

# Clinical relevance of sex differences in the treatment of heart failure



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Dutch Diabetes Academy  
December 1, 2020



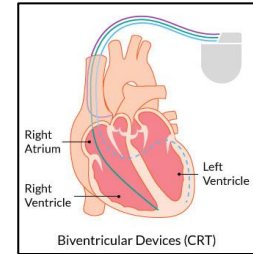
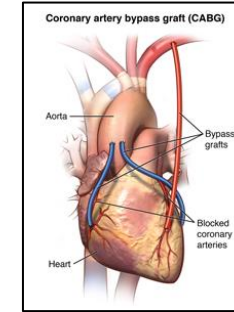
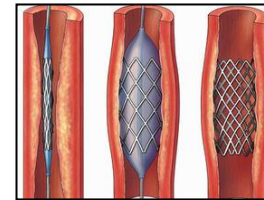
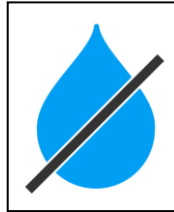
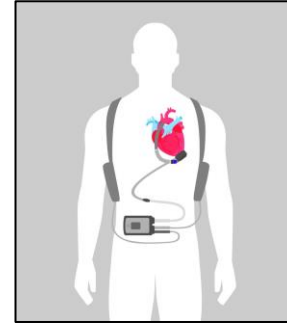
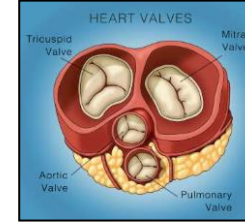
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# Conflicts of interest

