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FASTTRACK – CLINICAL RESEARCH
Clinical trials

Beta-blockers after myocardial infarction: effects according to sex in the REBOOT trial

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Abstract

Background and Aims Recent trials have challenged the guideline recommendation of beta-blockers for post-myocardial infarction (MI) patients without reduced left ventricular ejection fraction (LVEF). Whether these recent findings apply equally to women and men remains unknown.

Methods Using data from REBOOT (tREatment with Beta-blockers after myOcardial infarction withOut reduced ejection fracTion), the largest randomized trial evaluating the effect of beta-blockers after acute MI with LVEF > 40%, a pre-specified sex-specific subgroup analysis was performed. A total of 8438 out of the 8505 randomized patients comprised the intention-to-treat population.

Results Among 8438 patients, 1627 were women, who were older, had more comorbidities, and received fewer guideline-based therapies than men. Over a median follow-up of 3.7 years, women had overall higher rates of the primary composite outcome (death, MI, or heart failure hospitalization) than men. The incidence rate of the primary endpoint in women was 30.4 and 21.0/1000 patient-years in the beta-blocker group and no beta-blocker group, respectively (hazard ratio

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1.45, 95% confidence interval 1.04–2.03). No significant differences were observed in men (hazard ratio .94, 95% confidence interval .79–1.13; *P* for interaction = .026). The excess risk in women was mainly driven by increased mortality and was most evident among those with preserved LVEF (*P* for interaction = .030) and those receiving higher beta-blocker doses (*P* for interaction = .045).

Conclusions In the REBOOT trial of MI patients managed according to contemporary standards, beta-blocker therapy was associated with evidence of harm in women—particularly those with preserved LVEF and receiving higher doses—an effect not observed in men.

Structured Graphical Abstract

Key Question

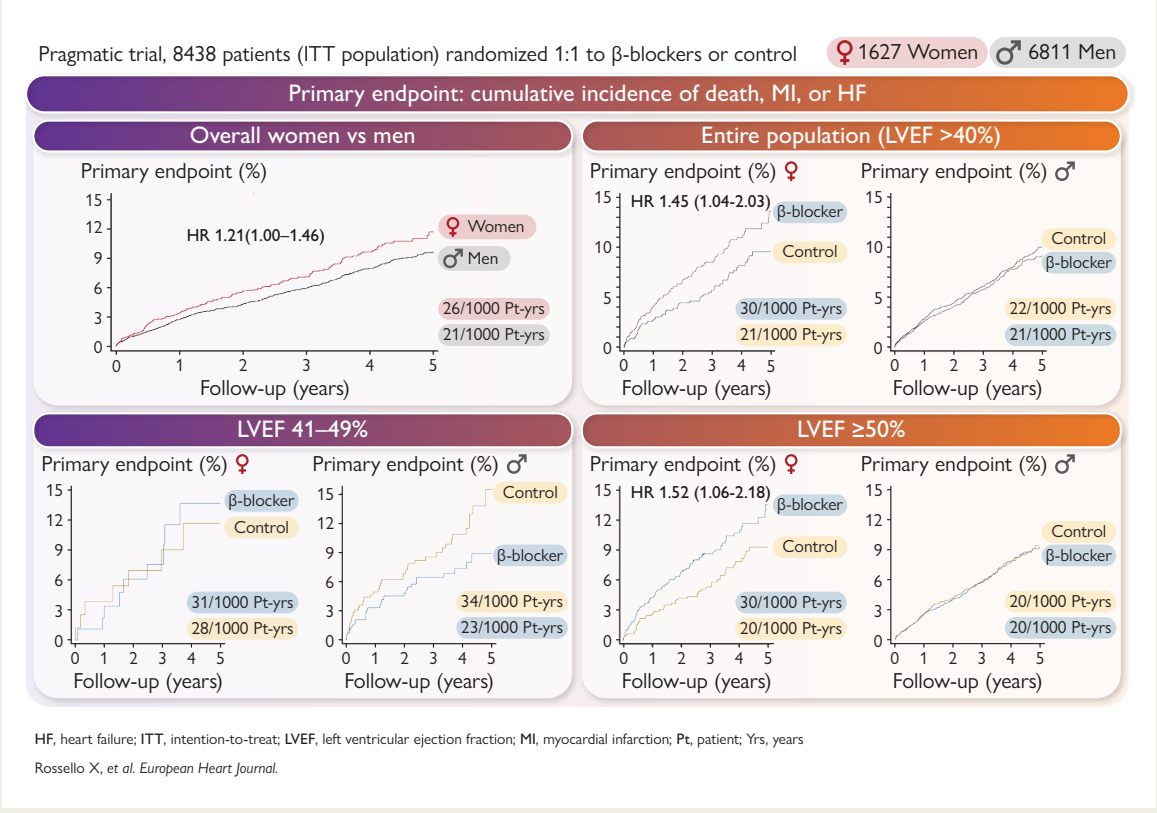
Women have a worse prognosis than men after acute coronary syndromes, yet few studies have assessed established therapies in a sex-specific manner. Recent trials have questioned the guideline recommendation for beta-blockers in post–myocardial infarction patients without reduced left ventricular ejection fraction (LVEF).

Key Finding

In this sex-specific pre-specified REBOOT trial analysis, women with myocardial infarction and LVEF >40% had higher risk and worse outcomes than men. Beta-blockers were associated with an increased incidence of major adverse events—including death—in women but not in men.

Take Home Message

Women with myocardial infarction and preserved LVEF derive no benefit from beta-blocker therapy, with a potential signal of harm. Future studies should specifically address sex-related differences in the effects of cardiovascular therapies.



HF, heart failure; ITT, intention-to-treat; LVEF, left ventricular ejection fraction; MI, myocardial infarction; Pt, patient; Yrs, years

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Kaplan–Meier plots for primary outcome (composite of death, reinfarction, or heart failure admission) in the REBOOT trial. Numbers represent events/1000 patient-years. HF, heart failure; ITT, intention-to-treat; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

Keywords Women • Beta-blockers • Myocardial infarction • Randomized controlled trial • Secondary prevention

Introduction

European Society of Cardiology (ESC) and American guidelines for the management of patients with acute coronary syndromes (ACS) recommend the use of beta-blockers regardless of left ventricular ejection fraction (LVEF) (class IIa for the 2023 ESC and class I for the 2025 ACC/AHA/ACEP/NAEMSP/SCAI guidelines).[1,2] These recommendations do not differentiate between women and men for this recommendation. However, there is a large body of evidence suggesting substantial differences in pharmacokinetics and pharmacodynamics of beta-blockers between women and men.[3–5]

Despite the underlying reasons being not fully understood, it is well established that women and men do not receive equal management—including pharmacological therapies—following an ACS.[6,7] Moreover, although findings vary across studies, several reports suggest that women may experience worse long-term outcomes than men after ACS.[8,9] These disparities have led some authors to propose the development of sex-specific cardiovascular guidelines.[10]

Landmark trials assessing beta-blocker therapy after myocardial infarction (MI) were conducted decades ago and included insufficient numbers of women to permit robust sex-specific analyses.[11,12] For instance, a historical meta-analysis of five randomized studies evaluating the effects of metoprolol on mortality included only 1121 post-MI women.[12] Although the analysis showed a similar reduction in cardiovascular death for both sexes, these findings—reported in 1992—are unlikely to be generalizable to contemporary MI patients, who are managed with modern standards of care including early invasive strategies, complete revascularization, troponin-based diagnostics, dual antiplatelet therapy (DAPT), and high-intensity statin treatment.[13]

Two recent randomized clinical trials—REBOOT ($n = 8505$)[14] and REDUCE-AMI ($n = 5020$)[15]—have evaluated the efficacy of beta-blockers in patients with MI without reduced LVEF, demonstrating a consistent lack of clinical benefit in populations treated according to contemporary standards of care. These findings challenge the long-standing paradigm that advocated beta-blocker use in all post-MI patients regardless of LVEF.[14,15] Whether this lack of benefit applies equally to women and men remains uncertain. However, there are plausible biological and clinical reasons to suspect that the treatment effect may differ by sex.[16]

In line with the long-standing need to address evidence gaps in women,[17] and the broader call to reassess established therapies in the context of contemporary care,[13,18] we analysed data from the REBOOT trial (tREatment with Beta-blockers after myOcardial infarction withOut reduced ejection fracTion) to evaluate whether the effect of beta-blocker therapy post-MI differs between women and men. REBOOT is not only a contemporary, international trial reflecting current standards of care but also includes the largest cohort of women ($n = 1627$) enrolled to date in a randomized beta-blocker study following MI.

