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Revisit of Beta-blocker in AMI

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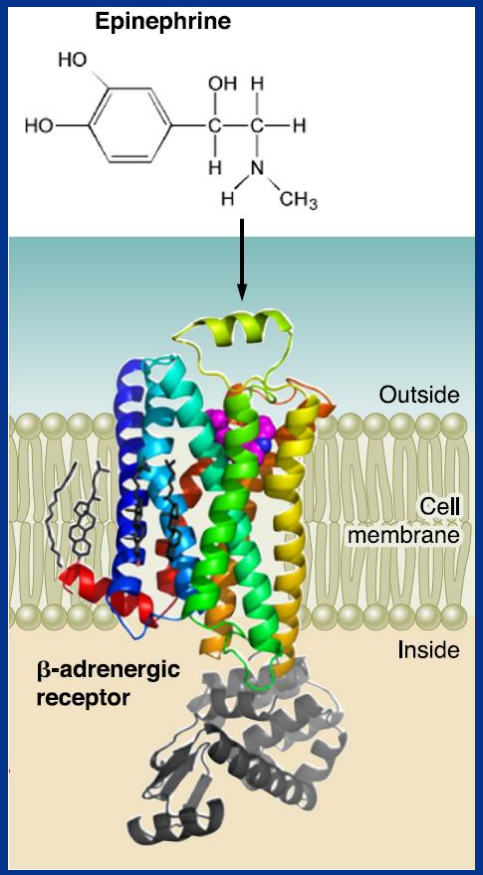
β-blockers for Myocardial Infarction



β1	Heart rate and contractility ↑ AV node conduction velocity ↑ Renin release from juxtaglomerular cells ↑
β2	Relaxation of smooth muscle Liver glycogenolysis and gluconeogenesis ↑ Skeletal muscle glycogenolysis ↑
β3	Lipolysis Endothelial nitric oxide dependent vasodilation

- **Myocardial oxygen demand ↓**
- **Ventricular arrhythmia ↓**
- **Ventricular remodelling**
- **Sympathetic activation ↓ → atherosclerosis progression ↓**

- **What guidelines tell us**
- **β-blockers in pre-reperfusion era**
- **Controversy ov' β-blockers in reperfusion era**
- **The roles of vasodilating β-blockers**

2013 ACC/AHA guideline for STEMI

8.1. Beta Blockers: Recommendations (Class I)

1. **Oral beta blockers should be initiated in the first 24 hours in patients with STEMI who do not have any of the following: signs of HF, evidence of a low output state, increased risk for cardiogenic shock, or other contraindications to use of oral beta blockers (PR interval more than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airways disease). (*Level of Evidence: B*)**
2. **Beta blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use. (*Level of Evidence: B*)**
3. **Patients with initial contraindications to the use of beta blockers in the first 24 hours after STEMI should be reevaluated to determine their subsequent eligibility. (*Level of Evidence: C*)**

2013 ACC/AHA guideline for STEMI

- …The benefit of beta blockers for secondary prevention has been established in numerous trials conducted in the prereperfusion era and appears to be greatest for patients with MI complicated by HF, LV dysfunction, or ventricular arrhythmias…

2012 ESC guideline for STEMI

Oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all STEMI patients without contraindications.	IIa	B
Oral treatment with beta-blockers is indicated in patients with heart failure or LV dysfunction.	I	A
Intravenous beta-blockers must be avoided in patients with hypotension or heart failure.	III	B
Intravenous beta-blockers should be considered at the time of presentation in patients without contraindications, with high blood pressure, tachycardia and no signs of heart failure.	IIa	B

- The benefit of long-term treatment with beta-blockers after STEMI is well established, although mostly from trials pre-dating the advent of modern reperfusion therapy and pharmacotherapy…

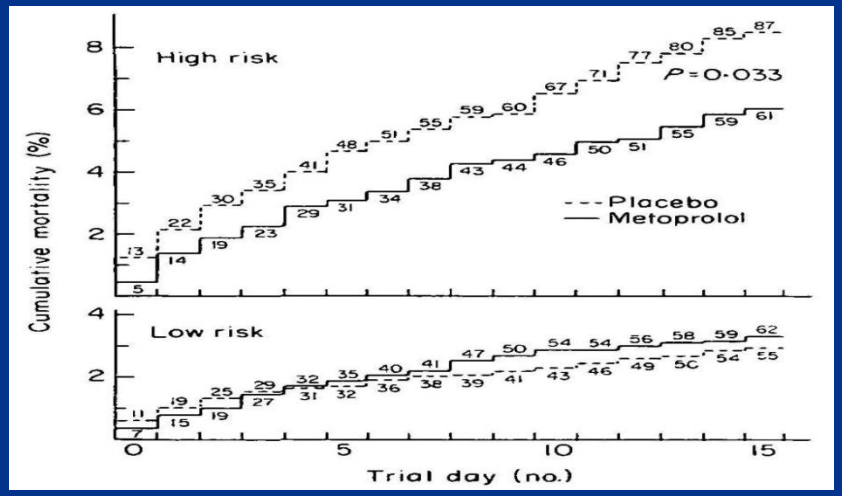
- In contemporary trials utilizing primary PCI, beta-blockers have NOT been investigated, although it is not unreasonable to extrapolate their benefit to this setting.

- What guidelines tell us
- β-blockers in pre-reperfusion era
- Controversy ov' β-blockers in reperfusion era
- The roles of vasodilating β-blockers

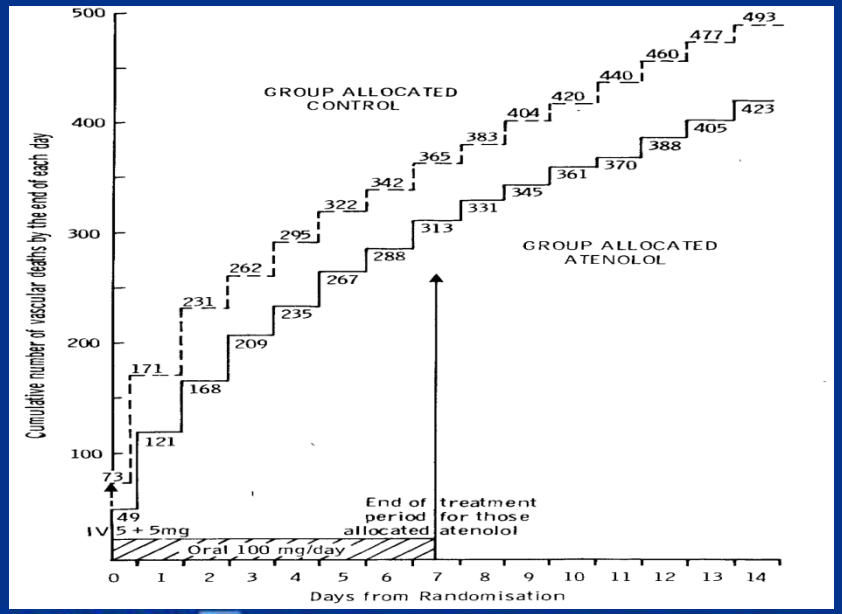
Oldies are Goodies..

- **Propranolol 10-20mg q8hrs for MI within 24hrs (P. Snow, et al. *Lancet* 1965)**
  - **28 days F/U**
  - **Mortality: propranolol 16% (n=45) vs ctrl 35% (n=46)**
- **Timolol 10mg bid vs. placebo for 7-28days after AMI (*NEJM* 1981)**
  - **Mean 17mo. F/U, multicenter double-blind RCT**
  - **Sudden-death: timolol 7.7% (n=945) vs. ctrl 13.9% (n=939) (p=0.0001)**
  - **Reinfarction: timolol 14.4% vs ctrl 20.1% (p=0.0006)**
- **Propranolol 20-40mg q8hrs for 5-21 days after MI (BHAT, *JAMA* 1982)**
  - **Mean 25mo. F/U, multicenter double-blind RCT**
  - **Mortality: propranolol 7.2% vs. ctrl 9.8%**
  - **Arteriosclerotic heart disease: propranolol 6.2% ctrl 8.5%**

β-blockers in pre-reperfusion era



- **MIAMI (*EHJ*, 1985)**
  - **Metoprolol** 15mg i.v. within 24 hrs of Sx. onset → 200mg po for 15 days
  - 2877 metoprolol vs. 2901 ctrl
  - **Mortality benefit** for high risk pts.