- I received funding from the Dutch Heart Foundation



# Treatment of heart failure

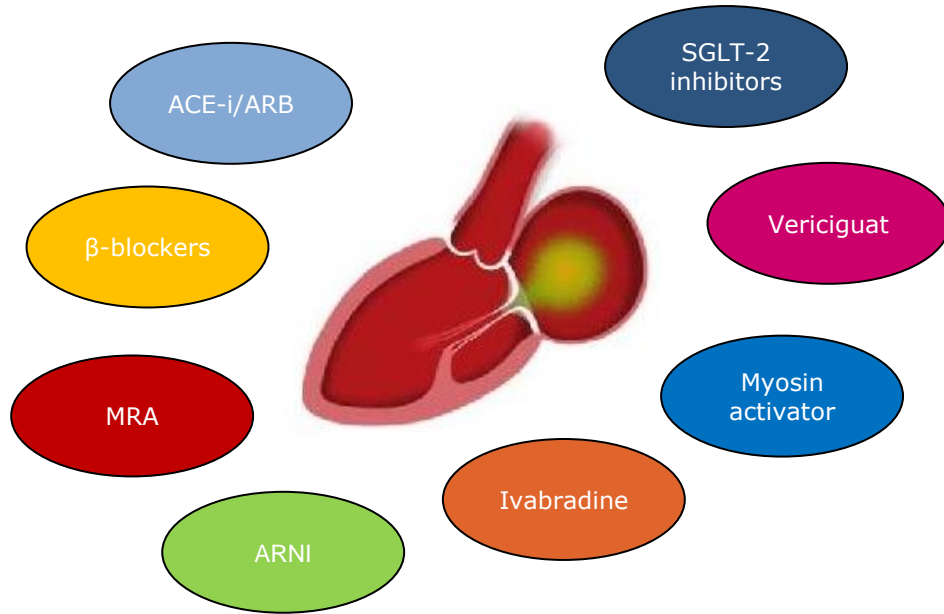


# Heart failure classification

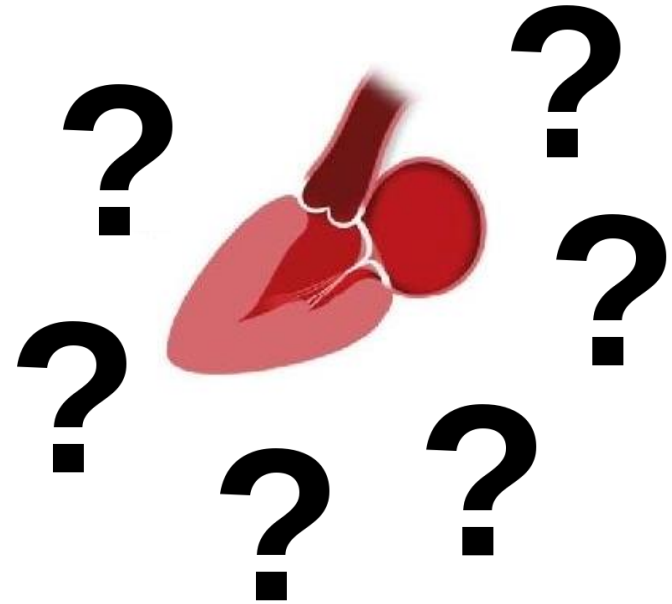
Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs	Symptoms ± Signs	Symptoms ± Signs
	2	LVEF <40%	LVEF 40-49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides. 2. At least one additional criterion: a. relevant structural heart disease (LVF and/or LAE); b. diastolic dysfunction (for details see Section 4.3.2.).	1. Elevated levels of natriuretic peptides. 2. At least one additional criterion: a. relevant structural heart disease (LVF and/or LAE); b. diastolic dysfunction (for details see Section 4.3.2.).



# HFrEF



# HFpEF



# HFrEF treatment

Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
An ACE-I <sup>d</sup> 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 <sup>d</sup> , for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A	167–173



# HFrEF treatment

icated or not tolerated in all symptomatic patients. ACEIs should be up-titrated to the maximum tolerated dose in order to achieve adequate inhibition of the renin–angiotensin–aldosterone system (RAAS). There is evidence that in clinical practice the majority of pa-

There is no evidence favouring the initiation of treatment with a beta-blocker before an ACEI has been started.<sup>176</sup> Beta-blockers should be initiated in clinically stable patients at a low dose and gradually up-titrated to the maximum tolerated dose.



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# Doses HFrEF treatment

**Table 1** Recommended doses of ACE-inhibitors, ARBs, and beta-blockers in ESC guidelines for patients with LVEF <40%

Drug	Class	Target dose	Total daily dose
Captopril	ACE-inhibitor	50 mg t.i.d.	150 mg
Enalapril	ACE-inhibitor	10 mg b.i.d.	20 mg
Lisinopril	ACE-inhibitor	35 mg q.d.	35 mg
Ramipril	ACE-inhibitor	5 mg b.i.d. or 10 mg q.d.	10 mg
Trandolapril	ACE-inhibitor	4 mg q.d.	4 mg
Perindopril	ACE-inhibitor	8 mg q.d.	8 mg
Candesartan	ARB	32 mg q.d.	32 mg
Valsartan	ARB	160 mg b.i.d.	320 mg
Losartan	ARB	150 mg q.d.	150 mg
Bisoprolol	Beta-blocker	10 mg q.d.	10 mg
Carvedilol	Beta-blocker	25–50 mg b.i.d.	50–100 mg <sup>a</sup>
Metoprolol CR/XL	Beta-blocker	200 mg q.d.	200 mg
Nebivolol	Beta-blocker	10 mg	10 mg

q.d. = once a day; b.i.d.= twice a day; t.i.d. = 3 times a day.

<sup>a</sup>25 mg b.i.d. for patients weighing <75 kg and 50 mg b.i.d. for patients weighing >75 kg.



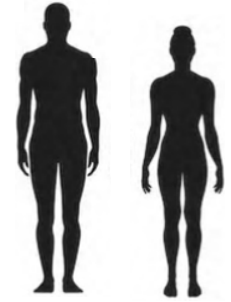
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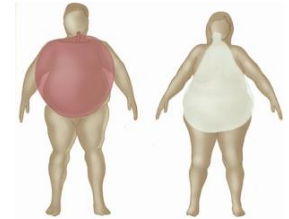
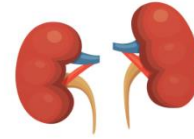
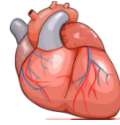
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# Physiology - pharmacokinetics



