Beta-blockers in patients with preserved left ventricular systolic function after AMI did not improve clinical outcomes

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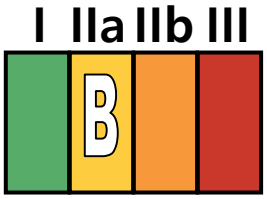
Disclosure of Interest

- This study was supported by Research Fund of Korea Center for Disease Control and Prevention.

- All investigators; Nothing to disclose

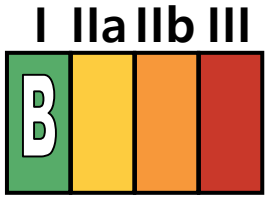
Recommendations of Beta-Blockers in STEMI

ESC guideline (*Eur Heart J.* 2012;33, 2569-2619)



Oral treatment of beta-blockers should be considered during hospital stay and continued thereafter in all STEMI patients without contraindications.

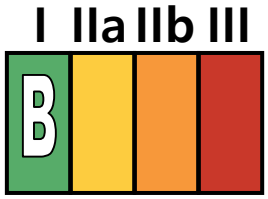
ACC/AHA guideline (*Circulation.* 2013;127:529-555)



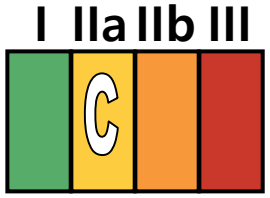
Beta blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use.

Recommendations of Beta-Blockers in NSTEMI

ACC/AHA guideline (*Circulation.* 2014;130:2354-94)



In patients with concomitant NSTE-ACS, *stabilized* HF, and reduced systolic function, it is recommended to continue beta-blocker therapy with 1 of the 3 drugs proven to reduce mortality in patients with HF: sustained-release metoprolol succinate, carvedilol, or bisoprolol.



It is reasonable to continue beta-blocker therapy in patients with normal LV function with NSTE-ACS.

Recent Observational Studies and Meta-Analysis about Beta-Blockers in AMI

- β-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease (*Bangalore S et al. JAMA.* 2012;308:1340-9)

  In this observational study of patients with either CAD risk factors only, known prior MI, or known CAD without MI, the use of β-blockers was not associated with a lower risk of composite cardiovascular events.

- Clinical outcomes with β-blockers for myocardial infarction: a meta-analysis of randomized trials (*Bangalore S et al. Am J Med.* 2014;127:939-53)

  In the reperfusion era, β-blockers were associated with no mortality benefit at most time points except MI and angina at 30 days, a significant increase in HF, cardiogenic shock at 30 days and between 30 days and 1 year.

Recommendations of Beta-Blockers in AMI

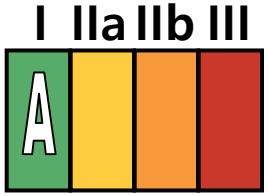
ESC NSTEMI guideline (*Eur Heart J.* 2016;37, 267-315)

Beta-blocker therapy is recommended in patients with LVEF ≤40%, unless contraindicated.

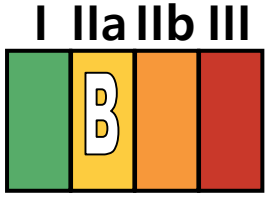
c.f) Beta-blocker after NSTE-ACS and no reduced LV function or HF

In a large-scale observational study, beta-blocker use was not associated with a lower risk of CV events or mortality.

ESC STEMI guideline (*Eur Heart J.* 2017)



Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF ≤ 40% unless contraindicated.