Methods

Study design, participants, and study intervention

The REBOOT trial (ClinicalTrials.gov identifier: NCT03596385; European Clinical Trials Database number: 2017-002485-40) was an independent, investigator-initiated study whose design has been previously described.[19] In summary, REBOOT was a pragmatic, multicentre, prospective, randomized, open-label, blinded-endpoint (PROBE) trial conducted in Spain and Italy.

ST-elevation MI or non-ST-elevation MI (NSTEMI) patients invasively managed during the index hospitalization (i.e. coronary angiography) and with a LVEF > 40% prior to discharge were eligible as long as they did not present a history of heart failure (HF) or the presence of Killip class ≥ II during index admission. Patients with an absolute contraindication to beta-blocker therapy or any condition (apart from acute MI) that requires beta-blocker prescription on discharge according to the treating physician were not included.

Patients meeting all criteria were randomized at discharge (mean 3.8 ± 2.6 days from index MI) to beta-blocker therapy or no beta-blocker therapy. In the intervention group, the type and dose of beta-blocker were determined by the managing physician. Apart from beta-blockers, all patients received standard-of-care treatment at the discretion of the treating physician.

All participants provided written informed consent before enrolment. The study protocol was approved by the relevant ethics committees in Spain (EC79-17/FJD) and Italy (Reg. sperimentazioni n.2085, Prot. 9144/2018; I.5/109).

After exclusions, 8438 patients (1627 women and 6811 men) were included in the intention-to-treat analysis and constitute the present study population. Primary results of the REBOOT trial have been published elsewhere.[14] The sample size was estimated to test the primary hypothesis for the overall population. There was not a pre-specified sample size for hypothesis testing by sex.

Outcomes, follow-up, and adjudication of events

The primary outcome of the REBOOT trial was a composite of all-cause mortality, non-fatal reinfarction, or HF admission. Secondary outcomes included individual components of primary endpoint (all-cause mortality, non-fatal reinfarction, and HF admission), cardiac death, and malignant ventricular arrhythmias (sustained ventricular tachycardia, ventricular fibrillation, or resuscitated cardiac arrest). Admission for stroke was a key tertiary safety endpoint.

Follow-up assessments of clinical outcomes were conducted at 3, 15, 36, and 48 months after randomization, through telephone interviews and review of medical records and national vital status registries. Events were centrally adjudicated by a panel blinded to the study treatment assignment.

Data analysis

Differences in baseline clinical characteristics by sex were described as frequency (%) and compared using χ^2 tests for categorical data, whereas baseline continuous data were expressed as mean and standard deviation (SD) or median with interquartile range and compared using *t*-tests or Wilcoxon rank sum tests, as appropriate.

Incidence rates [95% confidence intervals (CIs)] for each outcome were estimated by sex and treatment arm. Time-to-first-event curves for each outcome were obtained to compare subsets of patients by sex using the Kaplan–Meier method. Cox proportional hazards modelling was used to examine the association between cardiovascular outcomes and sex, estimating hazard ratios (HRs) and their 95% CI for each outcome. Proportional hazard assumption was evaluated.[20] Univariate and multivariate Cox regression modelling was performed to evaluate the interaction between sex and treatment arm for primary and secondary endpoints. Based on a risk model produced using REBOOT data, multivariate models were adjusted for age, prior MI, haemoglobin levels, oral anticoagulation, prior stroke, diabetes mellitus, chronic obstructive pulmonary disease, peripheral arterial disease, and estimated glomerular filtration rate.

The two-tailed significance level was set at $P < .05$. STATA software version 18.5 (Stata Corp, College Station, TX, USA) was used to perform the analyses and produce most graphs.

Results

Baseline data

A total of 1627 women (816 randomized to beta-blocker and 811 to no beta-blocker) and 6811 men (3391 randomized to beta-blocker and 3420

Table 1 Baseline patient characteristics by sex and treatment arm

	Women (*N* = 1627)	Men (*N* = 6811)	*P*-value*	Women		Men	
				Beta-blocker (*N* = 816)	No beta-blocker (*N* = 811)	Beta-blocker (*N* = 3391)	No beta-blocker (*N* = 3420)
Demographics							
Age (years)	65 [57–74]	60 [53–68]	<.001	66 [58–74]	65 [57–74]	60 [53–68]	60 [53–68]
Country			.71				
Spain	1256 (77.2)	5287 (77.6)		622 (76.2)	634 (78.2)	2638 (77.8)	2649 (77.5)
Italy	371 (22.8)	1524 (22.4)		194 (23.8)	177 (21.8)	753 (22.2)	771 (22.5)
Hypertension	981 (60.3)	3386 (49.9)	<.001	499 (61.2)	482 (59.4)	1683 (49.7)	1703 (50.0)
Diabetes mellitus	373 (23.0)	1421 (21.0)	.072	185 (22.8)	188 (23.3)	716 (21.2)	705 (20.8)
Dyslipidaemia	889 (54.7)	3435 (50.6)	.0027	449 (55.2)	440 (54.3)	1709 (50.5)	1726 (50.7)
Smoker	605 (38.7)	3070 (46.2)	<.001	307 (39.5)	298 (38.0)	1544 (46.5)	1526 (45.8)
Prior MI	124 (7.6)	678 (10.0)	.0038	60 (7.4)	64 (7.9)	348 (10.3)	330 (9.7)
Prior stroke	30 (1.8)	123 (1.8)	.93	17 (2.1)	13 (1.6)	69 (2.0)	54 (1.6)
Atrial fibrillation prior to admission	54 (3.3)	139 (2.0)	.0020	22 (2.7)	32 (4.0)	69 (2.0)	70 (2.1)
Peripheral arterial disease	45 (2.8)	194 (2.9)	.86	29 (3.6)	16 (2.0)	98 (2.9)	96 (2.8)
History of chronic obstructive pulmonary disease	42 (2.6)	236 (3.5)	.071	22 (2.7)	20 (2.5)	123 (3.6)	113 (3.3)
Treatment with beta-blockers before index admission	223 (13.8)	796 (11.7)	.024	111 (13.7)	112 (13.9)	399 (11.8)	397 (11.7)
MI type			<.001				
STEMI	767 (47.1)	3529 (51.8)		396 (48.6)	370 (45.6)	1749 (51.6)	1777 (52.1)
NSTEMI	860 (52.9)	3282 (48.2)		419 (51.4)	441 (54.4)	1642 (48.4)	1637 (47.9)
Infarct-related artery			<.001				
None	95 (5.9)	118 (1.7)		40 (4.9)	55 (6.8)	61 (1.8)	57 (1.7)
Left anterior descending	433 (26.7)	1841 (27.1)		206 (25.3)	227 (28.0)	929 (27.5)	912 (26.8)
Left circumflex system	169 (10.4)	857 (12.6)		96 (11.8)	73 (9.0)	436 (12.9)	421 (12.4)
Right coronary artery	465 (28.7)	1734 (25.6)		229 (28.2)	236 (29.1)	854 (25.3)	880 (25.8)
Secondary	84 (5.2)	376 (5.5)		53 (6.5)	31 (3.8)	187 (5.5)	189 (5.6)
Left main	14 (.9)	46 (.7)		6 (.7)	8 (1.0)	24 (.7)	22 (.6)
Multivessel	363 (22.4)	1814 (26.7)		183 (22.5)	180 (22.2)	890 (26.3)	924 (27.1)
Type of revascularization			<.001				
None	154 (9.6)	243 (3.6)		77 (9.5)	77 (9.6)	130 (3.9)	113 (3.3)