- Lower weight/height/BMI
- Smaller organ size
- Lower cardiac output
- Lower hepatic flow
- Lower glomerular filtration rate
- Lower peripheral distribution volume
- Higher proportion of body fat (lipophilic drugs)



# Aim

- To study potential sex differences in the association between doses of ACE-inhibitors/ARBs and  $\beta$ -blockers and clinical outcome in patients with HFrEF



# THE LANCET

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## Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study

*Bernadet T Santema, Wouter Ouwerkerk, Jasper Tromp, Izhah E Sama, Alice Ravera, Vera Regitz-Zagrosek, Hans Hillege, Nilesh J Samani, Faiez Zannad, Kenneth Dickstein, Chim C Lang, John G Cleland, Jozine M Ter Maaten, Marco Metra, Stefan D Anker, Pim van der Harst, Leong L Ng, Peter van der Meer, Dirk J van Veldhuisen, Sven Meyer, Carolyn S P Lam on behalf of the ASIAN-HF investigators\*, Adriaan A Voors*



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# BIOSTAT-CHF

- 1,710 patients
  - ✓ 1,308 men, 402 women
  - ✓ 11 European countries
  - ✓ New-onset or worsening heart failure
  - ✓ LVEF <40%
  - ✓ Not previously treated with ACE-i/ARBs and/or  $\beta$ -blockers, or receiving  $\leq 50\%$  of target doses
  - ✓ Anticipated initiation or up-titration of ACE-i/ARB and/or  $\beta$ -blockers



**Primary endpoint:** composite of all-cause mortality or heart failure hospitalization



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# ASIAN-HF

- 4,500 patients
  - ✓ 3,539 men, 961 women
  - ✓ 11 Asian regions
  - ✓ Symptomatic heart failure
  - ✓ LVEF <40%



**Primary endpoint:** composite of all-cause mortality or heart failure hospitalization



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	Men (n=1308)	Women (n=402)	p value
<b>Clinical</b>			
Age	70 (12)	74 (12)	<0.0001
Weight (kg)	85 (18)	72 (16)	<0.0001
Height (cm)	174 (8)	162 (7)	<0.0001
BMI (kg/m <sup>2</sup> )	27.9 (5.2)	27.3 (5.8)	0.06
NYHA	..	..	0.27
Class I	120 (10%)	34 (10%)	..
Class II	639 (55%)	172 (49%)	..
Class III	372 (32%)	130 (37%)	..
Class IV	38 (3%)	12 (3%)	..
LVEF (%)	27 (7)	29 (6)	<0.0001
Systolic blood pressure (mm Hg)	123 (20)	126 (23)	0.01
Diastolic blood pressure (mm Hg)	76 (12)	75 (13)	0.21
Pulse pressure (mm Hg)	47 (15)	52 (17)	<0.0001
Heart rate (beats per min)	82 (21)	83 (20)	0.32
Smoking	..	..	<0.0001
Never	371 (28%)	245 (61%)	..
Past	725 (56%)	114 (28%)	..
Current	210 (16%)	43 (11%)	..
<b>Medical history</b>			
Coronary artery disease*	631 (48%)	139 (35%)	<0.0001
Valvular surgery	95 (7%)	25 (6%)	0.55
Atrial fibrillation	574 (44%)	140 (35%)	0.01
Stroke	111 (9%)	30 (8%)	0.58
Peripheral artery disease	140 (11%)	22 (6%)	0.01
Hypertension	759 (58%)	253 (63%)	0.10
Diabetes	431 (33%)	109 (27%)	0.03

	Men (n=1308)	Women (n=402)	p value
<b>Laboratory data</b>			
NT-proBNP (pg/mL)	2484 (1073-5032)	2724 (1193-5906)	0.18
Haemoglobin (g/L)	1.39 (1.24-1.49)	1.28 (1.18-1.3.8)	<0.0001
Creatinine (μmol/L)	106 (88-130)	88 (72-109)	<0.0001
Sodium (mmol/L)	140 (137-142)	140 (138-142)	0.12

- Women were older, lower body weight and height, higher systolic blood pressure
- NT-proBNP was comparable