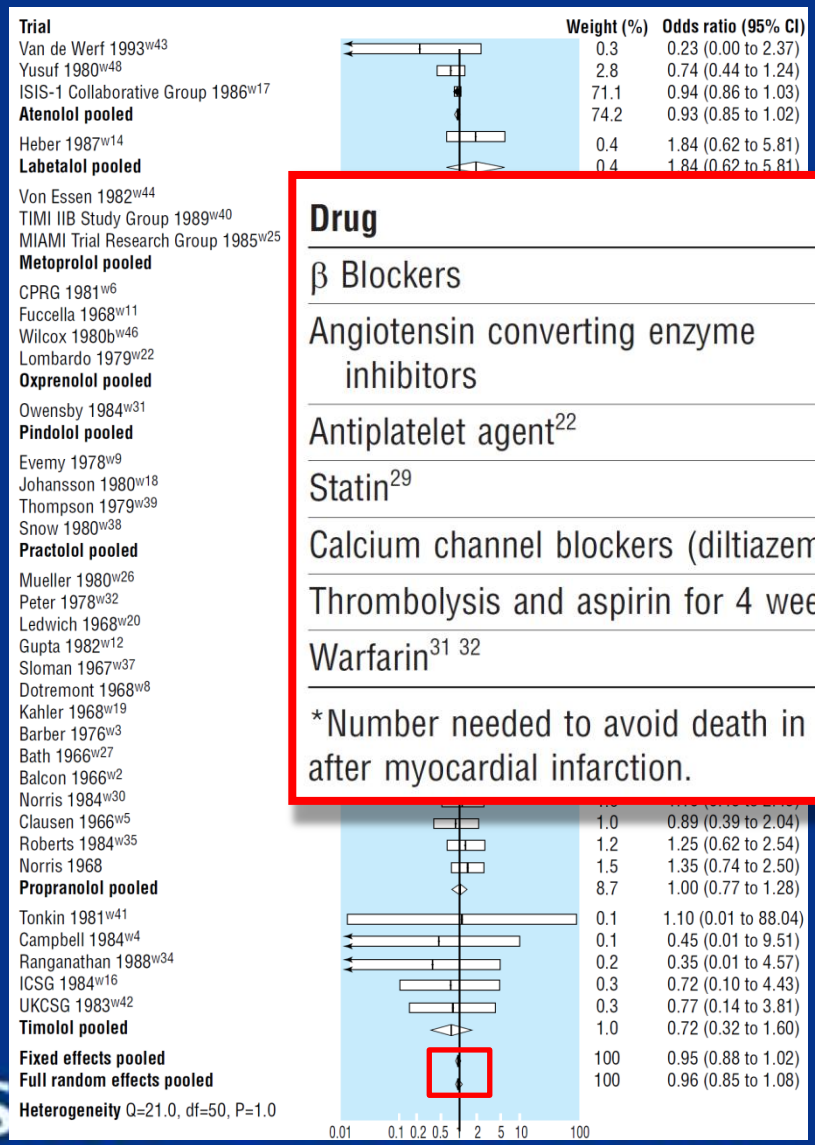
- **ISIS-1 (*Lancet*, 1986)**
  - **Atenolol** 5-10mg i.v. → 100mg po for 7days
  - **Mortality benefit** for 7days, even for 1yr

Meta-analysis: β-blockers for MI

N. Freemantle, et al. *BMJ* 1999

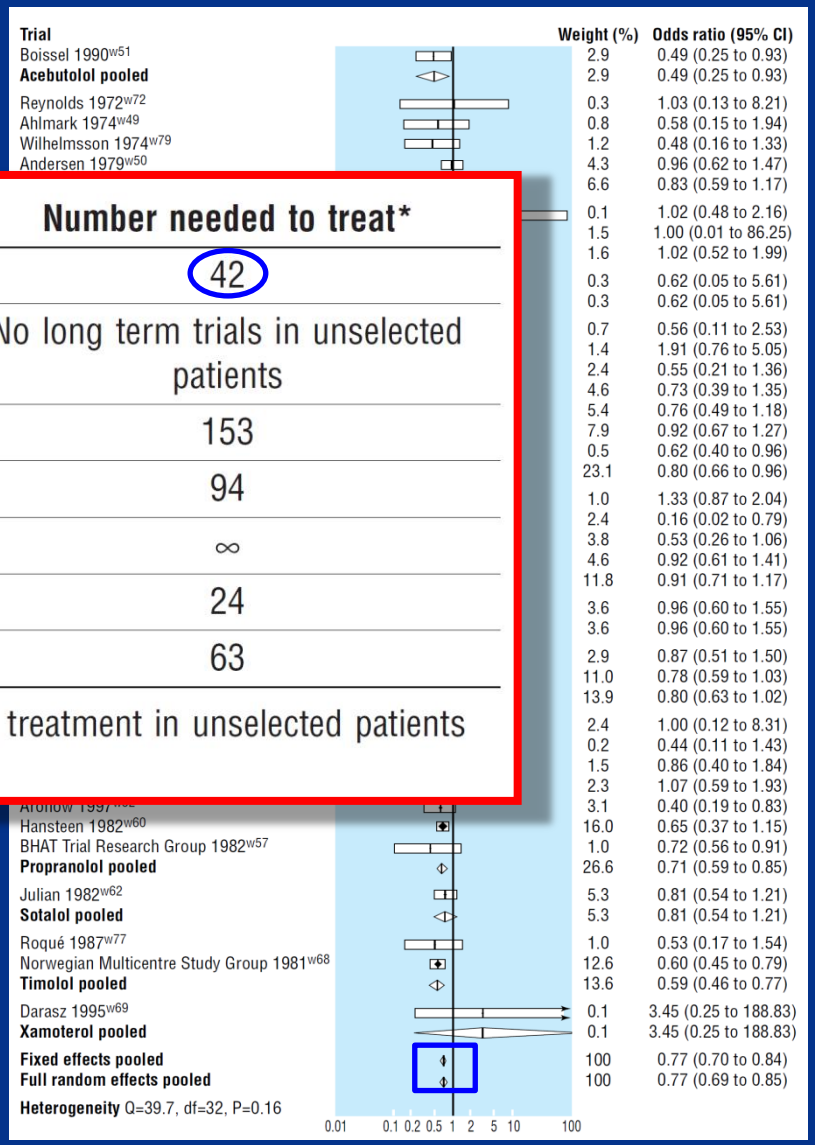
Short term trials: *no mortality benefit!*

Long term trials: *33% mortality benefit!*



Drug	Number needed to treat*
β Blockers	42
Angiotensin converting enzyme inhibitors	No long term trials in unselected patients
Antiplatelet agent[22]	153
Statin[29]	94
Calcium channel blockers (diltiazem)[30]	∞
Thrombolysis and aspirin for 4 weeks[16]	24
Warfarin[31 32]	63

*Number needed to avoid death in 2 years of treatment in unselected patients after myocardial infarction.



- What guidelines tell us
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- **Controversy ov' β-blockers in reperfusion era**
- The roles of vasodilating β-blockers

COMMIT trial

- 45,852 Pts. from 1,250 hospitals
- Aug., 1999 – Feb., 2005
- Inclusion: Suspected AMI (ST change or LBBB) within 24hrs of symptom onset
- Exclusion: Shock, SBP <100 mmHg, HR <50/min or II/III AV block, scheduled for primary PCI
- Treatment: metoprolol 15mg i.v. ov' 15min., then 200mg oral daily vs. matching placebo
- At the 1st discharge or at day 28 (whichever came first)
- Fibrinolysis in ≈ 55%

Z. Chen, et al. *Lancet* 2005

COMMIT trial: early IV, then oral metoprolol

	Metoprolol (n=22 929)	Placebo (n=22 923)	Odds ratio (95% CI)	Absolute difference per 1000 (SE)	p
Co-primary outcomes					
Composite*	2166 (9·4%)	2261 (9·9%)	0·96 (0·90–1·01)	−4·2 (2·8)	0·10
Death	1774 (7·7%)	1797 (7·8%)	0·99 (0·92–1·05)	−1·0 (2·6)	0·69
Death, by recorded cause					
Arrhythmia	388 (1·7%)	498 (2·2%)	0·78 (0·68–0·89)	−4·8 (1·3)	0·0002
Shock†	496 (2·2%)	384 (1·7%)	1·29 (1·13–1·47)	4·9 (1·3)	0·0002
Neither	890 (3·9%)	915 (4·0%)	0·97 (0·89–1·07)	−1·1 (1·8)	0·55
Reinfarction					
Any	464 (2·0%)	568 (2·5%)	0·82 (0·72–0·92)	−4·5 (1·4)	0·001
Died, any cause	206 (0·9%)	226 (1·0%)	0·91 (0·75–1·10)	−0·9 (0·9)	0·33
Survived	258 (1·1%)	342 (1·5%)	0·75 (0·64–0·88)	−3·7 (1·1)	0·0005
Ventricular fibrillation‡					
Any	581 (2·5%)	698 (3·0%)	0·83 (0·75–0·93)	−5·1 (1·6)	0·001
Died, any cause	492 (2·1%)	600 (2·6%)	0·82 (0·73–0·92)	−4·7 (1·4)	0·001
Survived	89 (0·4%)	98 (0·4%)	0·91 (0·68–1·21)	−0·4 (0·6)	0·51
Other cardiac arrest§					
Any	685 (3·0%)	632 (2·8%)	1·08 (0·97–1·21)	2·3 (1·6)	0·14
Died, any cause	624 (2·7%)	593 (2·6%)	1·05 (0·94–1·18)	1·3 (1·5)	0·38
Survived	61 (0·3%)	39 (0·2%)	1·55 (1·05–2·30)	1·0 (0·4)	0·03
Cardiogenic shock¶					
Any	1141 (5·0%)	885 (3·9%)	1·30 (1·19–1·41)	11·2 (1·9)	<0·0001
Died, any cause	755 (3·3%)	628 (2·7%)	1·20 (1·08–1·34)	5·5 (1·6)	0·0006
Survived	386 (1·7%)	257 (1·1%)	1·50 (1·28–1·75)	5·6 (1·1)	<0·0001
Death, reinfarction, cardiac arrest, or shock	2501 (10·9%)	2465 (10·8%)	1·02 (0·96–1·08)	1·5 (2·5)	0·54