Continued

Table 1 *Continued*

	Women (*N* = 1627)	Men (*N* = 6811)	*P*-value*	Women		Men	
				Beta-blocker (*N* = 816)	No beta-blocker (*N* = 811)	Beta-blocker (*N* = 3391)	No beta-blocker (*N* = 3420)
PCI—stent	1395 (86.7)	6309 (93.4)		705 (87.0)	690 (86.4)	3140 (93.3)	3169 (93.5)
Complete revascularization	1276 (86.9)	5672 (88.5)	.085	649 (87.6)	627 (86.2)	2815 (88.1)	2857 (88.9)
Included in cardiac rehabilitation programme, *n* (%)	378 (26.5)	2058 (34.3)	<.001	174 (24.1)	204 (28.8)	1023 (34.2)	1035 (34.4)
LVEF (%)	59 [53–61]	57 [50–60]	<.001	58 [52–60]	60 [53–62]	57 [50–60]	57 [51–60]
eGFR (mL/min/1.73 m^2)	91 [74–101]	95 [81–103]	<.001	85.9 (20.2)	86.2 (20.0)	90.6 (17.9)	90.9 (17.9)
Haemoglobin prior to discharge (g/dL)	13.2 [12.1–14.1]	14.6 [13.6–15.5]	<.001	13.1 (1.5)	13.1 (1.6)	14.5 (1.5)	14.5 (1.6)
Discharge medication				*n* (%)	*n* (%)	*n* (%)	*n* (%)
Aspirin	1585 (97.5)	6716 (98.7)	<.001	797 (97.9)	788 (97.2)	3339 (98.6)	3377 (98.9)
$P2Y_{12}$ inhibitors	1553 (95.6)	6696 (98.4)	<.001	786 (96.6)	767 (94.6)	3334 (98.4)	3362 (98.5)
ACEi/ARB	1183 (72.9)	5126 (75.5)	.032	580 (71.3)	603 (74.4)	2460 (72.8)	2666 (78.1)
Statins	1583 (97.4)	6708 (98.6)	<.001	795 (97.7)	788 (97.2)	3335 (98.4)	3373 (98.8)
Aldosterone receptor antagonist	44 (2.7)	133 (2.0)	.058	21 (2.6)	23 (2.8)	72 (2.1)	61 (1.8)
Oral anticoagulants	84 (5.2)	250 (3.7)	.0053	41 (5.0)	43 (5.3)	129 (3.8)	121 (3.5)
Diuretics[a]	209 (12.9)	567 (8.3)	<.001	91 (11.2)	118 (14.6)	275 (8.1)	292 (8.6)
Beta-blockers	802 (49.3)	3325 (48.8)	.72	802 (49.3)		3325 (48.8)	
Type of beta-blocker			.16				
Atenolol	2 (.2)	24 (.7)		2 (.2)		24 (.7)	
Bisoprolol	695 (86.7)	2854 (85.7)		695 (86.7)		2854 (85.7)	
Carvedilol	23 (2.9)	105 (3.2)		23 (2.9)		105 (3.2)	
Metoprolol	58 (7.2)	251 (7.5)		58 (7.2)		251 (7.5)	
Nebivolol	21 (2.6)	93 (2.8)		21 (2.6)		93 (2.8)	
Other	3 (.4)	2 (.1)		3 (.4)		2 (.1)	
Beta-blocker dose			.25				
≤Median dosage	696 (87.3)	2844 (85.8)		696 (87.3)		2844 (85.8)	
>Median dosage	101 (12.7)	472 (14.2)		101 (12.7)		472 (14.2)	

Categorical data are expressed as *n* (%), and continuous data are expressed as median [first and third quartiles].
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; SD, standard deviation.
[a]Diuretics include different agents (no breakdown between types is available).
**P*-value for men vs women overall.

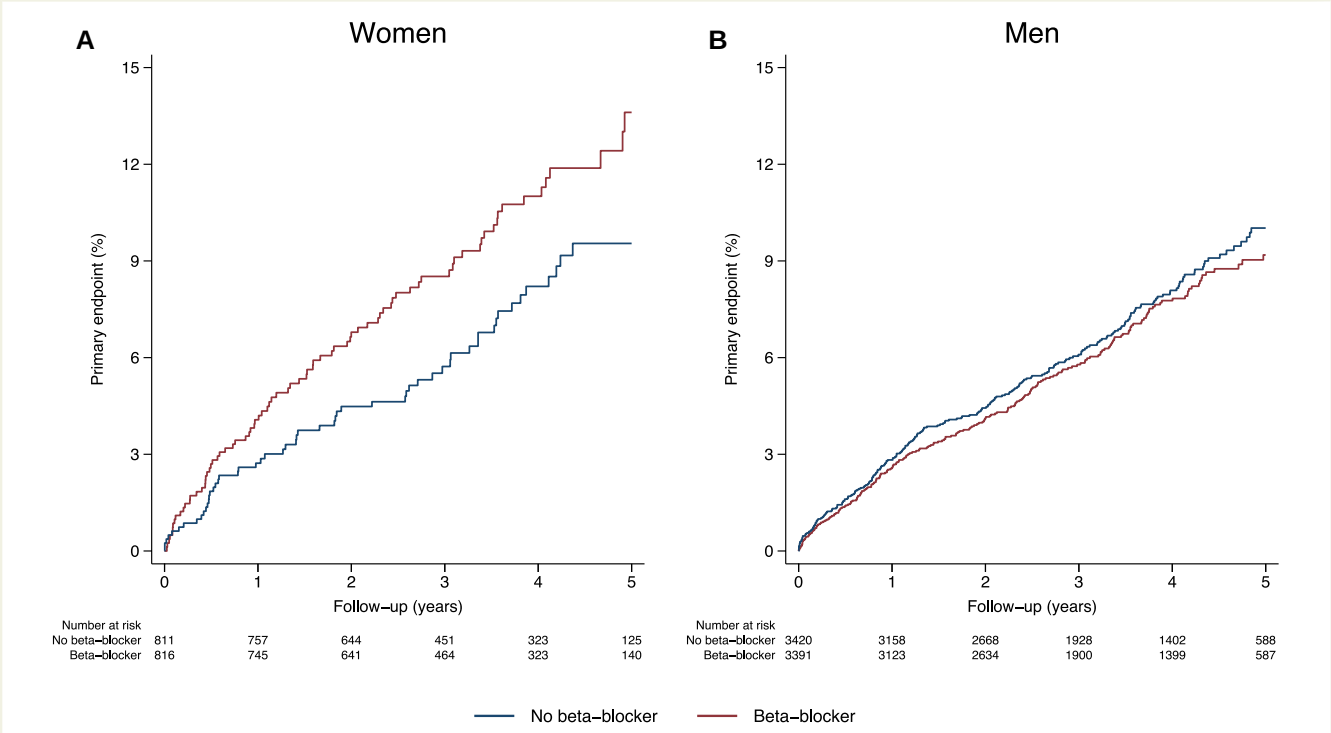


Figure 1 Kaplan–Meier plot for primary endpoint. Panel (*A*) shows the time to first occurrence of the primary composite outcome (all-cause death, non-fatal reinfarction, or heart failure admission) in women, while panel (*B*) shows the same for men. Hazard ratios and 95% confidence intervals are presented in *Table 2*