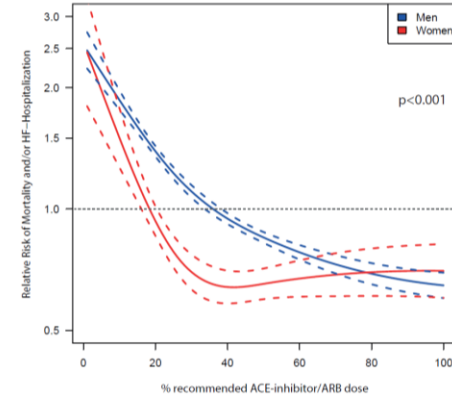
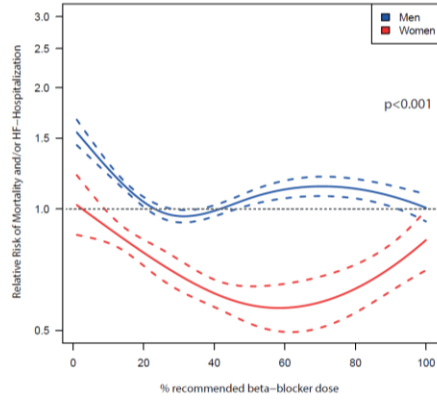
# Up-titration of therapies

	Men (n=1308)	Women (n=402)	<i>P</i> value
<b>On target dose:</b>			
ACE-i/ARB	23%	25%	0.61
$\beta$ -blocker	13%	14%	0.54
<b>Median dose level:</b>			
ACE-i/ARB	50% [25, 75]	50% [25, 75]	0.50
$\beta$ -blocker	25% [12, 50]	25% [12, 50]	0.54

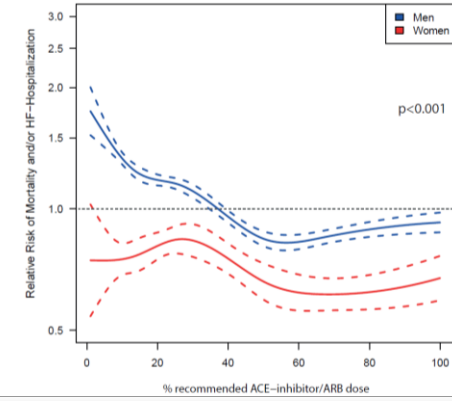
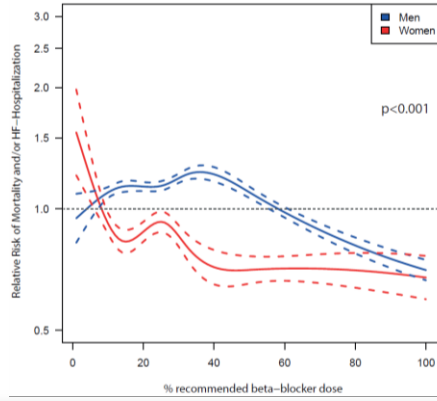
- No sex difference in % that was on target dose
- No sex difference in median dose level