Composite primary outcome: death, reinfarction, VF, or other arrest

Combined efficacy (death, reinfarction, VF, other arrest) and safety (cardiogenic shock)

	Metoprolol (n=22 929)	Placebo (n=22 923)	Odds ratio (95% CI)	Absolute difference per 1000 (SE)	p for trend
Day 0–1					
Low	509 (3·2%)	543 (3·4%)	0·94 (0·83–1·06)	−2·0 (2·0)	
Medium	424 (9·1%)	372 (7·9%)	1·16 (1·01–1·34)	11·8 (5·8)	<0·0001
High	454 (21·2%)	323 (15·7%)	1·42 (1·23–1·65)	55·3 (11·8)	
Day 2–28					
Low	540 (3·4%)	590 (3·7%)	0·91 (0·81–1·03)	−3·0 (2·0)	
Medium	343 (7·3%)	391 (8·3%)	0·89 (0·77–1·03)	−9·5 (6·1)	0·7
High	231 (10·8%)	246 (11·9%)	0·97 (0·81–1·16)	−11·5 (30·8)	
Day 0–28*					
Low	1049 (6·5%)	1133 (7·0%)	0·93 (0·85–1·01)	−5·1 (2·8)	
Medium	767 (16·4%)	763 (16·2%)	1·02 (0·92–1·13)	2·3 (6·2)	0·0002
High	685 (32·0%)	569 (27·6%)	1·22 (1·09–1·37)	43·7 (13·0)	

- **Metoprolol**
  - 5 fewer reinfarction, 5 fewer VF
  - 11 more cardiogenic shock per 1,000 treated
  - No difference in death

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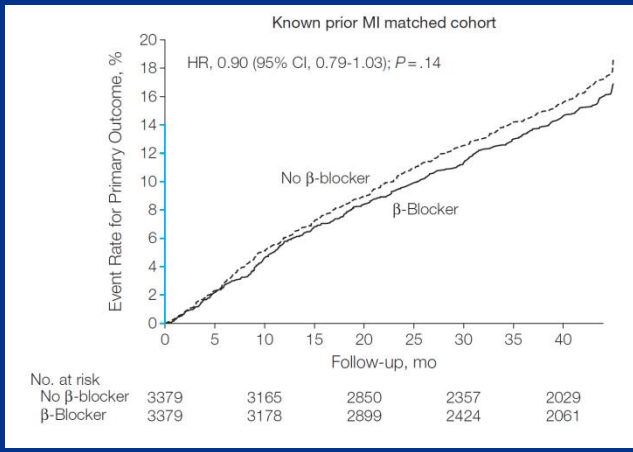
Z. Chen, et al. *Lancet* 2005

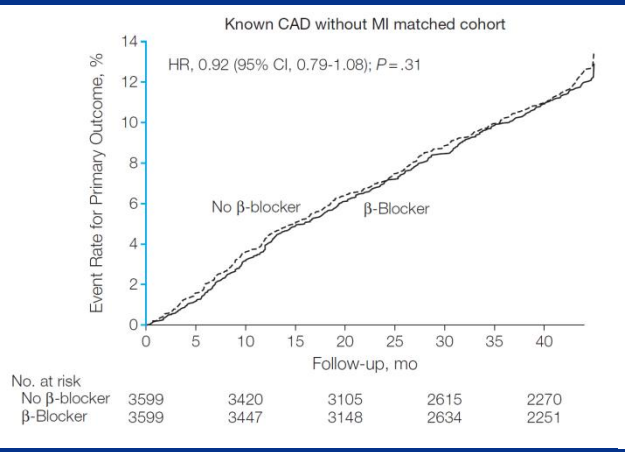
β-blocker in Stable Outpatients

- From REACH registry
- Age ≥ 45 with CAD, CV disease, PAD, or at least 3 atherothrombotic risk factors
- Enroll: Dec., 2003 – Dec. 2004, F/U: 44 mo.
- PS matching

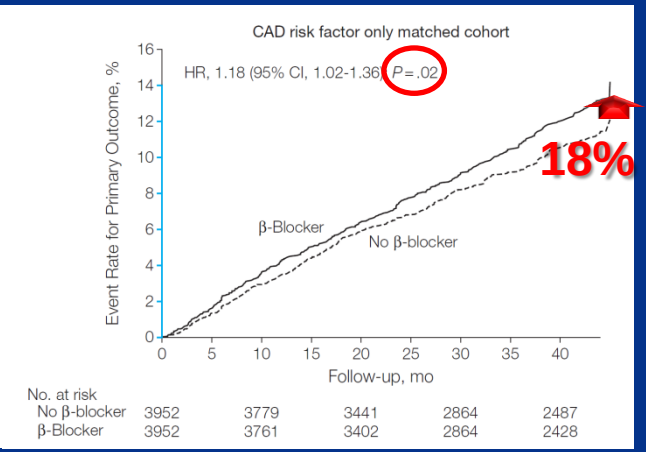
Known MI



Known CAD



CAD risk factor only



*** Primary outcome: composite of CV death, nonfatal MI, nonfatal stroke**

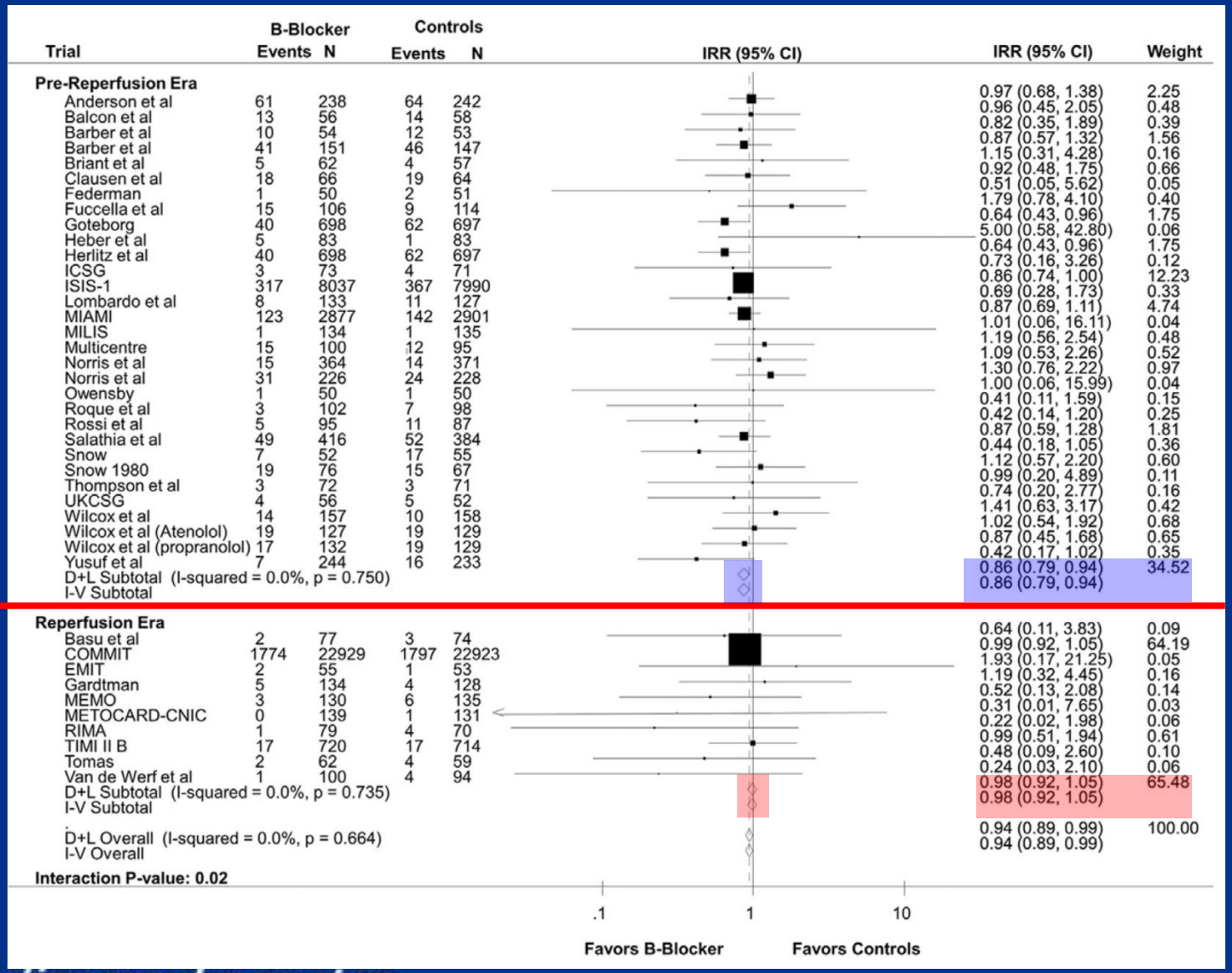
S. Bangalore, et al. *JAMA* 2012

Meta-analysis: β-blockers for MI

All-cause mortality

Pre-reperfusion era

Reperfusion era



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S. Bangalore, et al. *AJM* 2014