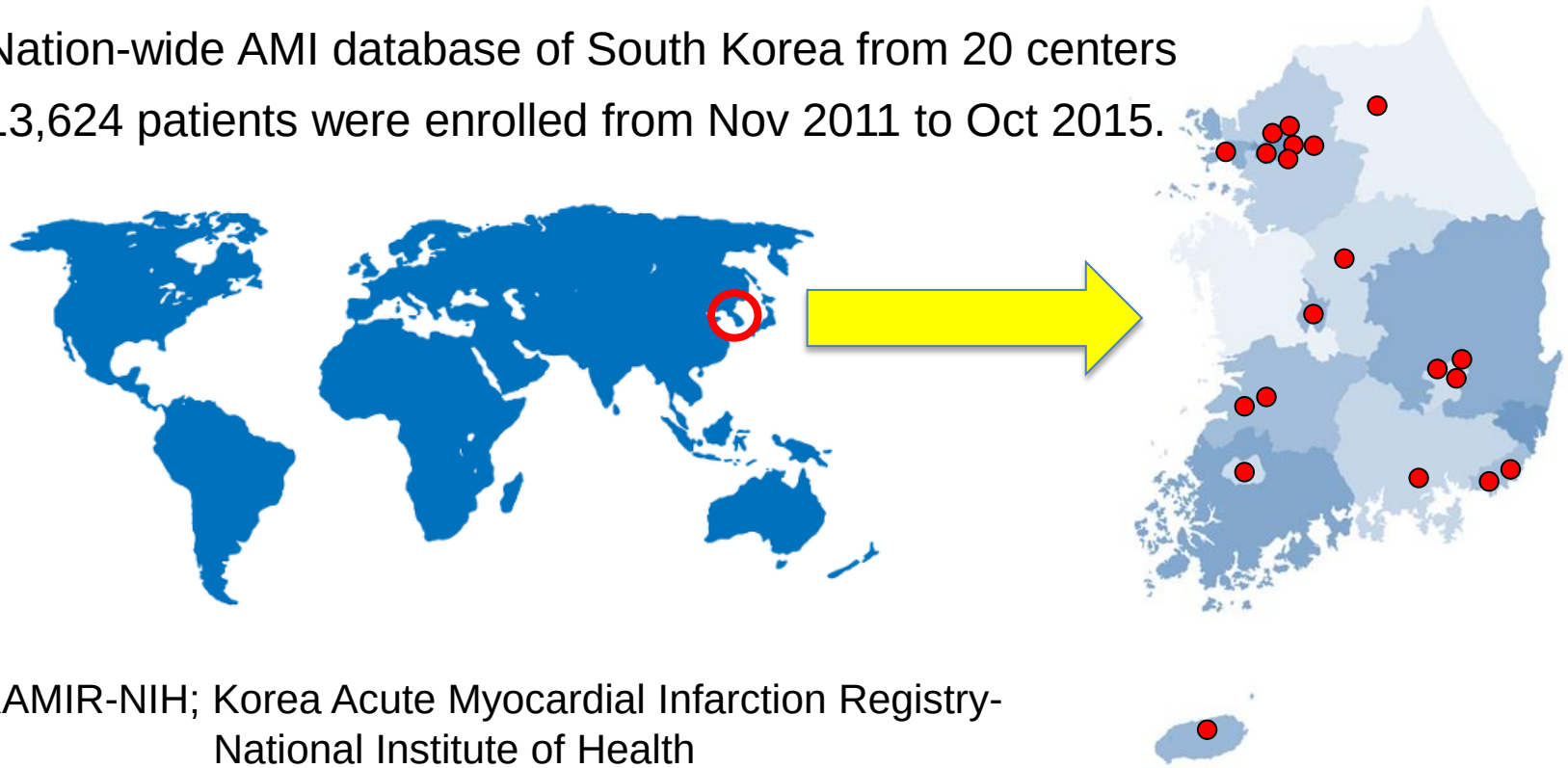
Routine oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications

Background and Purposes

- Current guidelines recommend early administration of β-blockers after acute myocardial infarction (AMI), but the evidence for their beneficial effects is based on early studies in the era of little usages of current evidence-based interventional or medical therapies.
- This study aimed to investigate the long-term clinical effects of β-blockers in patients with AMI, who survived the initial attack and, especially had preserved left ventricular ejection fraction.

