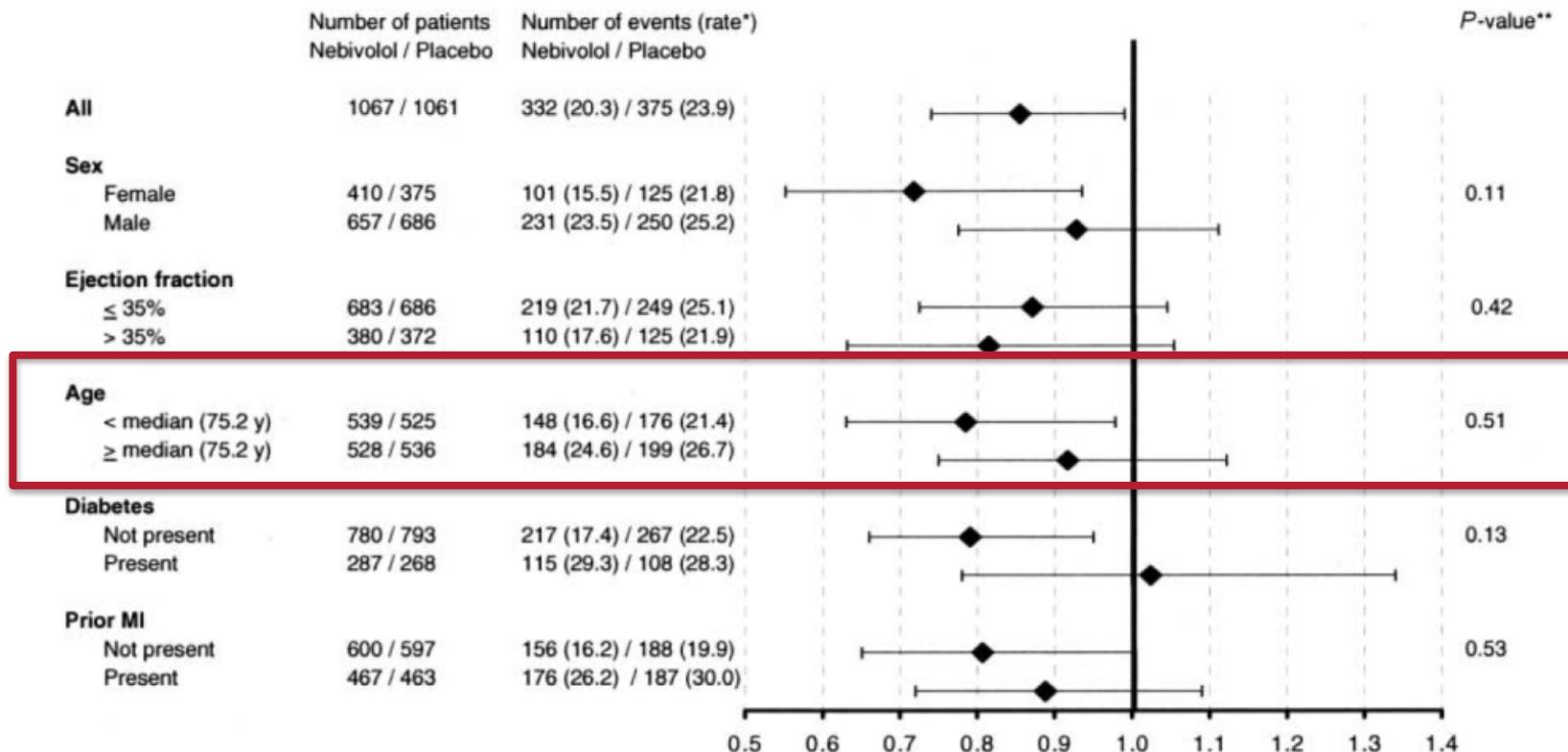
Nebivolol	1067	1010	871	621	407	238
Placebo	1061	1002	855	616	396	241

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Limited evidence on Beta-blockers in octogenarians from trials



SENIORS trial – Primary Outcome

Aim

To assess the use of **beta-blockers** in patients **aged ≥ 80 years**, and test their association with **all-cause mortality** and **CV mortality/HF hospitalization** in a **large, contemporary, real-world HFrEF cohort**



Methods

Patients: SwedeHF [enrol. patients with clinician-judge HF (any EF)] linked with the National Patient Registry, Cause of Death Registry and Statistics Sweden.