# BIOSTAT-CHF

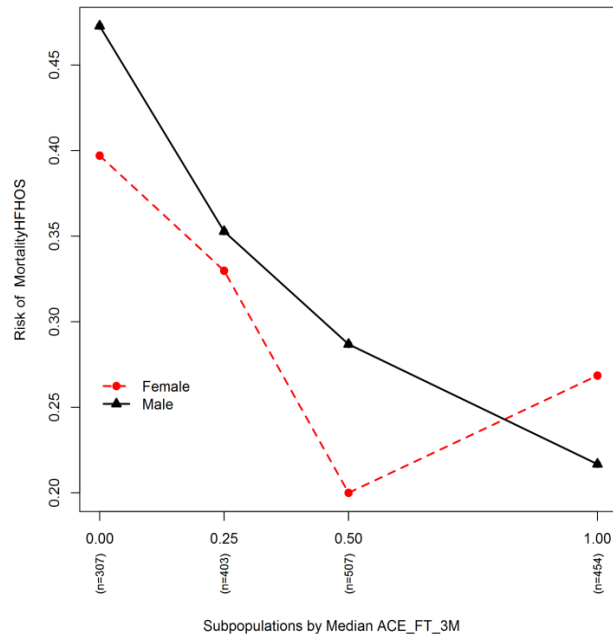
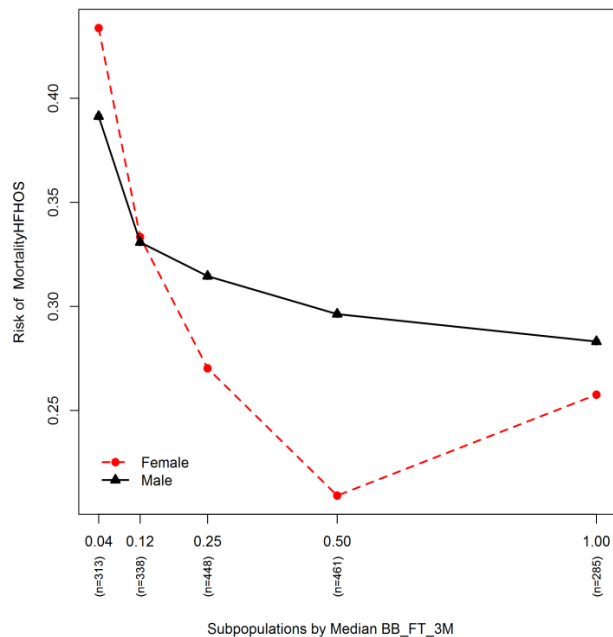


# ASIAN-HF





# STEPP analysis



- The optimal dose level of ACE-i/ARBs and  $\beta$ -blockers might be lower in women than in men



# Back to clinical practice

- Are we over-treating women with HFrEF?
- Are we under-treating men with HFrEF?



ORIGINAL INVESTIGATIONS

# Medical Therapy for Heart Failure With Reduced Ejection Fraction



## The CHAMP-HF Registry

Stephen J. Greene, MD,<sup>a,b</sup> Javed Butler, MD, MPH, MBA,<sup>c</sup> Nancy M. Albert, PhD,<sup>d</sup> Adam D. DeVore, MD, MHS,<sup>a,b</sup>  
Puza P. Sharma, MBBS, MPH, PhD,<sup>e</sup> Carol I. Duffy, DO,<sup>e</sup> C. Larry Hill, PhD,<sup>a</sup> Kevin McCague, MA,<sup>e</sup> Xiaojuan Mi, PhD,<sup>a</sup>  
J. Herbert Patterson, PHARM,<sup>f</sup> John A. Spertus, MD, MPH,<sup>g</sup> Laine Thomas, PhD,<sup>a</sup> Fredonia B. Williams, EdD,<sup>h</sup>  
Adrian F. Hernandez, MD, MHS,<sup>a,b</sup> Gregg C. Fonarow, MD<sup>i</sup>

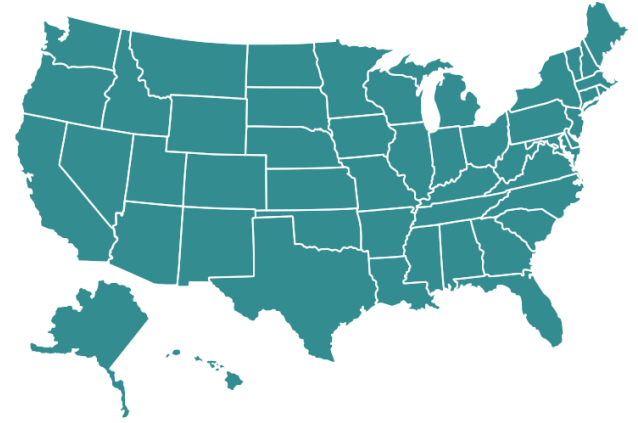


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# CHAMP-HF Registry



- 3,518 patients with chronic HFrEF
- 150 primary care and cardiology practices in U.S.