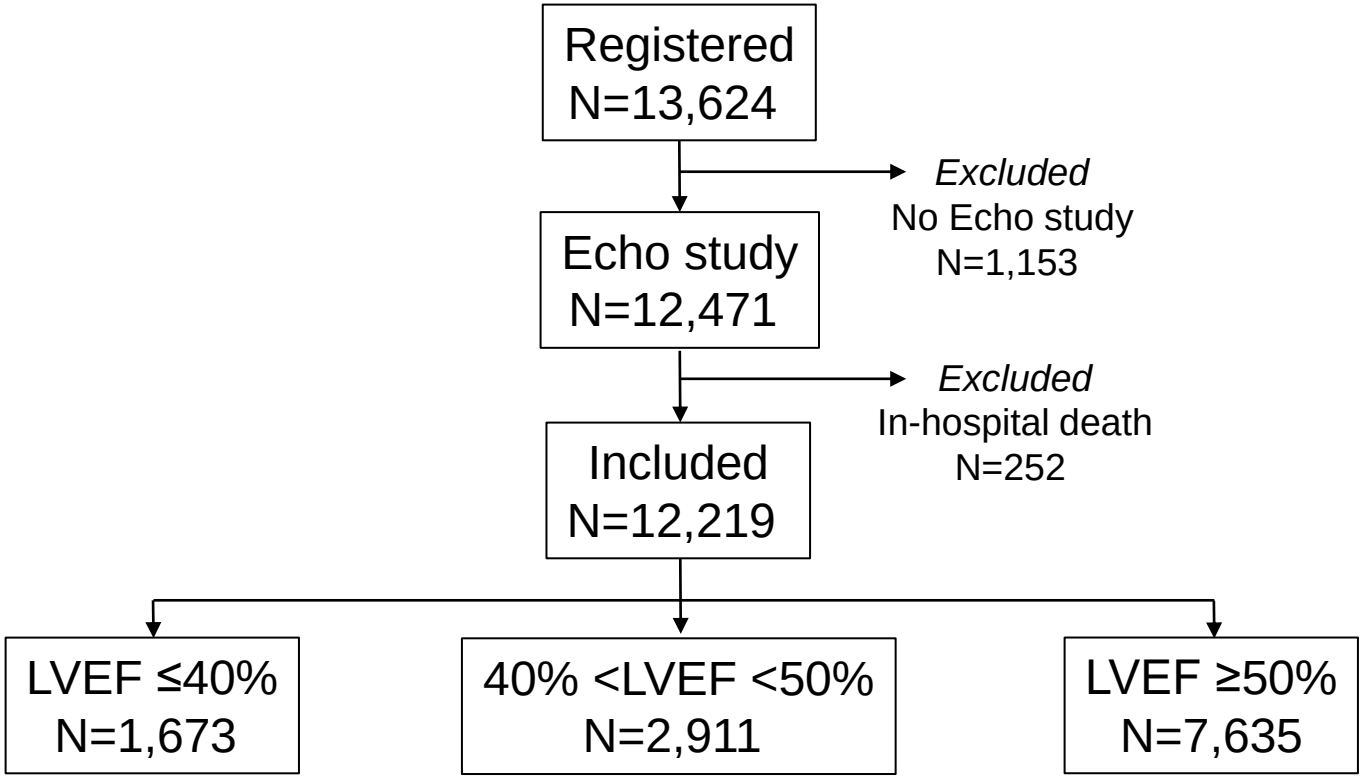
The KAMIR-NIH Registry

- Nation-wide AMI database of South Korea from 20 centers
- 13,624 patients were enrolled from Nov 2011 to Oct 2015.



*KAMIR-NIH; Korea Acute Myocardial Infarction Registry-National Institute of Health

Inclusion of Patients



*LVEF; left ventricular ejection fraction

Primary End-points

- 1-year major adverse cardiac events (MACE)

  A composite of

  - Cardiac death,
  - Myocardial infarction,
  - Revascularization,
  - Re-admission due to heart failure
  - Stent thrombosis

Baseline Characteristics of Patients

	With beta-blockers (N=10,265)	Without beta-blockers (N=1,954)	*P* value
Age (years)	63.3±12.5	65.6±12.9	<0.001
Male	7,664 (74.7%)	1,416 (72.5%)	0.044
Body mass index (kg/m^2)	24.15±3.29	23.53±3.38	<0.001
Hypertension	5,242 (51.1%)	930 (47.6%)	0.005
Diabetes mellitus	2,908 (28.3%)	510 (26.1%)	0.045
Hyperlipidemia	1,185 (11.5%)	204 (10.4%)	0.163
Prior angina pectoris	910 (8.9%)	253 (12.9%)	<0.001
Prior myocardial infarction	769 (7.5%)	167 (8.5%)	0.113
Prior heart failure	138 (1.3%)	43 (2.2%)	0.004
Prior stroke	677 (6.6%)	123 (6.3%)	0.651
Current smoker	4,125 (40.2%)	728 (37.3%)	0.016
Killip class ≥II	1,981 (19.3%)	460 (23.5%)	<0.001
CKD stage ≥3	1,791 (17.4%)	426 (21.8%)	<0.001
NSTEMI	5,179 (50.5%)	1,204 (61.6%)	<0.001
Successful PCI	9459 (92.7%)	1457 (74.6%)	<0.001
Coronary bypass graft	122 (1.2%)	42 (2.1%)	0.001

CKD; chronic kidney disease, NSTEMI; non-ST elevation myocardial infarction, PCI; percutaneous coronary intervention