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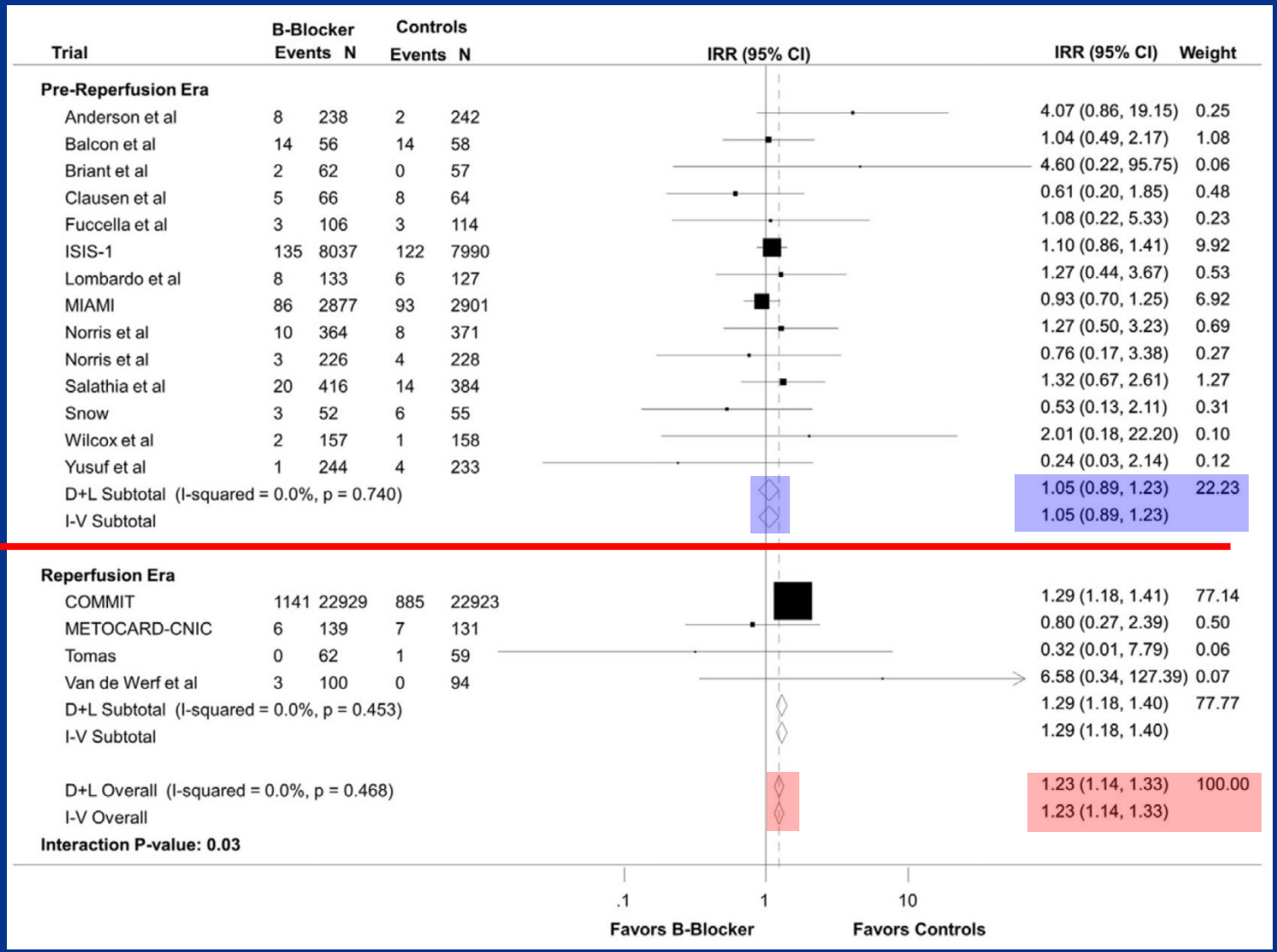
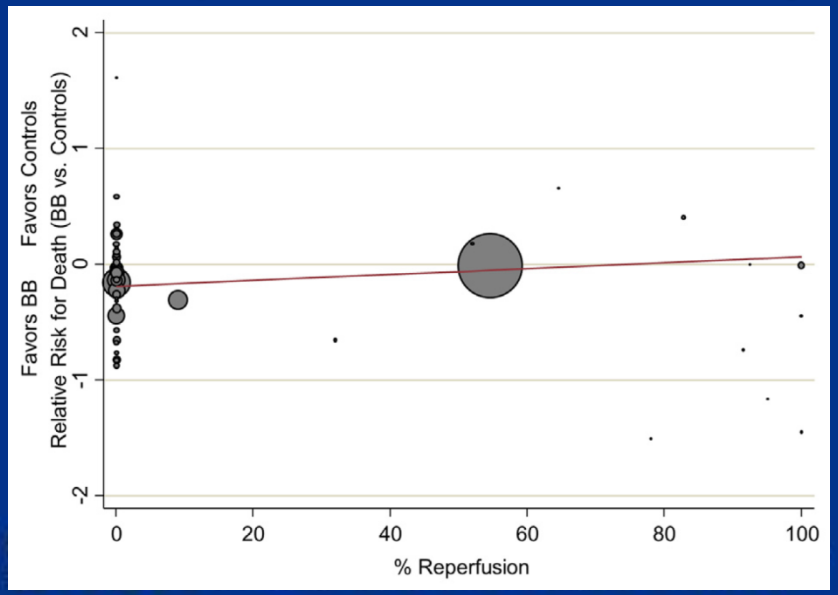


S. Bangalore, et al. *AJM* 2014

Meta-analysis: β-blockers for MI

	Death	CV Death	Sudden Death	MI	Angina	Stroke	Heart Failure	Cardiogenic Shock	Withdrawal
Events at 30 days									
Pre-reperfusion	0.87 (0.79, 0.96)	0.86 (0.77, 0.96)	0.82 (0.59, 1.13)	0.81 (0.63,1.04)	0.89 (0.83, 0.95)	2.96 (0.47, 18.81)	1.06 (0.97, 1.16)	1.03 (0.87, 1.21)	1.11 (1.00, 1.23)
Reperfusion era	0.98 (0.92, 1.05)	1.00 (0.91,1.10)	0.94 (0.86, 1.01)	0.72 (0.62, 0.84)	0.81 (0.66, 1.00)	1.09 (0.91, 1.30)	1.10 (1.05, 1.16)	1.29 (1.18, 1.41)	1.64 (1.55, 1.73)
Events between 30 days and 1 year									
Pre-reperfusion	0.79 (0.71, 0.88)	0.84 (0.71, 1.00)	0.61 (0.49, 0.76)	0.77 (0.64, 0.91)	0.94 (0.75, 1.18)	1.54 (0.60, 3.95)	1.07 (0.91, 1.27)	1.88 (0.51, 6.96)	1.16 (1.03, 1.30)
Reperfusion era	1.50 (0.53, 4.21)	1.50 (0.53, 4.21)	NA	0.71 (0.23, 2.25)	1.03 (0.72, 1.48)	4.00 (0.45, 35.79)	3.83 (1.56, 9.41)	NA	1.49 (1.01, 2.19)
Events > 1 year									
Pre-reperfusion	0.81 (0.66, 0.98)	0.73 (0.48, 1.11)	0.64 (0.43, 0.97)	0.81 (0.62, 1.06)	NA	0.20 (0.01, 4.20)	0.25 (0.03, 2.25)	NA	1.00 (0.65, 1.54)
Reperfusion era	NA	NA	NA	NA	NA	NA	NA	NA	NA

% of reperfusion Tx. and mortality



- **β-blockers**
  - Reduced the risk of events, including mortality in the pre-reperfusion era, but not in reperfusion era.
  - Short term (30 days) β-blocker use reduce recurrent MI and angina at the expense of ↑ HF, cardiogenenic shock, and drug discontinuation.