Inclusion criteria: HFrEF (EF<40%), age \geq 80 years, HF duration \geq 3 months (similar to the inclusion for BB HF trials), no missing for BB

Outcomes: Primary outcomes - 5-year all-cause death; 5-year composite of CV Death and HF Hospitalization;
Secondary outcomes - 5-year CV death, 5-year HF hospitalization; **Safety outcome:** 5-year hospitalization for syncope

Statistical methods:

- Chained equations multiple imputation for missing data (10 datasets generated)
- Propensity-score for BB use based on 34 baseline characteristics
- Propensity-score matching (1:1, caliper <0.01 and no replacement) in BB vs. no-BB
- COX regressions in the matched cohort and in overall cohort adjusting for PS
- Positive control consistency analysis in age<80 (where BB are known to be effective)
- Negative control analysis (outcome: hospitalization for cancer) to explore residual confounding
- Subgroup analysis (COX regressions with interaction terms)

Results

Baseline characteristics

	Beta-blocker non-users 922 (14%)	Beta-blocker users 5640 (86%)	p-value
Demographics/Clinical			
Age (years, mean (SD))	85.4 (4.2)	84.6 (3.6)	<0.001
Sex = Female (%)	30.5	35.4	0.004
Follow-up location = Specialty (%)	36.6	47.0	<0.001
NYHA class >2 (%)	68.1	58.9	<0.001
Clinical measures			
SBP (mmHg, mean (SD))	124.8 (19.8)	124.7 (20.1)	0.862
Heart Rate (bpm, median [IQR])	72.0 [63.0, 82.0]	72.0 [64.0, 82.0]	0.611
eGFR (mL/min/1.73m ²), median [IQR])	45.3 [34.2, 59.6]	44.5 [33.5, 58.0]	0.222
Medical history (%)			
Atrial fibrillation	65.5	68.4	0.088
Anemia	50.0	44.7	0.003
Diabetes	21.9	28.9	<0.001
Hypertension	58.8	69.2	<0.001
Ischemic heart disease	66.8	74.4	<0.001
Peripheral artery disease	16.3	13.3	0.016
Cancer in the previous 3 years	14.1	12.9	0.346
Dementia	2.4	2.6	0.828
Procedures (%)			
Devices (CRT or ICD)	3.3	5.5	0.008
Pacemaker (CRT-D, CRT-P or pacemaker)	19.2	19.5	0.137
Medication use (%)			
RAS-inhibitors	72.4	81.7	<0.001
MRA	32.3	32.5	0.958
Diuretics	89.9	91.0	0.321
Socioeconomics			
Marital status			0.723
Married	45.7	47.0	
Single / Widowed	54.2	53.0	
Education level			0.867
Compulsory school	57.9	57.4	
Secondary school	30.5	31.3	
University	11.6	11.3	
Income > median	42.2	42.8	0.763

Together with

6,562 HFrEF patients aged ≥80

86% received BB

Median fup 1.76 (IQR: 0.64-3.39)
years

BB vs. no-BB patients:

- Younger
- More follow-up in specialty care
- Less severe HF
- More HF therapies

Results

Propensity score matching

Before matching:

- Different distributions of PS in BB vs. no-BB (dashed lines)

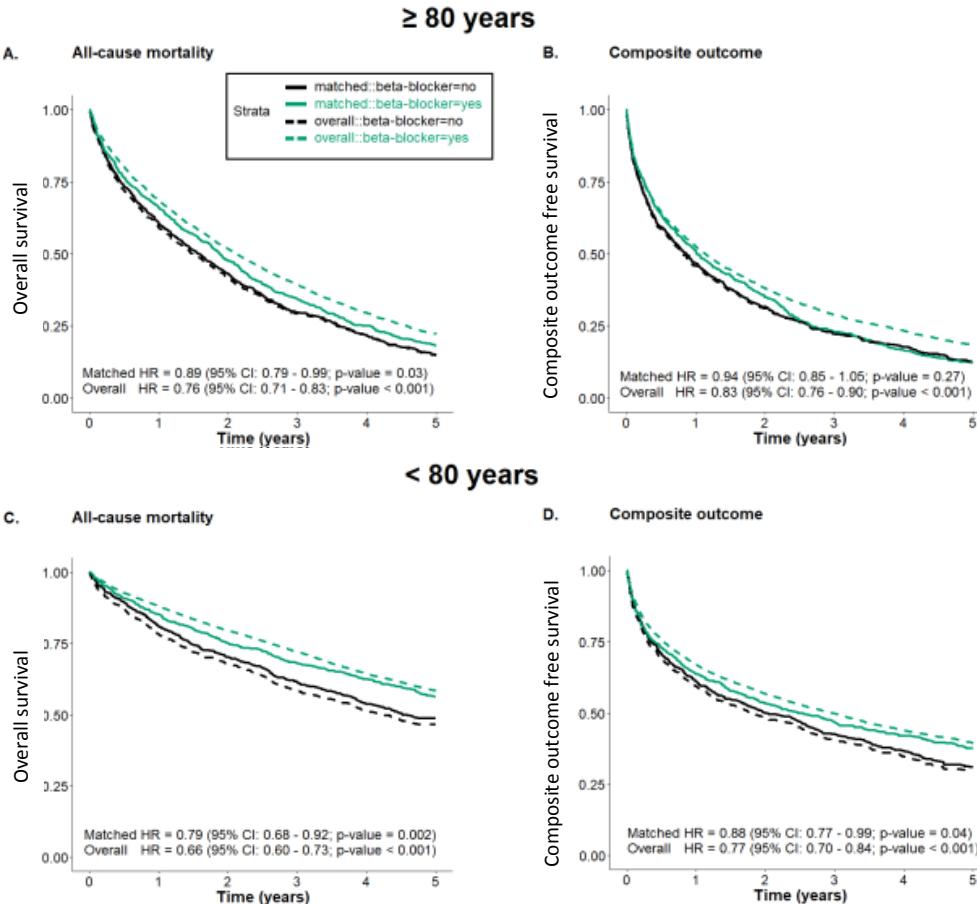
After matching:

- No difference in PS distributions in BB vs. no-BB (solid lines)
- Study arms comparable for baseline characteristics (~40)
- 1,732 patients selected, 866 (50%) receiving BB



Results

Primary outcomes (All-cause death and CV death/HF hospitalization)



Age ≥ 80 years

- BB use was associated with reduced overall mortality
- BB use was not associated with significantly reduced risk of CV death/HF hospitalization
- In PS-adjusted models, BB use was associated with significantly reduced risk of both outcomes [HR: 0.89 (0.82-0.97) for mortality and 0.90 (0.83-0.97) for the composite]

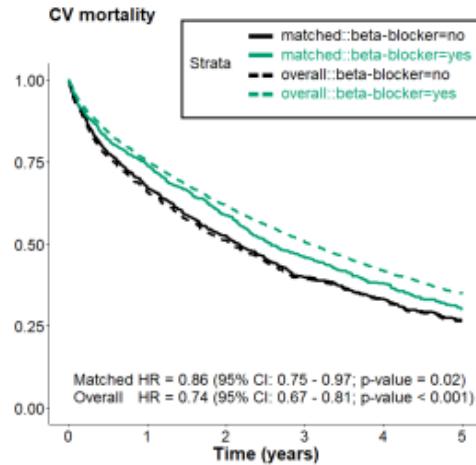
Age < 80 years

- Overall cohort: 13,351 patients (BB 93%)
- Matched cohort: 1,662 patients (BB 50%)
- BB use was associated with reduced overall mortality, and CV death/HF hospitalization

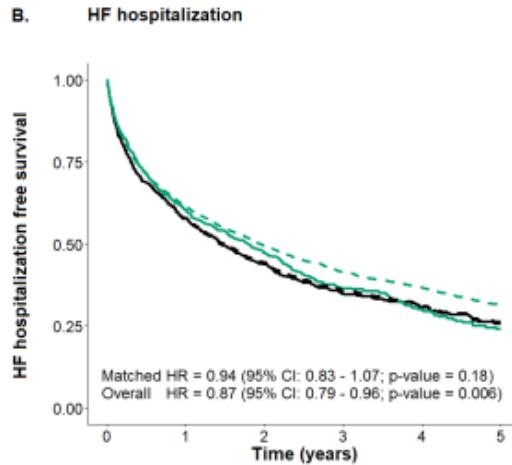
Results

Secondary (CV death and HF hospitalization) and safety outcomes

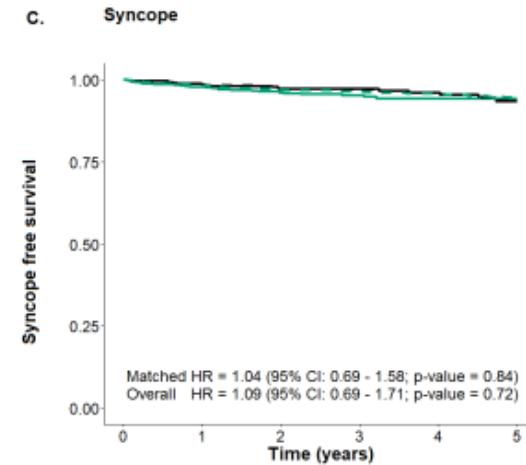
A.



B.



C.