to no beta-blocker) were included in the study. Compared with men, women were older and had more comorbidities, such as hypertension, diabetes and dyslipidaemia. Women presented more often with NSTEMI (52.9% vs 48.2% in men). Women more frequently presented non-obstructive coronary arteries on index angiography (5.9% vs 1.7% in men) and less frequently underwent revascularization. Compared with men, women were less frequently prescribed with DAPT, statins, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs) and were less frequently referred to cardiac rehabilitation programme. Median dose of prescribed beta-blocker was not different between men and women (see Supplementary data online, *Table S1*). Further details on patient characteristics by sex are shown in *Table 1*. Due to the randomization process, there were not substantial differences between women allocated in the intervention and the control group (*Table 1*).

Primary and secondary endpoints

Overall, the primary composite outcome of all-cause death, non-fatal reinfarction, or HF admission occurred more frequently in women than in men: 140 primary outcome events (25.8/1000 patient-years) vs 483 in men (21.2/1000 patient-years) (unadjusted HR 1.21, 95% CI 1.00–1.46; $P = .04$). Overall, the rate of death was also higher in women (70 deaths, rate 12.5/1000 patient-years vs 244 deaths, 10.5/1000 patient-years in men), although it did not reach statistical significance (HR 1.19, 95% CI .91–1.55; $P = .20$).

Women randomized to beta-blockers had more primary outcome events than those randomized to control: in women, the primary composite endpoint occurred in 83 patients (30.4/1000 patient-years) in the beta-blocker group and 57 patients (21.0/1000 patient-years) in the no beta-blocker group (HR 1.45, 95% CI 1.04–2.03). Conversely, event rate in men in the beta-blocker and control groups was not different: in men, the primary composite endpoint occurred in 233 participants (20.6/1000 patient-years) in the beta-blocker group and 250 patients (21.8/1000 patient-years) in the no beta-blocker group (HR .94, 95% CI .79–1.13). An interaction test suggested heterogeneity in treatment effects across sex categories ($P = .026$). Survival curves for the primary outcome according to sex are shown in *Figure 1*.

Differences in secondary outcomes by sex are presented in *Table 2*, and their survival curves are shown in *Figure 2*. Women randomized to beta-blockers had a higher death rate than those randomized to control: in women, there were 46 deaths (16.3/1000 patient-years) and 24 deaths (8.6/1000 patient-years) in the beta-blocker and no beta-blocker groups, respectively (HR 1.90, 95% CI 1.16–3.12). Conversely, death rate in men was not different across treatment arms: in men, there were 115 deaths (10.0/1000 patient-years) and 129 deaths (11.0/1000 patient-years) in the beta-blocker group and the no beta-blocker group, respectively (HR .91, 95% CI .70–1.16). The interaction test suggested heterogeneity in treatment effects by sex categories ($P = .007$). The difference in treatment effects on all-cause death was driven mainly by cardiac mortality (*Table 2*; P for interaction = .048). There were no relevant by-sex differences in treatment effects in the other secondary endpoints (*Table 2*). The negative effect of beta-blocker therapy on the primary outcome in women was consistent across all key pre-specified subgroups (*Figure 3*). Subgroup analysis of the primary outcome in men is shown in Supplementary data online, *Figure S1*.

Table 2 **Unadjusted analysis of primary, secondary, and tertiary endpoints by sex**

	Women				Men				*P* for interaction
	N (rate per 1000 patient-years)		Rate difference (95% CI)	HR (95% CI)	*N* (rate per 1000 patient-years)		Rate difference (95% CI)	HR (95% CI)	
	Beta-blocker	No beta-blocker			Beta-blocker	No beta-blocker			
Primary endpoint									
All-cause death, non-fatal reinfarction, or heart failure admission	83 (30.4)	57 (21.0)	9.4 (.9, 18.0)	1.45 (1.04, 2.03)	233 (20.6)	250 (21.8)	−1.2 (−5.0, 2.6)	.94 (.79, 1.13)	.026
Secondary endpoints									
All-cause death	46 (16.3)	24 (8.6)	7.71 (1.9, 14.0)	1.90 (1.16, 3.12)	115 (10.0)	129 (11.0)	−1.0 (−3.7, 1.6)	.91 (.70, 1.16)	.0073
Non-fatal reinfarction	35 (12.8)	29 (10.7)	2.10 (−3.6, 7.8)	1.20 (.73, 1.97)	108 (9.5)	114 (9.9)	−.4 (−3.0, 2.2)	.96 (.74, 1.25)	.43
Heart failure admission	12 (4.3)	13 (4.7)	−.4 (−4.0, 3.1)	.91 (.42, 1.99)	27 (2.3)	31 (2.7)	−.3 (−1.6, 1.0)	.88 (.53, 1.48)	.95
Cardiac death	19 (6.7)	8 (2.9)	3.9 (.2, 7.5)	2.34 (1.02, 5.34)	46 (4.0)	49 (4.2)	−.20 (−1.8, 1.4)	.95 (.64, 1.43)	.048
Tertiary safety endpoint									
Admission for stroke	8 (2.9)	2 (.7)	2.1 (−.1, 4.3)	3.95 (.84, 18.61)	29 (2.5)	23 (2.0)	.5 (−.7, 1.8)	1.28 (.74, 2.22)	.15

HRs were estimated using Cox proportional hazards models with an interaction between sex and treatment arm and estimate the effect of taking beta-blocker vs no beta-blocker. *P*-values were calculated using likelihood ratio tests.
CI, confidence interval; HR, hazard ratio.