Medications Other Than Beta-blockers

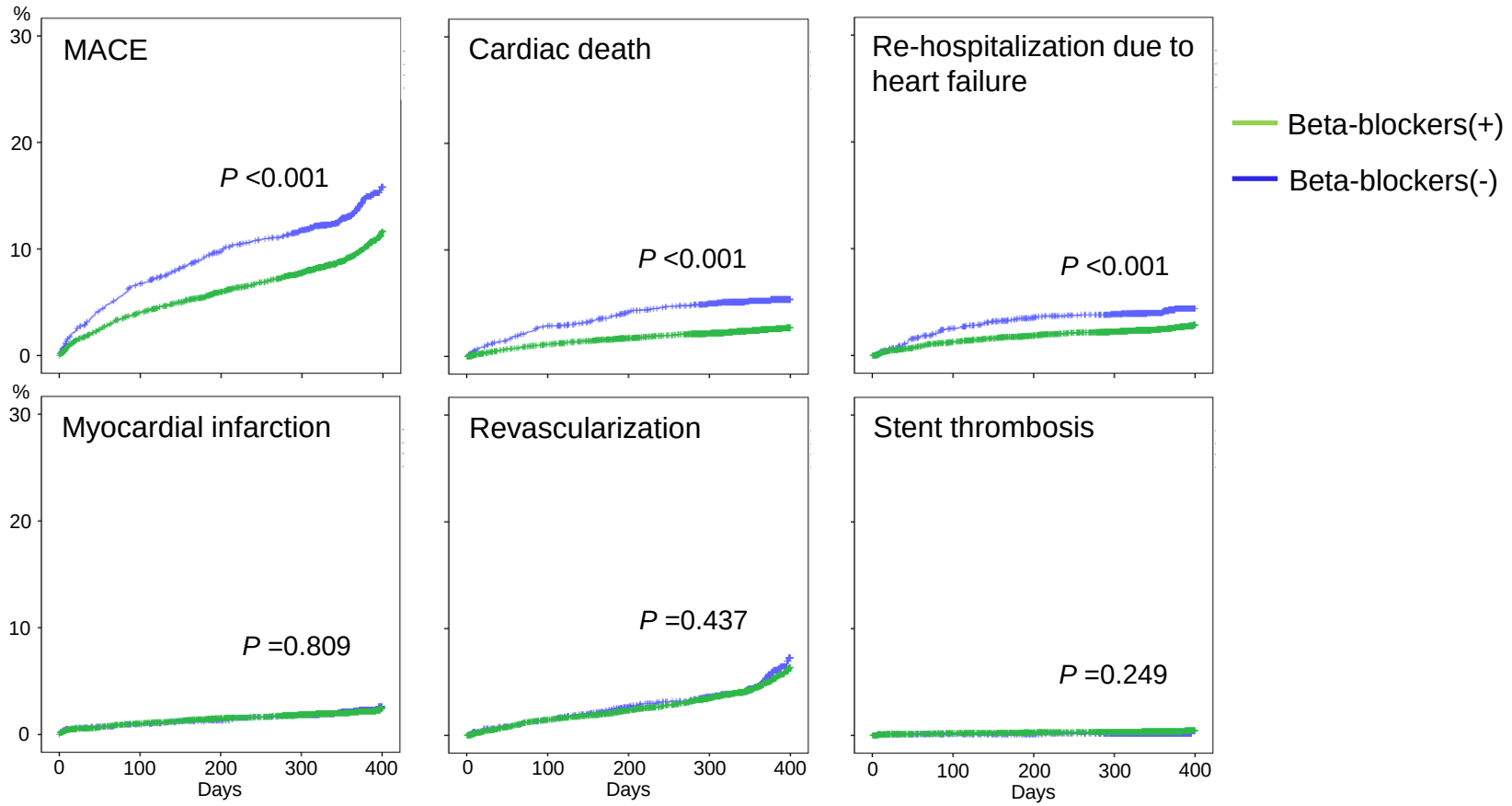
	With beta-blockers (N=10,265)	Without beta-blockers (N=1,954)	*P* value
Aspirin	10,249 (99.8%)	1,930 (98.8%)	<0.001
Clopidogrel	8,001 (77.9%)	1,546 (79.1%)	0.257
Prasugrel	1,314 (12.8%)	194 (9.9%)	<0.001
Ticagrelor	2,335 (22.7%)	450 (23.0%)	0.793
P2Y12 inhibitors	10,000 (97.4%)	1,685 (86.2%)	<0.001
Calcium channel blockers	583 (5.7%)	489 (25.0%)	<0.001
ACE inhibitors	5,329 (51.9%)	478 (24.5%)	<0.001
ARB	3,409 (33.2%)	599 (30.7%)	0.028
RAS inhibitors	8,673 (84.5%)	1,071 (54.8%)	<0.001
Statins	9,738 (94.9%)	1,694 (86.7%)	<0.001
Oral anticoagulants	308 (3.0%)	84 (4.3%)	0.003