S. Bangalore, et al. *AJM* 2014

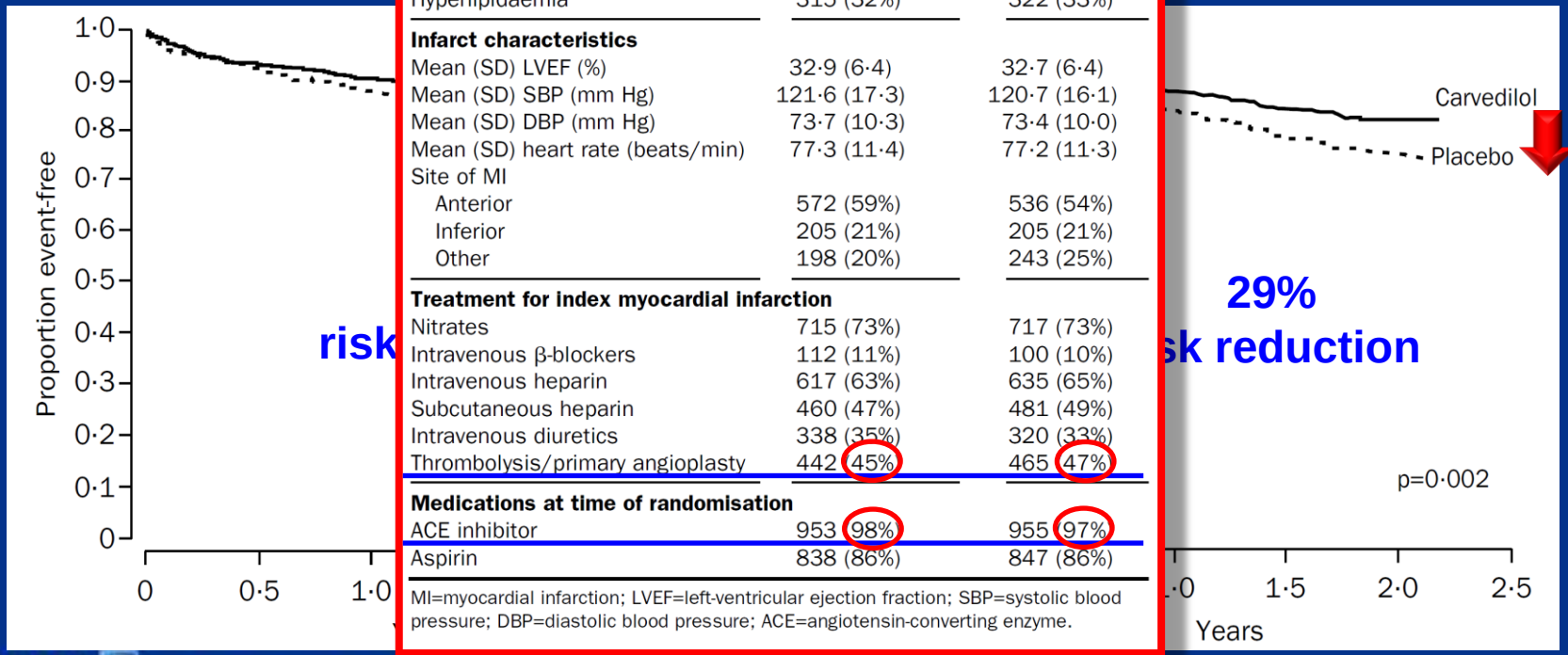
β-blocker sfunction:

- Multicenter ranc
- 1,959 Pts. with A)
- Carvedilol 6.25n id ov' 4-6wks.
- Mean F/U: 1.3yr

All cause lity or non-fatal MI

	Carvedilol group (n=975)	Placebo group (n=984)
Demographics		
Mean (range) age (years)	63 (29–88)	63 (25–90)
Sex		
Men	716 (73%)	724 (74%)
Women	259 (27%)	260 (26%)
Smoking history		
Current	326 (33%)	319 (32%)
Previous	264 (27%)	243 (25%)
Never	383 (39%)	418 (43%)
Medical history		
Previous MI	299 (31%)	290 (29%)
Previous angina	559 (57%)	531 (54%)
Previous hypertension	541 (55%)	514 (52%)
Previous diabetes	207 (21%)	230 (23%)
Other vascular disease	168 (17%)	159 (16%)
Previous revascularisation	118 (12%)	107 (11%)
Hyperlipidaemia	315 (32%)	322 (33%)
Infarct characteristics		
Mean (SD) LVEF (%)	32·9 (6·4)	32·7 (6·4)
Mean (SD) SBP (mm Hg)	121·6 (17·3)	120·7 (16·1)
Mean (SD) DBP (mm Hg)	73·7 (10·3)	73·4 (10·0)
Mean (SD) heart rate (beats/min)	77·3 (11·4)	77·2 (11·3)
Site of MI		
Anterior	572 (59%)	536 (54%)
Inferior	205 (21%)	205 (21%)
Other	198 (20%)	243 (25%)
Treatment for index myocardial infarction		
Nitrates	715 (73%)	717 (73%)
Intravenous β-blockers	112 (11%)	100 (10%)
Intravenous heparin	617 (63%)	635 (65%)
Subcutaneous heparin	460 (47%)	481 (49%)
Intravenous diuretics	338 (35%)	320 (33%)
Thrombolysis/primary angioplasty	442 (45%)	465 (47%)
Medications at time of randomisation		
ACE inhibitor	953 (98%)	955 (97%)
Aspirin	838 (86%)	847 (86%)

MI=myocardial infarction; LVEF=left-ventricular ejection fraction; SBP=systolic blood pressure; DBP=diastolic blood pressure; ACE=angiotensin-converting enzyme.



risk

29%

sk reduction

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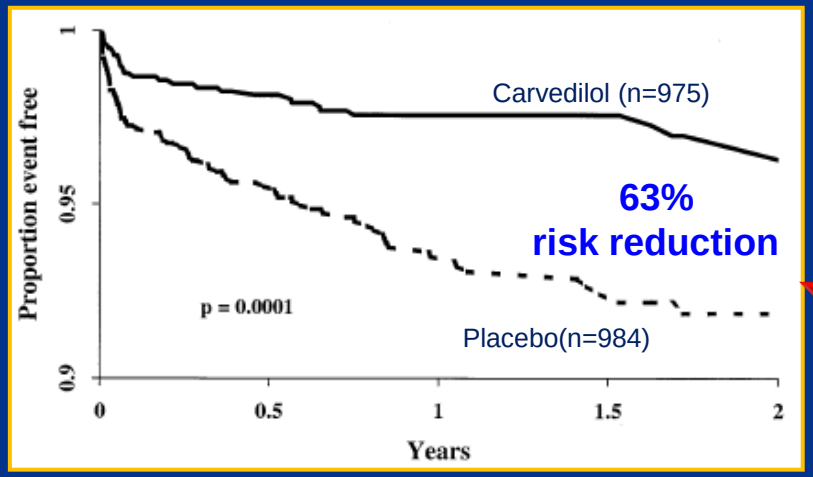
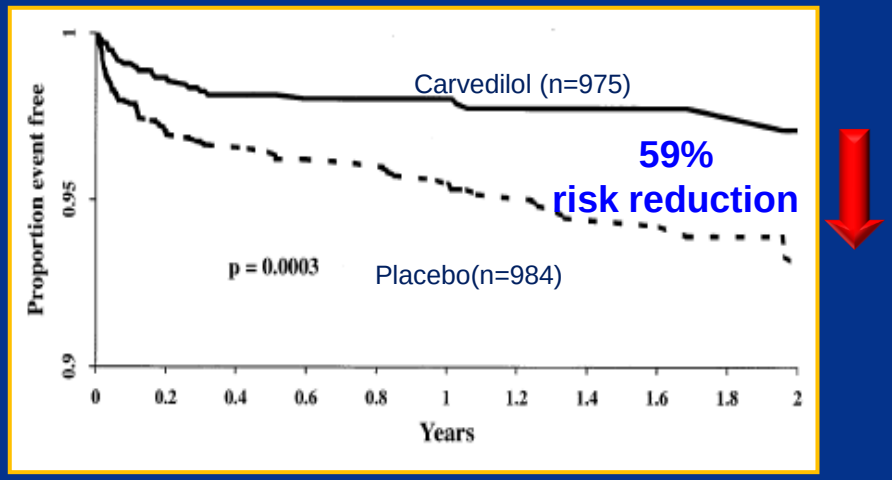
H. Dargie, et al. *Lancet* 2001