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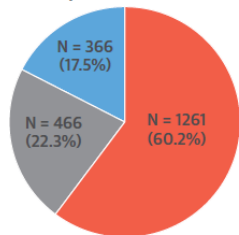
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**TABLE 1** Baseline Patient Characteristics by Dose of ACEI/ARB Therapy

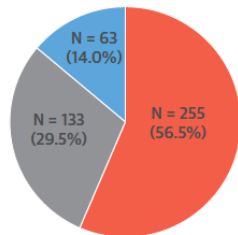
	None (n = 1,374)	<50% Target Dose (n = 1,261)	50% to <100% Target Dose (n = 466)	≥100% Target Dose (n = 366)
Age, yrs	69 (59-76)	67 (58-75)	67 (58-75)	67 (58-74)
Female	428 (31.3)	359 (28.5)	133 (28.5)	90 (24.7)
Systolic blood pressure, mm Hg	120 (108-130)	120 (109-130)	122 (110-134)	128 (115-140)
Diastolic blood pressure, mm Hg	70 (64-80)	70 (64-80)	74 (67-80)	76 (70-84)
Heart rate, beats/min	72 (66-82)	73 (66-82)	72 (65-81)	72 (64-80)
Obese, BMI ≥30 kg/m <sup>2</sup>	547 (40.2)	492 (39.1)	220 (47.3)	168 (45.9)
Hemoglobin, g/dl*	13.0 (11.8-14.3)	13.3 (12.0-14.6)	13.3 (12.2-14.5)	13.4 (12.1-14.5)
Serum sodium, mmol/l†	139 (137-141)	139 (137-141)	140 (138-142)	140 (138-142)
BUN, mg/dl‡	21 (16-30)	19 (15-26)	20 (15-26)	19 (15-26)
eGFR, mL/min per 1.73 m <sup>2</sup> §				
<30	74 (8.9)	22 (2.9)	7 (2.5)	10 (4.8)
30-44	159 (19.2)	81 (10.5)	32 (11.4)	27 (12.9)
45-60	188 (22.7)	186 (24.2)	65 (23.1)	44 (21.1)
>60	409 (49.3)	479 (62.4)	177 (63.0)	128 (61.2)
NT-proBNP, pg/ml	2,308 (804-5,530)	2,613 (919-5,348)	1,320 (695-2,106)	1,120 (396-2,790)
Hemoglobin A1c, %#	6.6 (5.8-7.7)	6.4 (5.8-7.5)	6.4 (5.9-7.7)	6.4 (6.0-7.5)
Medical history**				
HF hospitalization within past 12 months	566 (41.4)	495 (39.3)	155 (33.3)	94 (25.7)
Coronary artery disease	848 (62.2)	795 (63.0)	284 (61.1)	229 (62.6)
Hypertension	1,112 (81.5)	984 (78.0)	401 (86.2)	341 (93.2)
Hyperlipidemia	1,014 (74.3)	954 (75.7)	352 (75.7)	298 (81.4)
Diabetes mellitus	581 (42.7)	473 (37.6)	196 (42.2)	163 (44.5)
Atrial fibrillation	557 (40.9)	439 (34.8)	137 (29.5)	115 (31.4)
Chronic renal insufficiency	333 (24.5)	208 (16.5)	79 (17.0)	59 (16.1)
Asthma/COPD	422 (31.0)	389 (30.9)	142 (30.5)	86 (23.5)



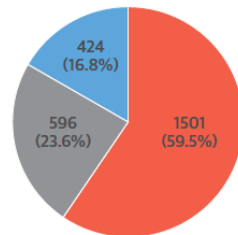
Angiotensin-Converting Enzyme Inhibitor (ACEI)/Angiotensin II Receptor Blocker (ARB)



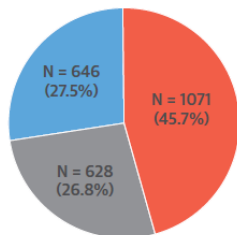
Angiotensin Receptor-Nepriylsin Inhibitor (ARNI)



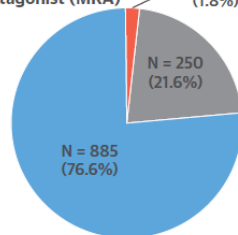
ACEI/ARB/ARNI



Beta-Blocker



Mineralocorticoid Receptor Antagonist (MRA)