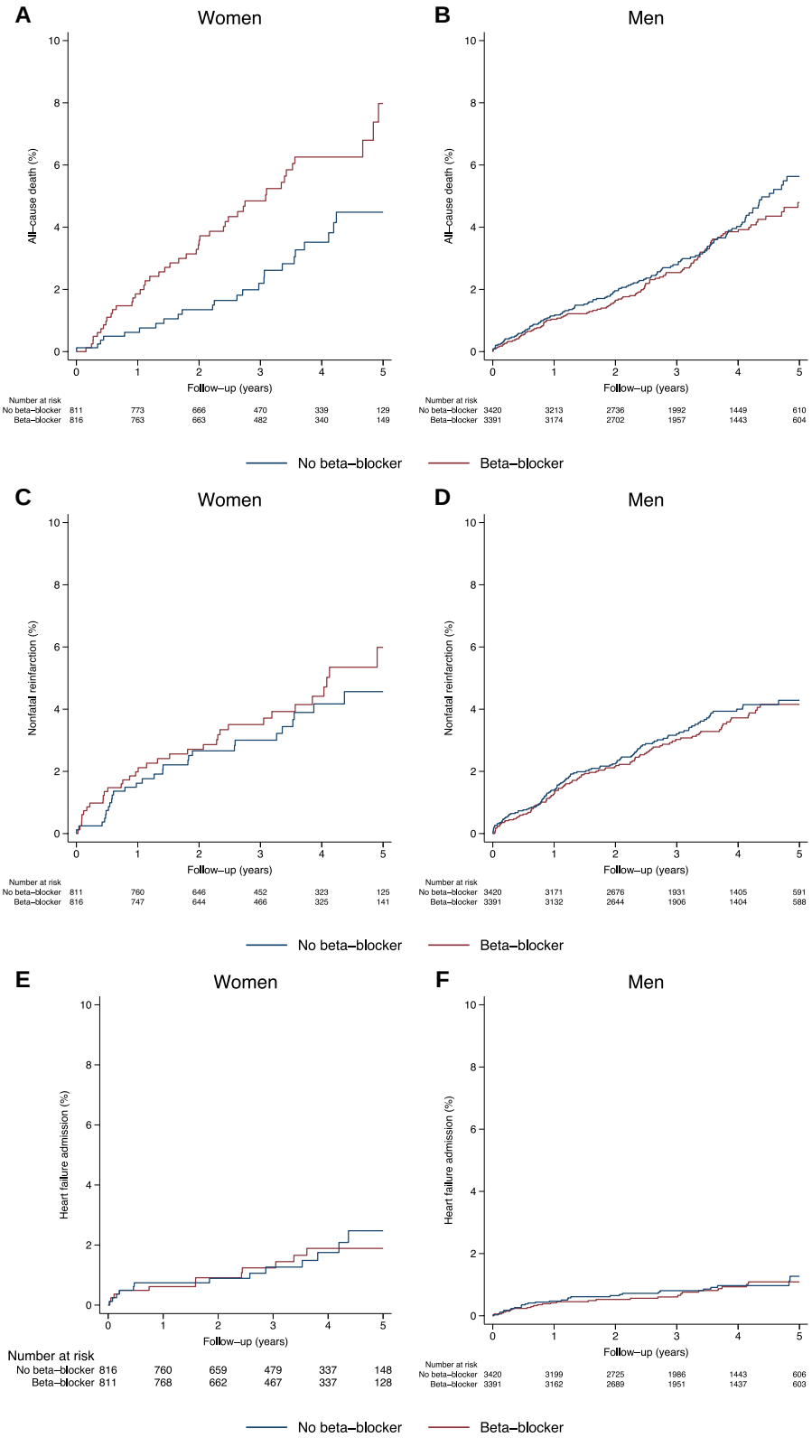


Figure 2 Kaplan–Meier plot for secondary outcomes. (*A* and *B*) Kaplan–Meier plots for the incidence of all-cause death in women (left) and men (right) according to treatment arm (beta-blocker of no beta-blocker) (control). (*C* and *D*) Kaplan–Meier plots for the incidence of reinfarction in women (left) and men (right) according to treatment arm (beta-blocker of no beta-blocker) (control). (*E* and *F*) Kaplan–Meier plots for the incidence of heart failure admission in women (left) and men (right) according to treatment arm (beta-blocker of no beta-blocker) (control). Hazard ratios and 95% confidence intervals are presented in *Table 2*

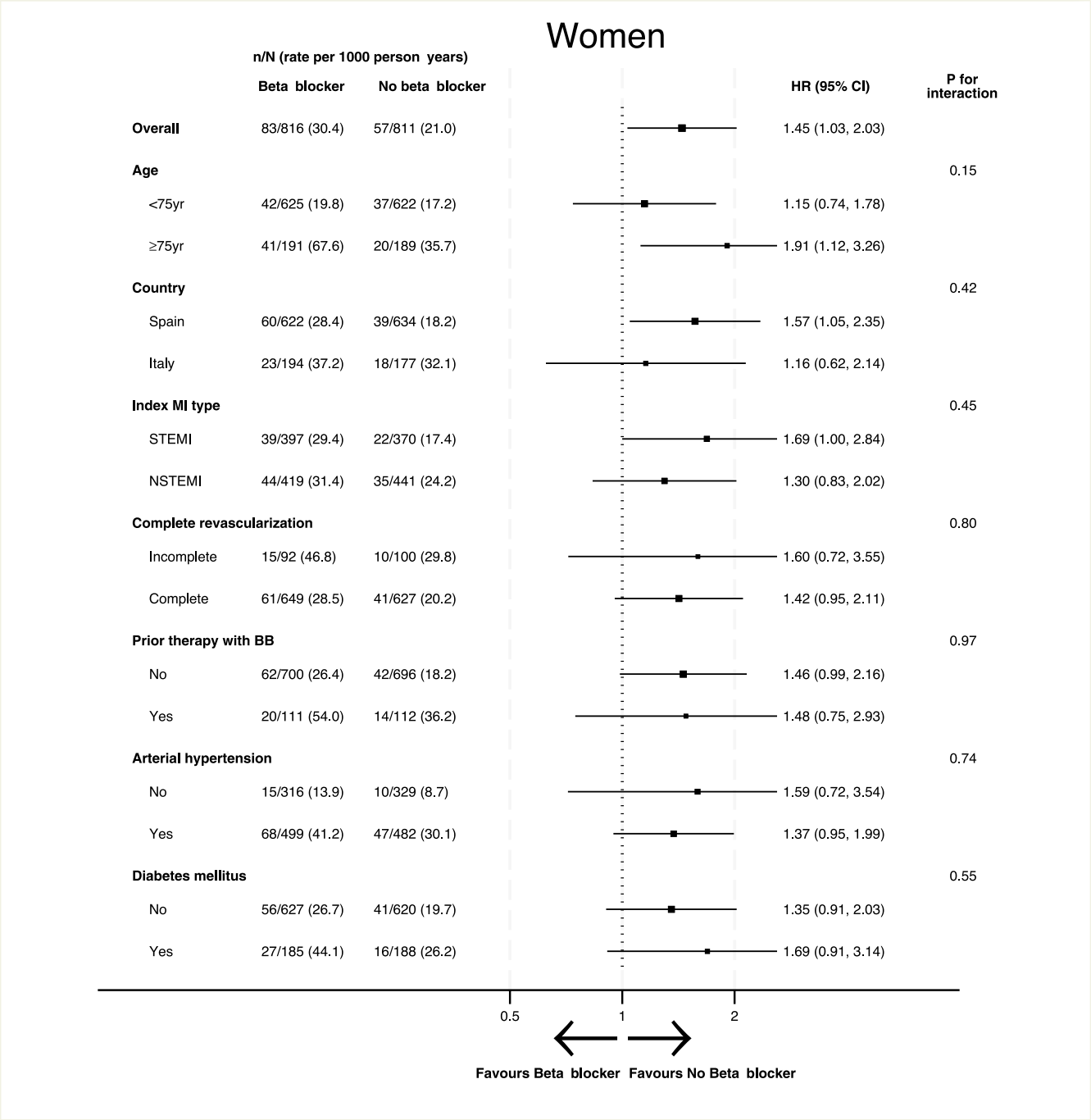


Figure 3 Subgroup analysis of the primary composite outcome all-cause death, non-fatal reinfarction and heart failure admission in women. MI, myocardial infarction; BB, beta-blockers

Sensitivity analysis

The interaction between sex and beta-blocker effect was further evaluated in adjusted models for the primary and secondary endpoints (*Table 3*; Supplementary data online, *Figure S2*), showing overall consistent findings.

An assessment of the crossovers by sex and treatment arm was also evaluated. At 15 months, 15.6% of women and 17.2% of men in the beta-blocker group were no longer receiving the intervention, while 25.8% of women and 20.6% of men in the no beta-blocker group were started on beta-blockers. However, per-protocol analyses showed consistent findings (see Supplementary data online, *Table S2*).