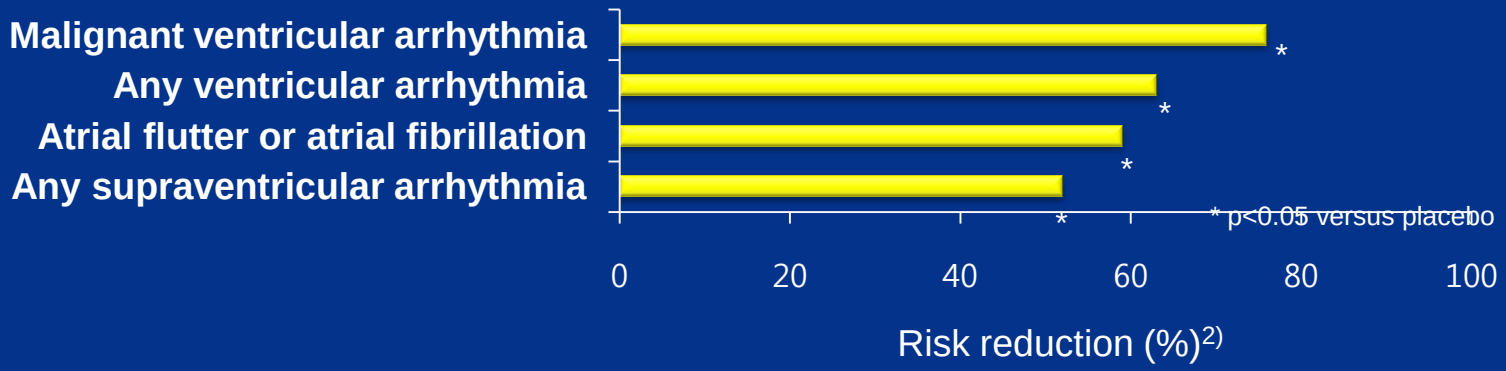
CAPRICORN: antiarrhythmic effects

Survival free of any ventricular arrhythmia



Survival free of atrial fibrillation or atrial flutter



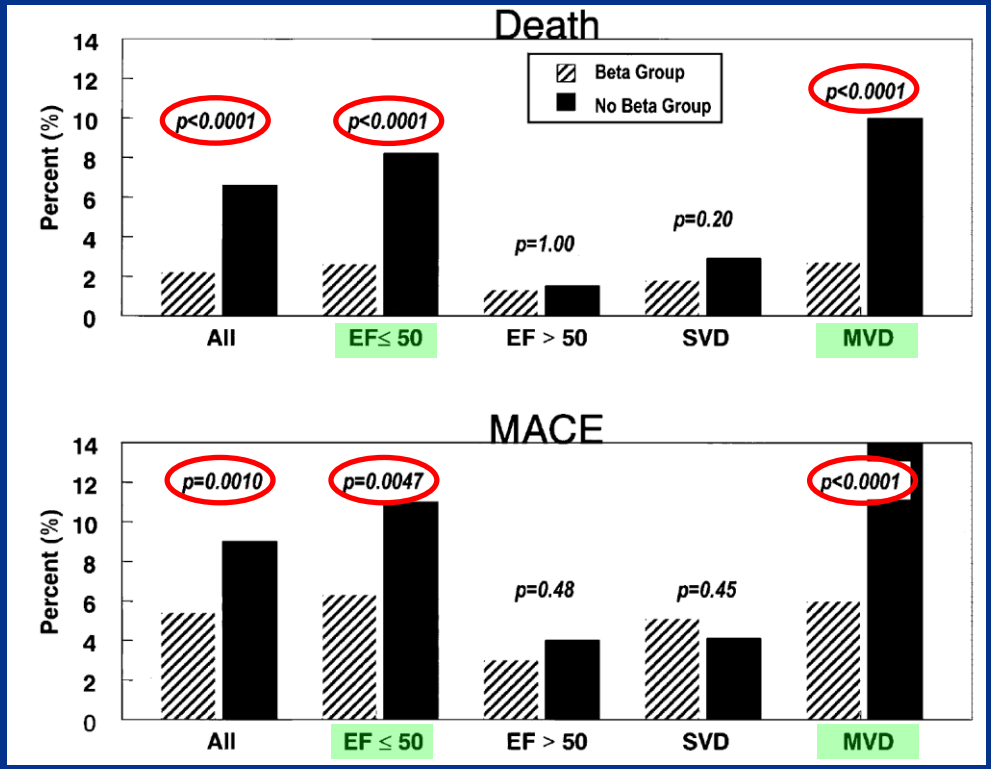


J. McMurray, et al. *JACC* 2005

PR. Kowey, et al. *J Cardiovasc Pharmacol Ther.* 2005

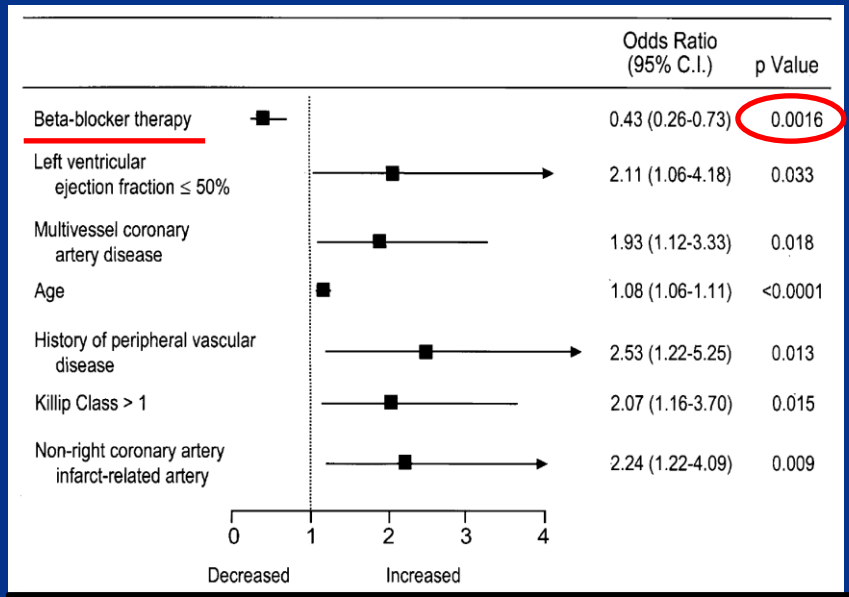
β-blocker Tx. for AMI after PCI

- 2,442 Pts. undergoing successful primary PCI from PAMI-2, noSOS, Stent-PAMI, Air-PAMI
- F/U: 6mo.



S. Kernis, et al. *JACC* 2004

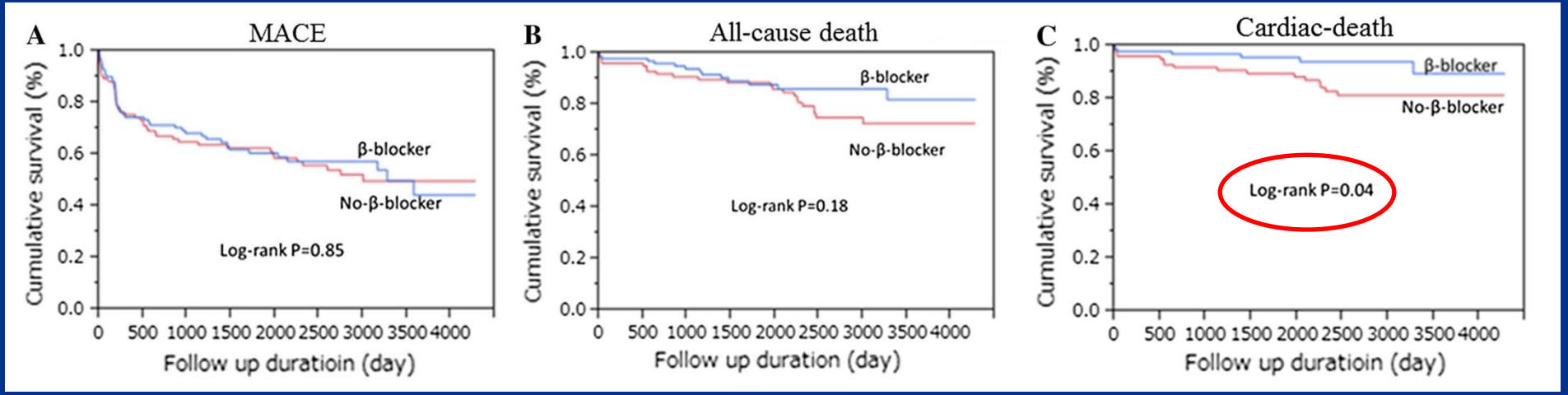
Multivariate predictors of 6mo. mortality



- Multivariate analysis
  - β-blockers as an insig. predictor of MACE (OR 0.87, 95% CI 0.66-1.13)
  - In pts. without in-hospital MACE, insing. for death (OR 0.58, 95% CI 0.29-1.17), MACE (OR 0.80, 95% CI 0.59-1.10)

β-blocker in STEMI Pts. with preserved LVEF

- Observational study
- Single center in Japan
- Jan. 1997 – Oct. 2011
- STEMI Pts. undergoing PCI, LVEF > 40%
- Exclusion: Hx. of CHF, previous MI
- After PS-matching, β-blocker 103 vs. non-β-blocker 103
- Median F/U: 4.7 yrs



H. Konishi, et al. *Heart Vessels* 2015

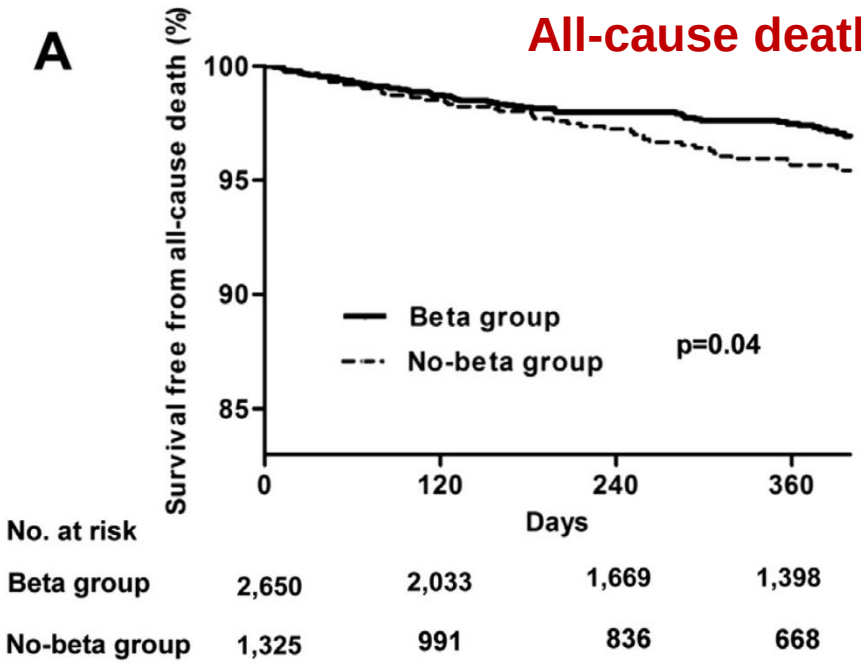
β-blockers for STEMI after primary PCI: KAMIR/KorMI data