ACE; angiotension-converting enzyme, ARB; angiotensin receptor blocker, RAS; renin-angiotensin system

Discontinuation of Beta-Blockers

- 1-year follow-up rate
  - Patients with beta-blockers; 96.6%
  - Patients without beta-blockers; 95.8%
- Discontinuation in patients with beta-blockers at discharge
  - 1,419/9,404 patients (15.1%) **data availability 91.6%*
- New-start in patients without beta-blockers at discharge
  - 590/1,704 patients (34.6%) **data availability 87.2%*

Beta-blockers reduced cardiac death and re-hospitalization due to heart failure



Beta-blockers reduced MACE, cardiac death and re-hospitalization due to heart failure

	HR	95% CI	*P* value
MACE	0.683	0.596 - 0.782	<0.001
Cardiac death	0.468	0.371 - 0.591	<0.001
Re-hospitalization due to HF	0.602	0.467 - 0.776	<0.001
Myocardial infarction	0.960	0.687 - 1.341	0.809
Revascularization	0.918	0.740 - 1.139	0.438
Stent thrombosis	1.815	0.649 - 5.078	0.256

CI; confidence interval, HF; heart failure, HR; hazard ratio, MACE; major adverse cardiac events

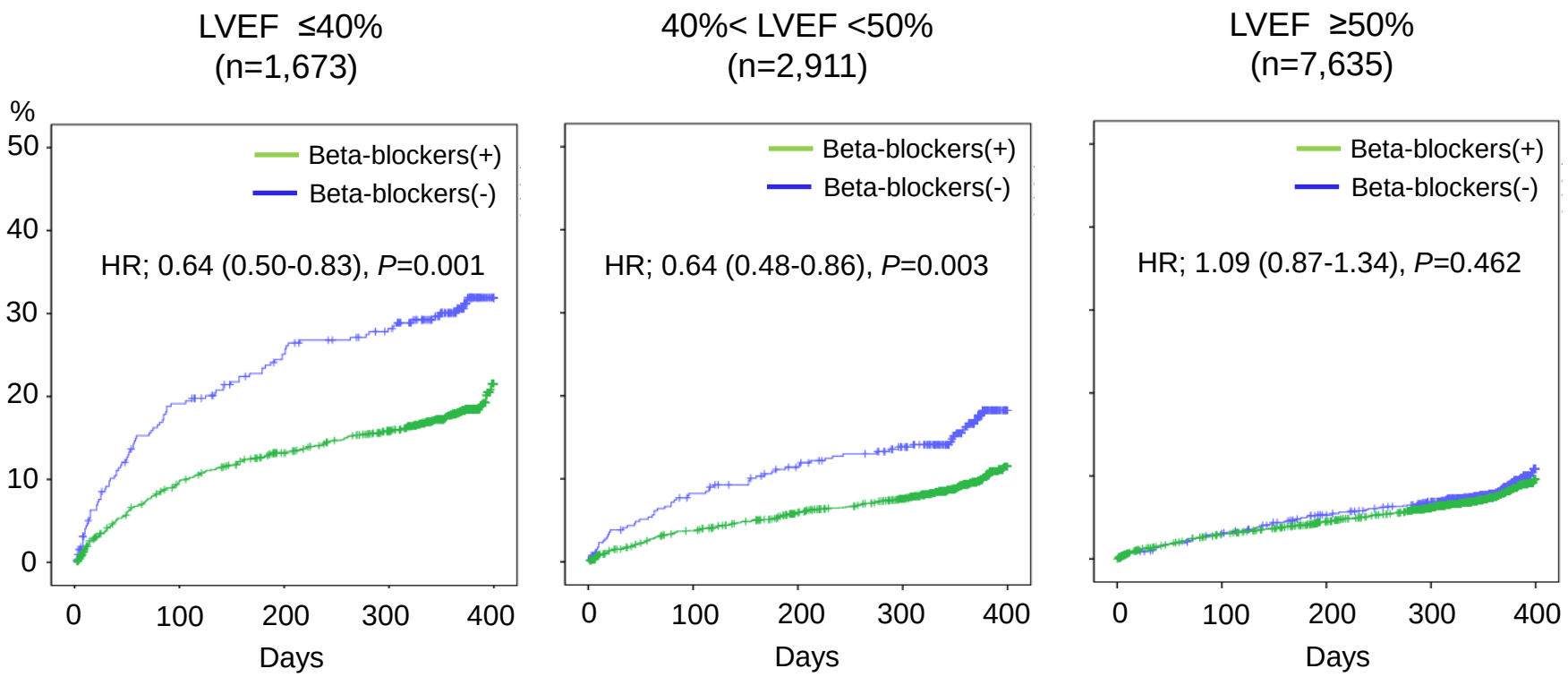
* Multivariate Cox-proportional hazard analysis including age, sex, Killip class, body mass index, hypertension, diabetes mellitus, prior myocardial infarction, prior angina, prior heart failure, prior stroke, smoker, chronic kidney disease, use of renin-angiotensin system inhibitors, type of myocardial infarction, and left ventricular ejection fraction