Effect of beta-blockers in women and men with mildly reduced ejection fraction

Both women and men with mildly reduced LVEF showed a consistent lack of treatment effect of beta-blockers on the primary endpoint. However, for those with preserved LVEF (*Figure 4*), there was evidence

Table 3 Adjusted analysis of primary and secondary endpoints by sex

	Women				Men				*P* for interaction
	N (rate per 1000 patient-years)		Rate difference (95% CI)	HR (95% CI)	N (rate per 1000 patient-years)		Rate difference (95% CI)	Adj HR (95% CI)	
	Beta-blocker	No beta-blocker			Beta-blocker	No beta-blocker			
Primary endpoint									
All-cause death, non-fatal reinfarction, and heart failure admission	83 (30.4)	57 (21.0)	9.4 (.9, 18.0)	1.42 (1.01, 1.99)	233 (20.6)	250 (21.8)	−1.2 (−5.0, 2.6)	.92 (.77, 1.09)	.024
Individual components									
All-cause death	46 (16.3)	24 (8.6)	7.7 (1.9, 13.5)	1.83 (1.11, 3.00)	115 (10.0)	129 (11.0)	−1.0 (−3.7, 1.6)	.87 (.68, 1.12)	.0075
Cardiac death	19 (6.7)	8 (2.9)	3.9 (.2, 7.5)	2.18 (.95, 4.98)	46 (4.0)	49 (4.2)	−.2 (−1.8, 1.4)	.93 (.62, 1.39)	.062
Non-cardiac death	27 (9.6)	16 (5.7)	3.8 (−.7, 8.4)	1.65 (.89, 3.07)	69 (6.0)	80 (6.8)	−.8 (−2.9, 1.2)	.84 (.61, 1.15)	.053
Non-fatal reinfarction	35 (12.8)	29 (10.7)	2.1 (−3.6, 7.8)	1.21 (.74, 1.99)	108 (9.5)	114 (9.9)	−.4 (−3.0, 2.2)	.94 (.72, 1.23)	.38
Heart failure admission	12 (4.3)	13 (4.7)	−.4 (−3.9, 3.1)	.87 (.39, 1.92)	27 (2.3)	31 (2.7)	−.3 (−1.6, 1.0)	.87 (.52, 1.46)	1.00

HRs were estimated using Cox proportional hazards models with an interaction between sex and treatment arm and estimate the effect of taking beta-blocker vs no beta-blocker. HRs were adjusted for age, prior myocardial infarction, haemoglobin, oral anticoagulant at discharge, prior stroke, diabetes mellitus, prior chronic obstructive pulmonary disease, peripheral artery disease, and estimated glomerular filtration rate. *P*-values were calculated using likelihood ratio tests.
CI, confidence interval; HR, hazard ratio.

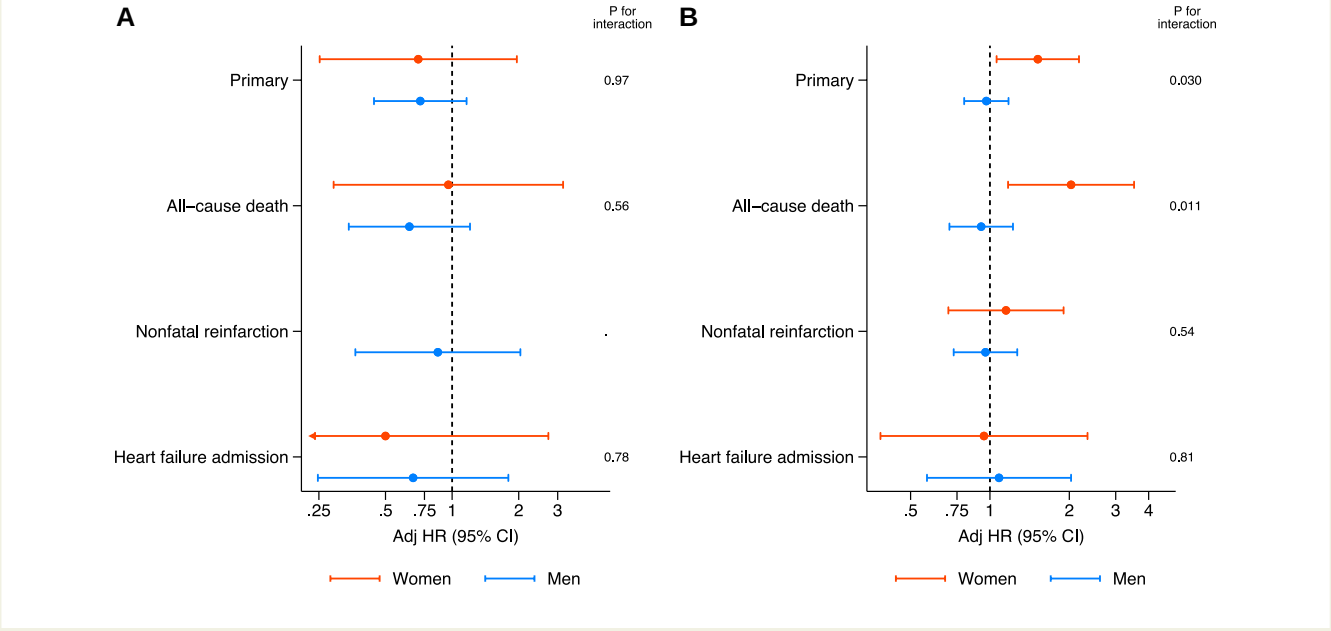


Figure 4 Treatment effect by left ventricular ejection fraction. Forest plot showing estimates for different outcomes in women and men for patients with left ventricular ejection fraction 41–49% (left) and ≥50% (right). Estimates to the left of the vertical line (hazard ratio < 1) indicate lower event rates with beta-blocker therapy, whereas estimates to the right (hazard ratio > 1) indicate higher event rates with beta-blocker therapy

of treatment heterogeneity by sex (*P* for interaction = .030). Women on beta-blockers were at higher risk than those in control, while there was no effect observed in men.