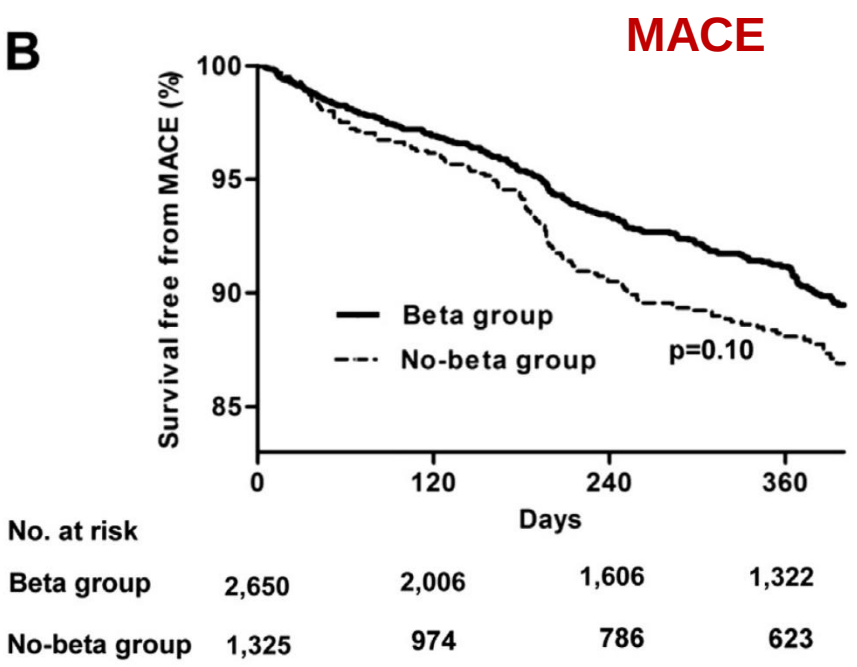
- KAMIR, Nov. 2005 – Dec. 2007
- KorMI, Jan. 2008 – Sep. 2010
- STEMI Pts. undergoing primary PCI (n=9,370)
- Exclusion: in-hospital death (n=549)
- β-blocker 6,873, non-β-blocker 1,637
- After PS-matching, β-blocker 2,650, non-β-blocker 1,325
- Median F/U: ≈ 1 yrs.

J. Yang, et al. *JACC CVI* 2014

Clinical Outcomes (median F/U 364 days)

Table 4. Clinical Outcomes in the Beta-Blocker Group Compared With No–Beta-Blocker Group in Propensity-Matched Population During Follow-Up Period (n = 3,975)



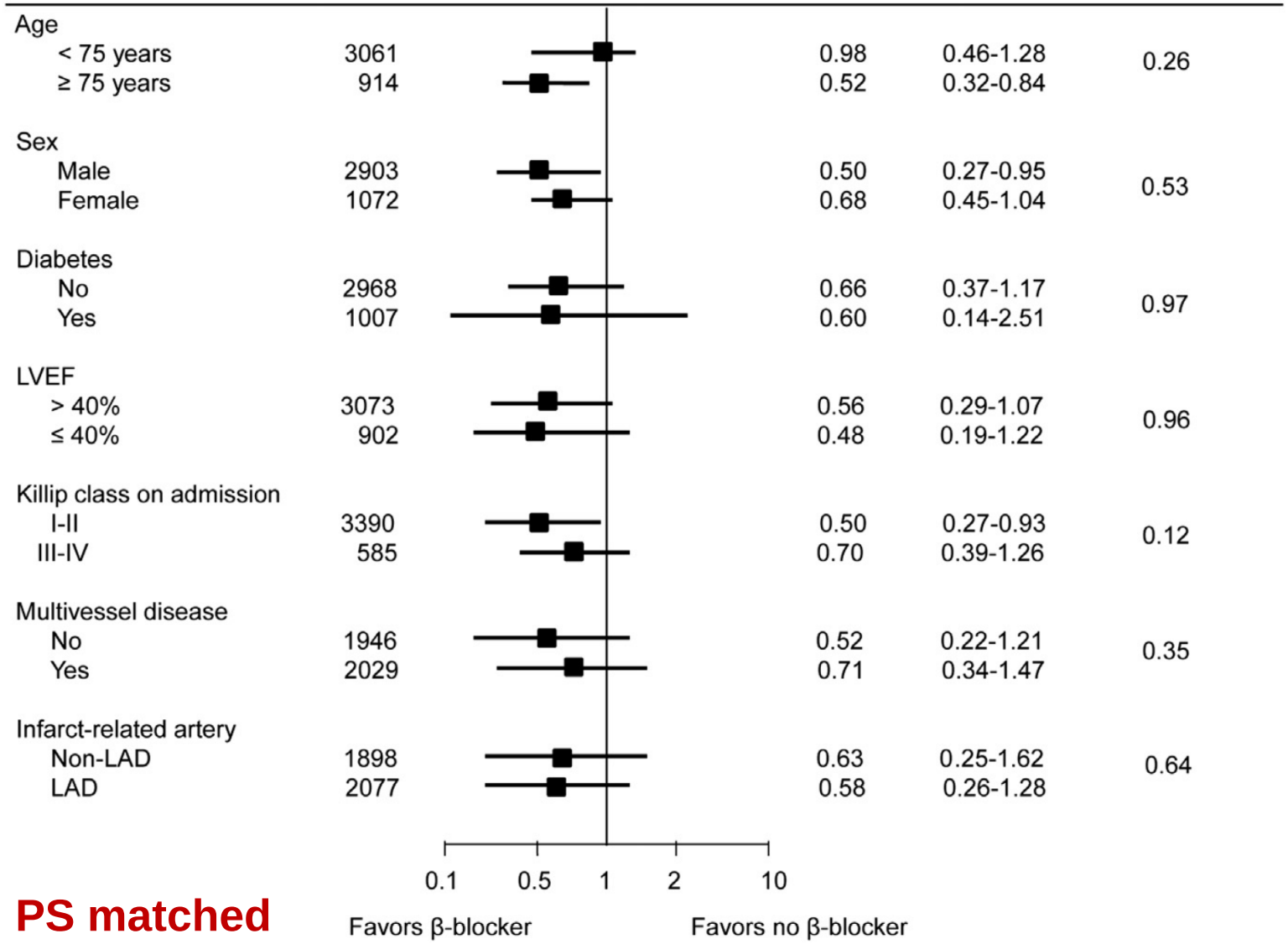


- Cox regression model: significant predictors of all-cause death
  - Age (HR: 1.06, 95% CI: 1.03 to 1.09, p < 0.001)
  - LAD lesion (HR: 2.51, 95% CI: 1.36 to 4.65, p=0.003)
  - No use of BB (HR: 2.19, 95% CI: 1.29 to 3.72, p=0.004)