■ <math><50\%</math> ■ 50 to <math><100\%</math> ■

- Only 1% on target dose ACE/ARB/ARNI +  $\beta$ -blocker + MRA
- <math><25\%</math> received any dose of these 3 medications



CLINICAL RESEARCH

# Contemporary Drug Treatment of Chronic Heart Failure With Reduced Ejection Fraction



## The CHECK-HF Registry

Hans-Peter Brunner-La Rocca, MD,<sup>a</sup> Gerard C. Linssen, MD, PhD,<sup>b</sup> Frank J. Smeele, MD, PhD,<sup>c</sup>  
Annemarie A. van Drimmelen, RN,<sup>d</sup> Henk-Jan Schaafsma, MD,<sup>e</sup> Paul H. Westendorp, MD,<sup>f</sup> Philip C. Rademaker, MD,<sup>g</sup>  
Hendrik J. van de Kamp, MSc,<sup>h</sup> Arno W. Hoes, MD, PhD,<sup>i,j</sup> Jasper J. Brugts, MD, PhD, MSc,<sup>k</sup>  
for the CHECK-HF Investigators



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# CHECK-HF Registry

- 10,910 patients with heart failure
- 34 centers in The Netherlands



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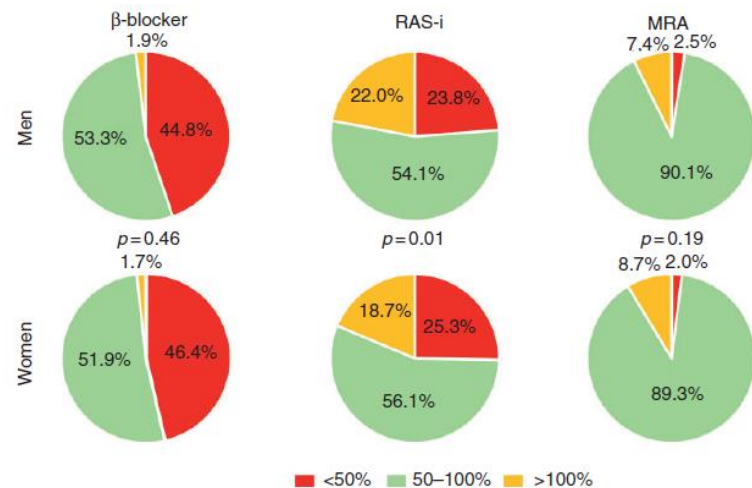
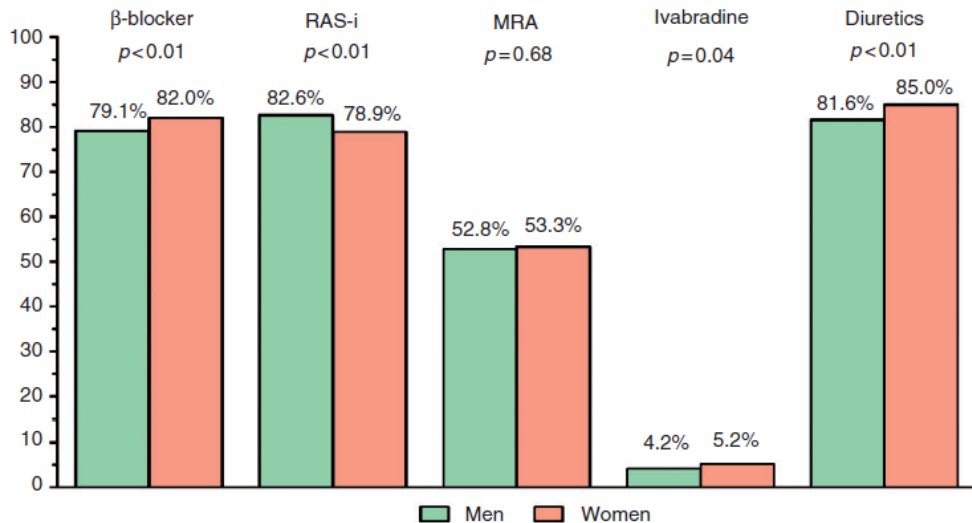