Effect of Beta-Blockers on MACE in Subgroups of Interest

	HR	95% CI	P for interaction
Overall	0.816	0.706 - 0.943	
Age <65	1.017	0.772 - 1.314	0.210
65≤ Age<80	0.727	0.588 - 0.899	
Age ≥80	0.785	0.583 - 1.056	
Male	0.828	0.692 - 0.991	0.943
Female	0.786	0.614 - 1.006	
Killip class 1	0.853	0.708 - 1.027	0.235
Killip class ≥2	0.768	0.608 - 0.971	
CKD	0.715	0.573 - 0.892	<0.001
No CKD	0.891	0.734 - 1.082	
RAS inhibitors	0.840	0.695 - 1.016	0.001
No RAS inhibitors	0.793	0.630 - 0.999	
LVEF ≤40%	0.641	0.497 - 0.826	0.004
40 <LVEF <50%	0.638	0.475 - 0.857	
LVEF ≥50%	1.088	0.869 - 1.364	
STEMI	0.704	0.563 - 0.881	0.386
NSTEMI	0.902	0.745 - 1.092	

CI; confidence interval, CKD; chronic kidney disease, LVEF; left ventricular ejection fraction, NSTEMI; non-ST elevation myocardial infarction, RAS; renin-angiotensin system, STEMI; ST-elevation myocardial infarction

Beta-blockers did not reduce MACE in patients with LVEF ≥50%



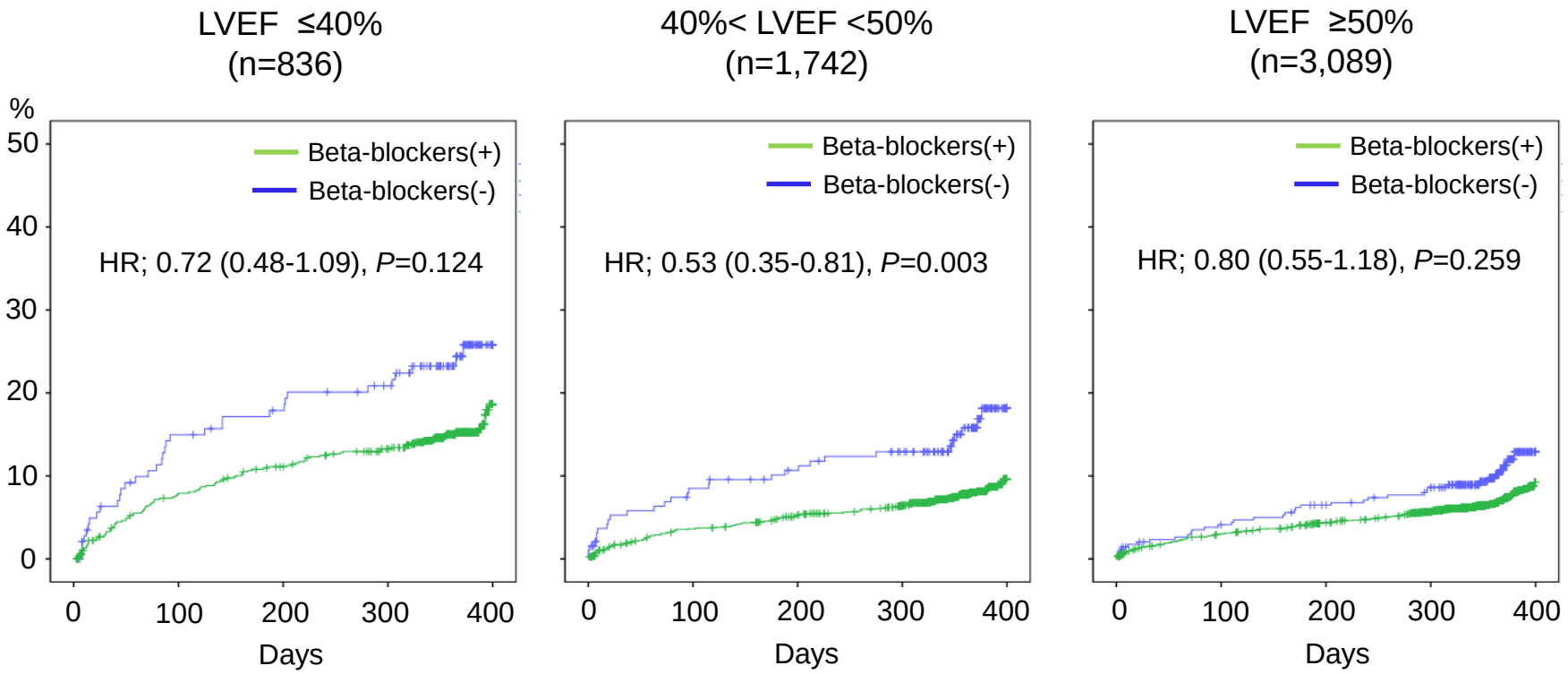
Multivariate Cox-proportional Hazard Analysis