Impact of beta-blocker dose on primary outcomes in women and men

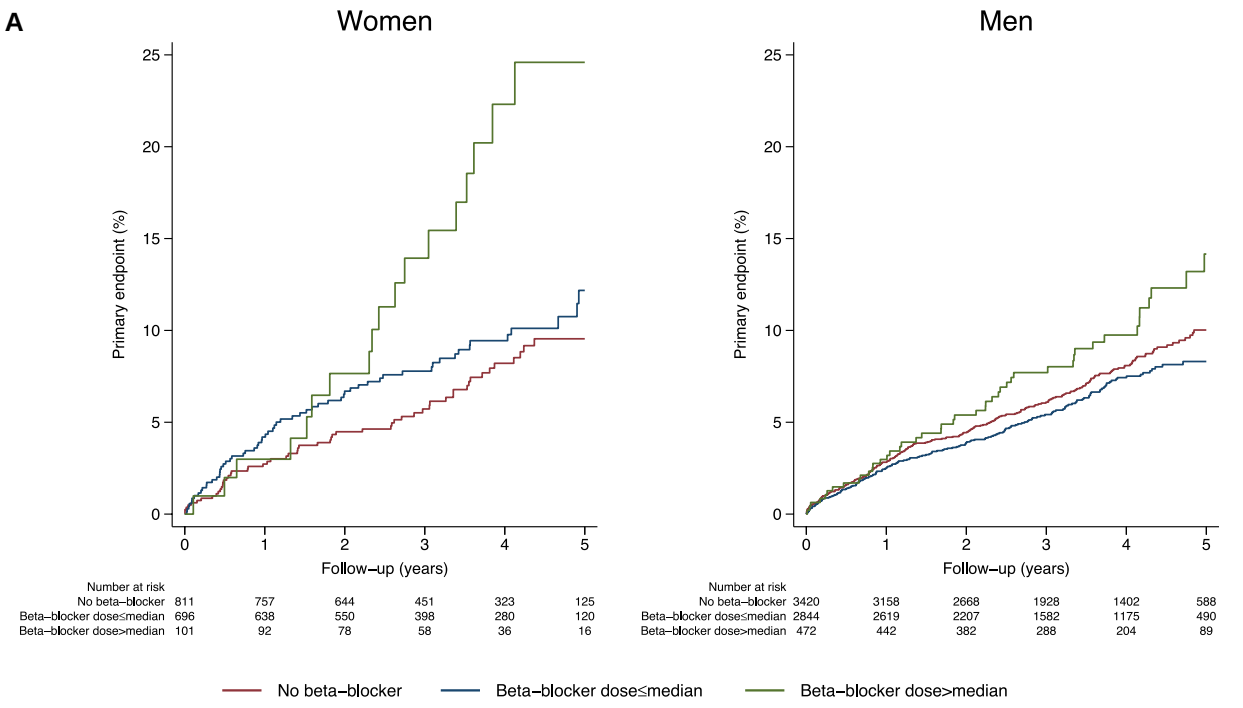
A *post hoc* analysis revealed treatment heterogeneity for the primary endpoint based on beta-blocker dose (*Figure 5*). Among women, there were 64 events (27.4 per 1000 patient-years) in those receiving beta-blocker doses below the median and 18 events (54.2 per 1000 patient-years) in those receiving doses above the median. Compared with women not receiving beta-blockers, the HRs were 1.31 (95% CI .91–1.87) and 2.58 (95% CI 1.52–4.39), respectively. These dose-related differences were not observed in men (*Figure 5*). The interaction test indicated a significant heterogeneity in treatment effect by sex (*P* = .045).

Discussion

In this pre-specified analysis of the REBOOT trial including 8438 MI patients with LVEF >40% (1627 women), we assessed sex differences in the effect of beta-blocker therapy on the primary composite outcome of all-cause death, MI, or HF hospitalization, as well as on secondary and safety endpoints. The main findings are summarized as follows: (i) women had a higher cardiovascular risk profile than men, being older and presenting with a greater burden of comorbidities. They also more frequently presented with NSTEMI. Despite highly significant, these differences were small in absolute numbers; (ii) women more often had MI without obstructive coronary arteries (6% vs 2% in men) and were less frequently revascularized; (iii) although the overall prescription rates of guideline-directed secondary prevention therapies were high in both sexes, women were less frequently prescribed DAPT, statins, and ACEi/ARBs and were less often referred to cardiac rehabilitation programmes; (iv) over a median follow-up of 3.7 years, women experienced a 21% higher rate of the primary composite endpoint (death, MI, or HF hospitalization) compared with men; (v) a significant interaction was observed between sex and treatment allocation. Women randomized to beta-blockers had a 45% higher relative risk (corresponding to an excess absolute risk of approximately .9% per year) of the primary composite outcome compared with those in the control group, mainly driven by increased all-cause mortality. These findings were consistent after adjustment for potential confounders and in per-protocol analyses and remained across all subgroup analyses. In contrast, no excess risk was observed in men receiving beta-blockers; and (vi) the potential harm associated with beta-blockers in women appeared to be confined to those with preserved LVEF and those receiving higher beta-blocker doses—patterns not observed in men (*Structured Graphical Abstract*).

The primary outcome of the REBOOT trial (composite of death, MI, or HF) was selected because it captures all possible mechanisms associated with a potential benefit of beta-blockers. All-cause mortality was prioritized to capture both cardiovascular and potential non-cardiac effects of beta-blockers, given prior reports of harm (e.g. increased stroke-related mortality in POISE).[21] Cardiac death was pre-specified as a key secondary outcome, and differences in mortality in REBOOT appeared mainly driven by cardiac causes. Heart failure was included based on strong evidence of beta-blocker benefit in patients with prior HF or reduced LVEF, and the trial population included patients with mildly reduced LVEF. Reinfarction, rather than all ACS hospitalizations, was chosen because unstable angina is harder to adjudicate and accounts for a minority of ACS events.

Most randomized controlled trials evaluating the role of beta-blockers in post-MI patients have not demonstrated sex-related heterogeneity in treatment effects. However, unlike REBOOT, the



B

	Women			Men			
	No. patients	No. event (rate per 1000 person-years)	HR (95% CI)	No. patients	No. events (rate per 1000 person-years)	HR (95% CI)	P for interaction
No beta-blocker	811	57 (21.0)	Reference group	3420	250 (21.8)	Reference group	0.045
Beta-blocker dose<=median	696	64 (27.4)	1.31 (0.91, 1.87)	2844	182 (19.3)	0.88 (0.73, 1.07)	
Beta-blocker dose>median	101	18 (54.2)	2.58 (1.52, 4.39)	472	47 (28.5)	1.31 (0.96, 1.79)	

Figure 5 Treatment effect by beta-blocker dose. (*A*) Kaplan–Meier plots for the incidence of the primary composite endpoint of death, reinfarction, or heart failure admission in women (left) and men (right) according to beta-blocker dose. (*B*) Event rate and hazard ratio for women and men according to beta-blocker dose

majority of these trials were conducted in an era of limited therapeutic options for MI and generally found beta-blockers to be beneficial overall.[22] The present findings are unique in that they derive from a contemporary cohort managed according to current standards of care. Although the REDUCE-AMI trial produced results broadly consistent with those of REBOOT, it did not detect a significant interaction between sex and beta-blocker therapy.[15] Several factors may account for this discrepancy, differences in the predominant beta-blocker used (bisoprolol in REBOOT vs metoprolol in REDUCE-AMI), the sample size of women enrolled (1627 in REBOOT vs 1131 in REDUCE-AMI), and the inclusion criteria regarding LVEF (>40% in REBOOT vs >50% in REDUCE-AMI). Another trial testing beta-blockers in post-MI patients [ABYSS (Assessment of Beta-Blocker Interruption 1 Year after an Uncomplicated Myocardial Infarction on Safety and Symptomatic Cardiac Events Requiring Hospitalization) trial] did not found a significant interaction between sex and the effect of the intervention.[23] However, ABYSS tested a different question: does beta-blocker withdrawal years after infarction is non-inferior to continue them? ABYSS randomized 3698 patients with LVEF ≥ 40%, who were on beta-blockers for a median of 2.9 years after MI, to stop or continue them.[23] In ABYSS, the primary outcome (composite of all-cause death, non-fatal MI, non-fatal stroke, or hospitalization for a cardiovascular cause) occurred more frequently in the discontinuation group than in those who continued beta-blockers (HR 1.16; 95% CI 1.01–1.33). These differences were mostly driven by the hospitalization for cardiovascular cause. There were no differences in the individual endpoints of death, MI, or stroke between groups. A pre-specified subgroup analysis in ABYSS trial did not reveal heterogeneity in the primary outcome between women and men. However, interpreting this apparent lack of heterogeneity is challenging in the context of our study, as neither our primary outcome (death, MI, or HF) nor individual components were stratified by sex in the ABYSS trial. Moreover, in our study, the Kaplan–Meier curves in women show progressive separation between treatment arms from randomization to Year 3, remaining parallel thereafter. Since ABYSS enrolled patients nearly 3 years post-MI, a selection bias may have occurred. Women who experienced adverse outcomes while on beta-blockers early after MI—and any potential early harmful effect of beta-blocker therapy—may have been underrepresented or missed. Observational studies have similarly failed to provide robust evidence of sex-related treatment differences.[24,25] One exception is a large Canadian cohort of 33 811 patients with prior MI, which found no association between beta-blocker use and reduced risk of the composite endpoint of death, MI, or angina. Notably, there was a trend towards a significant sex interaction, suggesting potentially worse outcomes among women receiving beta-blockers compared with men.[26] Several pharmacokinetic studies have shown that, at equivalent doses, women exhibit higher peak plasma concentrations of beta-blockers than men.[5,16] This can be attributed to physiological differences: women typically have lower body weight, a higher proportion of body fat, and reduced plasma volume, factors that together lead