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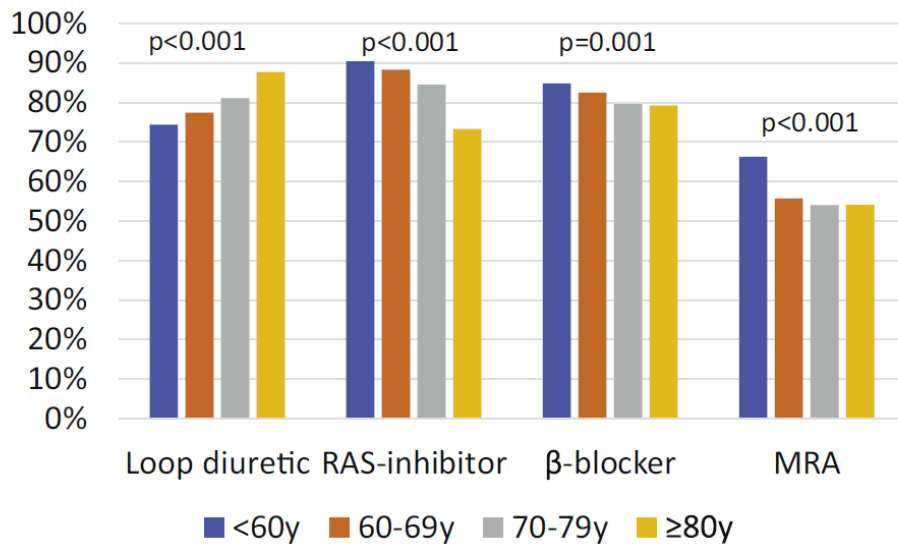
**Table 1.** Patient characteristics in heart failure with reduced ejection fraction (HFrEF) patients.

	Men (n = 5320)	Women (n = 3003)	p-Value
Age (years) (n = 8314)	71.6 ± 11.4	73.4 ± 12.4	<0.01
BMI, kg/m <sup>2</sup> (n = 7638)	27.3 ± 4.8	27.1 ± 5.8	0.32
NYHA (n = 8226)			
I	913 (17.4)	395 (13.3)	<0.01
II	3000 (57.1)	1671 (56.2)	
III	1248 (23.8)	850 (28.6)	
IV	90 (1.7)	59 (2.0)	
LVEF, % (n = 6154)	32.2 ± 10.4	33.5 ± 10.8	<0.01
Cause of HF (n = 8058)			
Ischaemic	3016 (58.5)	1149 (39.6)	<0.01
Non-ischaemic	2137 (41.5)	1756 (60.4)	
Systolic BP, mm Hg (n = 8209)	125.3 ± 20.5	126.4 ± 21.0	0.02
Diastolic BP, mm Hg (n = 8215)	71.5 ± 11.3	70.7 ± 11.4	<0.01
Heart rate, bpm (n = 8211)	71.2 ± 13.7	73.5 ± 14.0	<0.01
Atrial fibrillation (n = 8216)	1366 (26.0)	734 (24.8)	0.25
LBBB (n = 8323)	838 (15.8)	574 (19.1)	<0.01
QRS ≥ 130 ms (n = 6908)	1877 (42.5)	887 (35.7)	<0.01
eGFR (n = 5883)	61.4 ± 24.8	56.6 ± 24.0	<0.01
eGFR (n = 5883)			
<30	364 (9.8)	303 (14.0)	<0.01
30–59	1510 (40.6)	932 (43.0)	
≥60	1844 (49.6)	930 (43.0)	
Comorbidities (n = 7459)			
Hypertension	1801 (37.9)	1168 (43.2)	<0.01
Diabetes mellitus	1380 (29.0)	789 (29.2)	0.87
COPD	904 (19.0)	466 (17.2)	0.06
OSAS	401 (8.4)	92 (3.4)	<0.01
Thyroid disease	257 (5.4)	300 (11.1)	<0.01





**FIGURE 3** Prescription Rate of Medication in Different Age Groups in HFREF Patients



# Conclusion

- The optimal dose level of ACE-i/ARBs and  $\beta$ -blockers might be lower in women than in men with HFrEF
- In clinical practice: doses that might already be appropriate in women, under-treatment of men



- **Thank you!**



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