Beta-blockers reduced MACE in patients with LVEF <50%

	All patients			LVEF ≤40%			40< LVEF <50%		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Beta-blockers	0.816	0.706-0.943	0.006	0.641	0.497-0.826	0.001	0.638	0.475-0.857	0.003
Age	1.019	1.012-1.025	<0.001	1.016	1.004-1.028	0.011	1.026	1.014-1.039	<0.001
Female	1.020	0.953-1.090	0.572	0.967	0.851-1.100	0.613	1.116	0.974-1.279	0.113
Killip class ≥2	1.373	1.204-1.564	<0.001	1.385	1.097-1.749	0.006	1.165	0.897-1.514	0.253
Body mass index	0.979	0.961-0.997	0.024	0.974	0.940-1.009	0.145	1.006	0.969-1.044	0.749
Hypertension	1.256	1.107-1.426	<0.001	1.385	1.073-1.783	0.012	1.567	1.207-2.035	0.001
Diabetes mellitus	1.134	1.001-1.284	0.048	1.068	0.844-1.352	0.583	0.996	0.771-1.287	0.974
Prior MI	1.176	0.980-1.412	0.081	0.855	0.615-1.189	0.352	1.192	0.826-1.720	0.347
Prior angina	1.215	1.029-1.435	0.022	1.112	0.813-1.522	0.507	1.114	0.778-1.595	0.556
Prior HF	1.446	1.066-1.962	0.018	1.136	0.714-1.806	0.591	2.235	1.122-4.453	0.022
Prior stroke	0.938	0.764-1.152	0.543	0.959	0.679-1.355	0.813	0.888	0.584-1.349	0.577
Smoker	1.030	0.895-1.184	0.683	1.056	0.802-1.391	0.697	1.230	0.919-1.646	0.164
CKD stage ≥3	1.763	1.542-2.016	<0.001	1.821	1.422-2.333	<0.001	1.624	1.234-2.137	0.001
RAS inhibitors	0.769	0.673-0.880	<0.001	0.787	0.611-1.013	0.063	0.865	0.657-1.138	0.300
NSTEMI	1.012	0.954-1.073	0.695	1.054	0.938-1.184	0.378	1.039	0.922-1.171	0.529

CI; confidence interval, CKD; chronic kidney disease, HF; heart failure, HR; hazard ration, MI; myocardial infarction, NSTEMI; non-ST elevation myocrdial infarction, RAS; renin-angiotensin system

Effect of Beta-Blockers on MACE in Patients with STEMI and Successful Coronary Reperfusion