to longer drug half-lives for lipophilic agents and higher peak concentrations for hydrophilic drugs.[27] Additionally, women tend to have lower cardiac output, which contributes to reduced hepatic blood flow and glomerular filtration rates, and they also express lower levels of certain cytochrome P450 isoenzymes, further contributing to altered drug metabolism and higher systemic drug levels.[27]

Interestingly, clinical studies have demonstrated that women experience greater reductions in heart rate and blood pressure compared with men when treated with similar doses of beta-blockers.[3,4] Women generally have smaller left ventricular cavity sizes compared with men. Prior studies have demonstrated that reduced left ventricular dimensions are associated with poorer functional capacity in patients with HF and preserved LVEF.[28] It is therefore plausible that beta-blocker therapy may exert detrimental effects in women with smaller left ventricular cavities. Consistent with these observations, our study found that women (with theoretically smaller left ventricular cavity sizes) receiving higher beta-blocker doses had an increased risk of the primary composite endpoint compared with those not on beta-blockers—a pattern not observed in men.

In patients with HF and reduced LVEF, robust evidence suggests that women may derive optimal benefit from lower doses of ACEi, ARBs, and beta-blockers compared with men and from doses lower than those recommended in current HF guidelines.[16] However, similar data are scarce for patients with MI. For instance, in a cohort of hypertensive patients with a prior MI, beta-blocker therapy was associated with a higher incidence of HF in women than in men.[29] In the SWEDEHEART registry, which included first-time MI patients on beta-blockers, no difference in cardiovascular outcomes was observed between patients receiving ≥50% vs <50% of the target dose. Notably, among those treated, women had a higher 1-year risk of death or MI compared with men.[30] Similarly, in the OBTAIN (Outcomes of Beta-Blocker Therapy After Myocardial Infarction) registry, which included 3004 1-year post-MI survivors (regardless of LVEF, with a mean of 50%), lower beta-blocker doses appeared more beneficial, while higher doses did not confer additional advantage.[31]

In our study, among patients with mildly reduced LVEF (41%–49%), we did not observe a significant interaction between sex and beta-blocker use. Notably, women within this subgroup had numerically fewer events when treated with beta-blockers, in contrast to women with preserved LVEF, who exhibited higher event rates under beta-blocker therapy. While these findings are hypothesis-generating and the study was underpowered to draw definitive conclusions, the observation is biologically plausible. Indeed, sex-specific interactions between the benefits of neurohumoral modulators and LVEF have been described in HF populations. Foundational HF drugs demonstrated clear benefit in patients with reduced LVEF, diminished benefit in those with LVEF 35%–60%, and no benefit in those with high-normal LVEF (>60%).[32] These sex-specific differences may be partially explained by smaller left ventricular cavity sizes in women. Whether this principle extends to post-MI women treated with beta-blockers is supported by our data as a plausible hypothesis, though it remains speculative at this stage.

Our study underscores the importance of women-centred analysis in clinical research studies,[17] given that the number of women has been historically small in randomized controlled trials[11] and that this new evidence may derive in further actionable data.[33] Despite women and men differ with respect to baseline risk, causes, and prognosis of MI, current guidelines do not differentiate between the use of beta-blockers in women and men. Although based on a subgroup analysis, our study provides robust evidence of an interaction between sex and beta-blocker therapy and suggests and increased risk of the composite endpoint of all-cause death, MI, or HF hospitalization, mainly in women with preserved LVEF receiving higher doses of beta-blockers. This finding is mostly driven by the hardest clinical outcome (all-cause death). Notably, we have found that women received less guideline-based secondary prevention interventions. Given the pragmatic nature of the study, these differences reflect real practice. The reasons for these differences are unclear but the higher prevalence of MI without obstructive lesions (5.9% vs 1.7%) in women might partially explain them. The significant interaction between sex and beta-blocker effect was still significant if the model was adjusted for these secondary prevention interventions.

In the REBOOT trial, the most commonly prescribed beta-blocker was bisoprolol, followed by metoprolol. This prescribing pattern aligns with other contemporary pragmatic studies, including the ABYSS and REDUCE-AMI trials.[15,23] Notably, before REBOOT, REDUCE-AMI, and ABYSS, there were no trials testing bisoprolol in the post-MI setting.[34] Furthermore, the largest trial investigating metoprolol in MI patients—the COMMIT—yielded neutral results; however, this study tested an acute beta-blocker strategy (intravenous administration followed by oral therapy) and limited follow-up to the in-hospital period.[35]

The recent trials evaluating beta-blockers, including REBOOT, were designed to be pragmatic, allowing treating physicians to select both the type and dose of beta-blocker, thereby reflecting real-world clinical practice. The smaller CAPITAL-RCT trial, which also reflected contemporary MI management, randomized patients specifically to carvedilol or control and found no clinical benefit with carvedilol.[36] Whether the efficacy—or lack thereof—of beta-blocker maintenance therapy after MI represents a class effect remains an open question.[34]

Limitations

REBOOT was an open-label trial; however, blinded central adjudication of events partially mitigates this limitation. Given the pragmatic design of the trial, placebo was not used as comparator. Subgroup analyses are generally considered exploratory and hypothesis-generating findings.[37] REBOOT was adequately powered to test the primary hypothesis, and any significant finding in subgroup analyses might result from the play of chance. Moreover, no adjustment of multiplicity was performed, as pre-specified in our statistical analysis plan.[38] However, it should be noted that the consistency of our findings in the per-protocol assessment, which is less well-powered, strengthens our results. Moreover, this is the largest cohort of women randomized to beta-blockers and therefore the most reliable source of data to date. Although we adjusted for prognostic predictors, we cannot rule out some residual confounding.

Conclusions

In this pre-specified analysis of the REBOOT trial, which includes the largest cohort of post-MI women randomized to beta-blockers, we observed an excess absolute risk of approximately .9% per year for the composite endpoint of all-cause death, MI, or HF hospitalization among women receiving beta-blockers compared with those not receiving them. Other contemporaneous trials did not find such an interaction between sex and the effect of beta-blockers on the primary outcome of their trials. Although hypothesis-generating, the detrimental effects of beta-blockers seem to concentrate on those women with preserved LVEF and those receiving higher doses of beta-blockers. These

associations were not observed in men. Further analysis of existing data and new prospective research is needed to confirm these associations.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

Data and code are available upon reasonable request.

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Ethical Approval

The study protocol was approved by the relevant ethics committees in Spain (EC79-17/FJD) and Italy (Reg. sperimentazioni n.2085, Prot. 9144/2018; I.5/109).

Pre-registered Clinical Trial Number

ClinicalTrials.gov identifier: NCT03596385; European Clinical Trials Database number: 2017-002485-40.

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