PS-adjusted models: HR: 0.87 (95%CI 0.79-0.95)

HR: 0.90 (95%CI: 0.82-0.99)

HR: 1.03 (95%CI: 0.65–1.64)

PS-matched models: HR: 0.79 (95%CI: 0.66–0.94)

Age<80 years

HR: 0.90 (95%CI: 0.79–1.03)

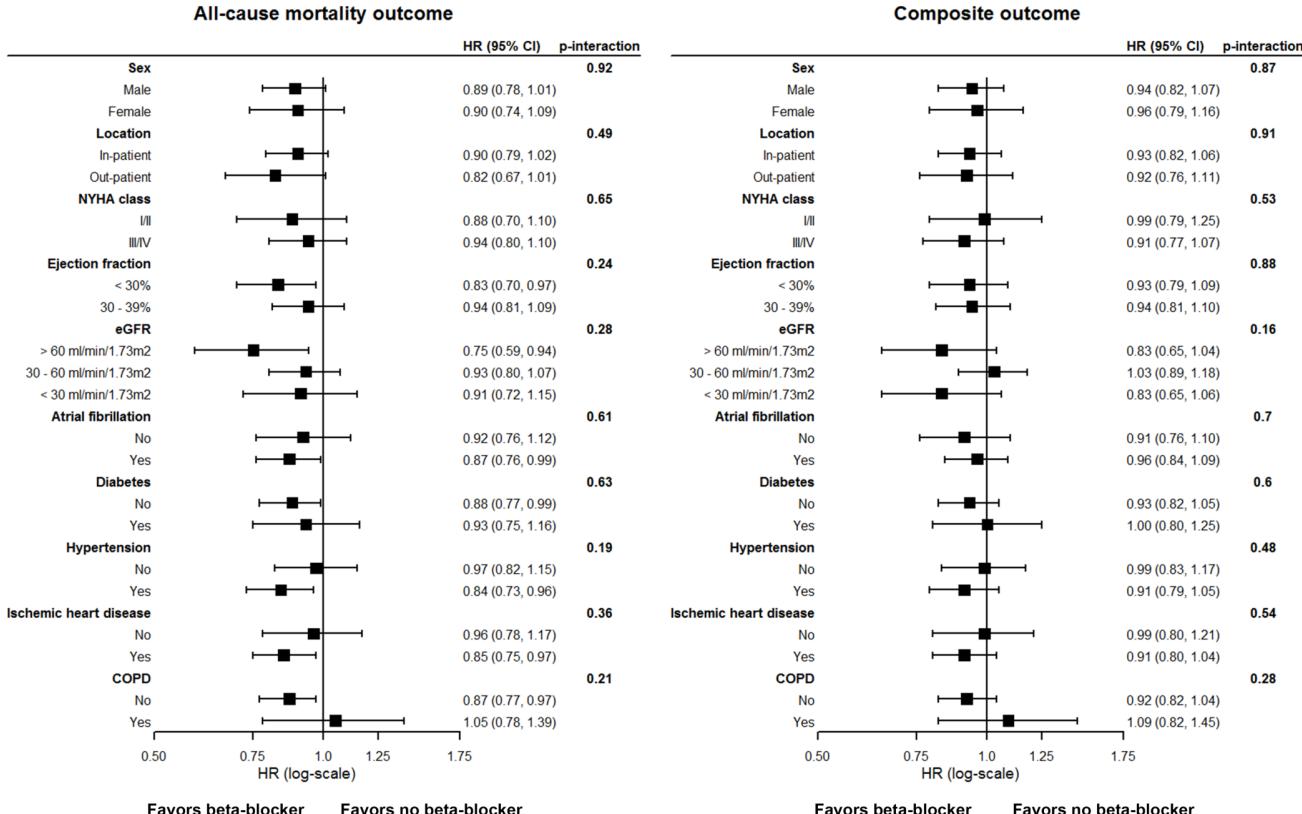
PS-adjusted models: HR: 0.84 (95%CI: 0.75-0.96)

HR: 0.84 (95%CI: 0.75-0.96)



Results

Subgroup analysis



Limitations

- Unmeasured confounders (although no association with negative control outcome)
- BB use defined at the baselines (potential cross-over)
- Missing data
- Matching reduced sample size
- Generalizability to other countries
- Observational design: association between exposure and outcomes but not causality

Conclusions

In HFrEF patients with age ≥ 80 years:

- BB use was less than in younger patients
- BB use was associated with improved all-cause and CV mortality without any increase in risk of hospitalization for syncope.

Our analysis supports current guidelines recommendation on beta-blocker therapy in HFrEF patients regardless of age.



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Association between beta-blocker use and mortality/morbidity in older patients with heart failure with reduced ejection fraction

A propensity score-matched analysis from the Swedish Heart Failure Registry

Davide Stolfo, Alicia Uijl, Lina Benson, Benedikt Schrage, Marat Fudim,
Folkert W. Asselbergs, Stefan Koudstaal, Gianfranco Sinagra, Ulf Dahlström,
Giuseppe Rosano, Gianluigi Savarese