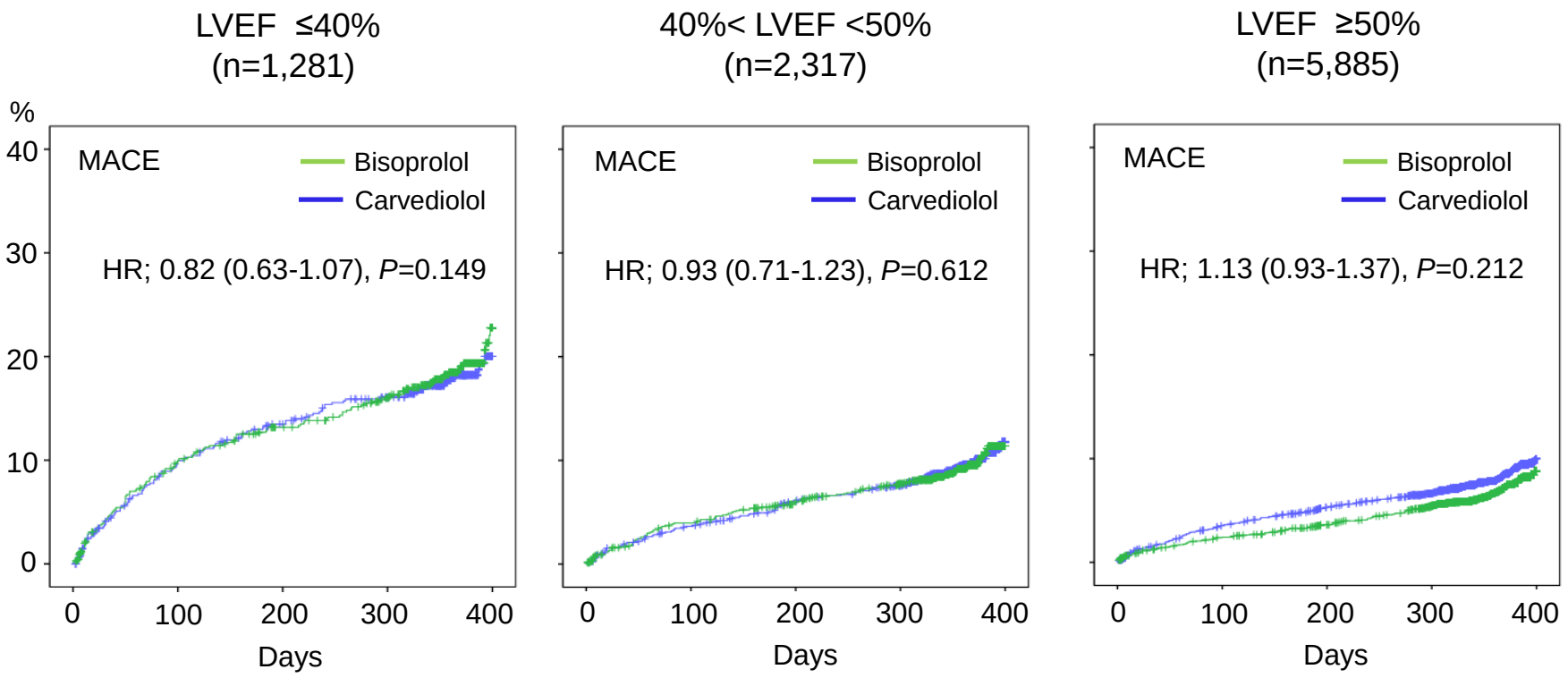


Generic Names of Beta-Blockers that Prescribed

	All patients N=10,265	LVEF ≤40% N=1,350	40<LVEF<50% N=2,512	LVEF ≥50% N=6,403
Bisoprolol	4,885 (47.6%)	617 (45.7%)	1,106 (44.0%)	3,162 (49.4%)
Carvedilol	4,598 (44.8%)	664 (49.2%)	1,211 (48.2%)	2,723 (42.5%)
Nebivolol	513 (5.0%)	45 (3.3%)	141 (5.6%)	327 (5.1%)
Metoprolol	186 (1.8%)	19 (1.4%)	32 (1.3%)	135 (2.1%)
Others	83 (0.8%)	5 (0.4%)	22 (0.9%)	53 (0.8%)

*$P<0.001$ by Chi-square test

Comparison of Beta-blockers Bisoprolol vs. Carvedilol



Summaries

- Beta-blockers were prescribed in 84% of patients at discharge.
- Beta-blockers reduced MACE, cardiac death and re-hospitalization due to heart failure at 1-year.
- Beta-blockers were more effective in patients with chronic kidney disease, not taking inhibitors of renin-angiotensin system, or LVEF<50%.
- Beta-blockers did not reduce MACE in patients with LVEF ≥50%.
- Beta-blockers were still effective in STEMI patients with LVEF <50% after successful coronary reperfusion.
- Bisoprolol and carvedilol showed comparable clinical effects.

Conclusions and Clinical Implications

- Beta-blockers reduced the clinical events in patients with reduced left ventricular systolic function, but not with preserved systolic function after AMI who survived the initial attack.
- Beta-blockers need not be prescribed in all patients with AMI if their left ventricular systolic function is preserved.