*M

J. Yang, et al. *JACC CVI* 2014

Consistent Outcomes across the subgroups



PS matched

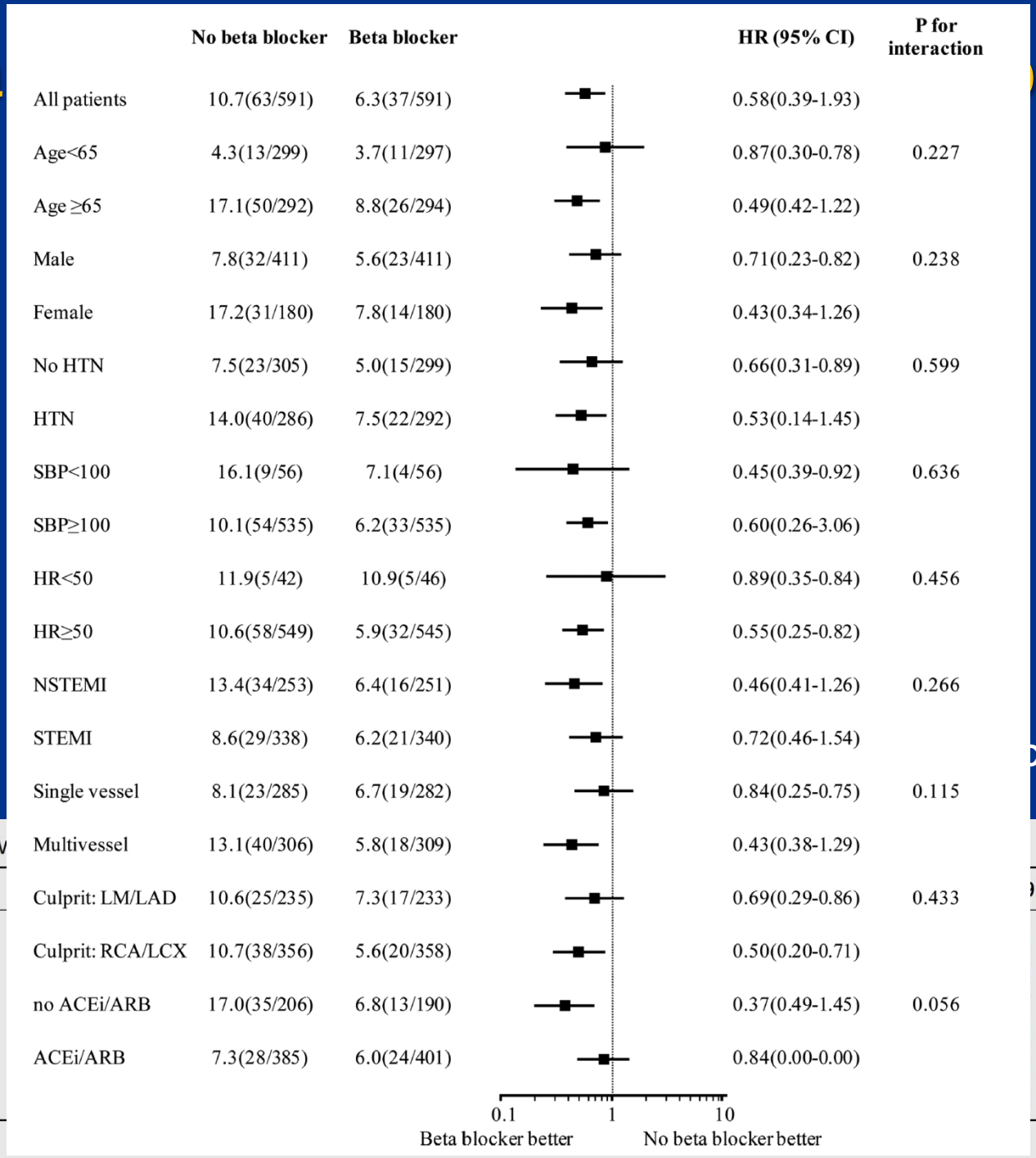
J. Yang, et al. *JACC CVI* 2014

β-blockers for AMI with preserved LVEF after PCI: COREA-AMI

- Jan., 2004 – Dec., 2009
- 3,019 AMI Pts. undergoing PCI who had LVEF ≥ 50%
- Primary outcome: all-cause mortality at 3 yrs.
- Among 3,019 AMI, STEMI 1754 (58.1%), NSTEMI 1265 (41.9%)
- Of STEMI, primary PCI 1342 (76.5%)
- BB
  - 2424 (80.3%) were prescribed BB
  - Carvedilol 1964 (81.0%), bisoprolol 256 (10.6%), atenolol 183 (7.5%), other BB 21 (0.9%)

E. Choo, et al. *Heart* 2014

Clinica ulation



Choo, et al. *Heart* 2014

Table 5 Cumulativ

	95% CI)	p Value
All cause death		0.008
Cardiac death		0.001
Stroke		0.209
Ischaemic stroke		0.123
Myocardial infarction		0.844
Any revascularisation		0.903

PS, propensity score.

Conclusion (1): pre- vs. repersufion era

- β-blockers in pre-reperfusion era
  - Extensive myocardial scarring: a substrate for re-entrant circuits and fatal arrhythmias
  - Benefits of preventing ventricular arrhythmias, SCD >> HF, cardiogenic shock
  - Lack of contemporary medical Tx.:
    - ISIS-1 trial (1986): 5% of Pts. on an antiplt. Tx., none for reperfusion
    - COMMIT trial (2005): all on aspirin, 50% on DAPT, 2/3 on ACEI, 54% for fibrinolysis
  - Not refined study design: (Bangalore's meta-analysis)
    - High risk for bias (36/48 trials), compared with relatively lower risk in reperfusion era trials (6/12 trials)

Conclusion (1): pre- vs. repersufion era

- β-blockers in reperfusion era
  - Lack of sufficient numbers of RCTs
  - F/U duration
  - When to start BB
    - COMMIT: within 24hrs after MI
    - CAPRICORN: 3-21 days after MI
  - Judicious selection of pts.
  - Further RCTs are warranted..

- What guidelines tell us
- β-blockers in pre-reperfusion era
- Controversy ov' β-blockers in reperfusion era
- **The roles of vasodilating β-blockers**

The Importance of Central BP

- **Central pressure : strongly related to future CV events**

Table 6 Independent Predictors of Cardiovascular Events

	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (yrs)	1.09 (1.07–1.12)	<0.0001	1.09 (1.07–1.12)	<0.0001	1.10 (1.06–1.13)	<0.0001	1.09 (1.06–1.13)	<0.0001
Male gender	1.84 (1.29–1.64)	0.001	1.84 (1.29–1.64)	0.001	1.92 (1.29–2.87)	0.001	1.97 (1.32–2.94)	0.001
Brachial SBP (/10 mm Hg)		0.119						
Brachial PP (/10 mm Hg)				0.063				
Carotid SBP (/10 mm Hg)					1.19 (1.08–1.31)	<0.0001		
Carotid PP (/10 mm Hg)							1.23 (1.10–1.37)	<0.0001

TABLE 4. Multivariable Cox Models of Relation of Traditional Risk Factors and Central and Brachial Blood Pressures to Cardiovascular Outcome

Variable	HR (95% CIs)	HR (95% CIs)	HR (95% CIs)	HR (95% CIs)	HR (95% CIs)
Age, year	1.06 (1.04–1.07)*	1.05 (1.04–1.07)*	1.06 (1.04–1.07)*	1.05 (1.03–1.07)*	1.05 (1.04–1.07)*
Male gender	1.13 (0.87–1.45)	1.17 (0.91–1.52)	1.13 (0.88–1.46)	1.22 (0.94–1.58)	1.10 (0.83–1.45)
BMI, kg/m^2	0.99 (0.97–1.01)	0.99 (0.97–1.01)	0.99 (0.97–1.01)	0.99 (0.97–1.01)	0.99 (0.97–1.01)
Smoking	1.45 (1.10–1.91)†	1.44 (1.09–1.89)†	1.42 (1.08–1.87)‡	1.39 (1.06–1.83)‡	1.37 (1.01–1.85)‡
Cholesterol:HDL	1.05 (0.98–1.13)	1.06 (0.99–1.13)	1.05 (0.98–1.13)	1.05 (0.98–1.13)	1.09 (1.01–1.18)‡
Creatinine, mg/dL	1.20 (1.12–1.28)*	1.18 (1.11–1.27)*	1.20 (1.12–1.28)*	1.18 (1.10–1.26)*	1.13 (1.03–1.23)‡
Fibrinogen, mg/dL	1.001 (1.000–1.002)†	1.001 (1.000–1.002)†	1.001 (1.000–1.002)†	1.001 (1.000–1.002)§	1.001 (1.000–1.002)‡
Diabetes mellitus	2.48 (1.91–3.22)*	2.44 (1.88–3.17)*	2.47 (1.91–3.21)*	2.41 (1.86–3.13)*	2.42 (1.838–3.22)*
Heart rate, bpm	1.012 (1.001–1.022)‡	1.013 (1.002–1.023)‡	1.013 (1.008–1.143)‡	1.012 (1.001–1.022)‡	1.013 (1.001–1.025)‡
Brachial SBP	1.08 (1.02–1.14)‡				
Brachial PP		1.10 (1.03–1.18)†			
Central SBP			1.07 (1.01–1.14)‡		
Central PP				1.15 (1.07–1.24)*	
Arterial stiffness					1.06 (1.01–1.11)‡

R. Pini, et al. *JACC* 2008
MJ Roman, et al., *Hypertension* 2007

Adverse Effects of BB: Central BP

- **Beta-blockers**
  - Different effects on brachial vs. central pressure
  - May explain adverse findings of atenolol
- **Drugs which lower central pressure the most will be more effective ?**

Comparative effect of anti-hypertensive drugs and nitrates on central systolic pressure

Class	Central systolic pressure
ACE inhibitors[61–63,95–102]	↓
Angiotensin receptor blockers[101,103–105]	↓↔
Beta-blockers[9,61–63,85,95,103,106,107]	↑↑
Calcium channel blockers[61–63,96]	↓↔
Diuretics[61–63,100,102]	↔
Nitrates[68,70,71,74]	↓↓

CM McEniery, et al. *EHJ* 2014

Vasodilating beta blockers: Central BP

- Central systolic BP, diastolic BP, and PP are obtained and indices of arterial stiffness such as augmentation index (Aix) and pulse wave velocity (PWV) are estimated
- Vasodilating beta blockers decrease central BP parameters better than older beta blockers

Table 2. Effects of different β-blockers on wave reflection and PWV

β-Blocker	Wave reflection (AIx)	PWV
Propranolol	NC	NC
Atenolol	NC	Improvement
Metoprolol	Possible improvement	NC
Labetalol	Improvement	Improvement
Carvedilol	Improvement	Improvement
Nebivolol	Improvement	Improvement

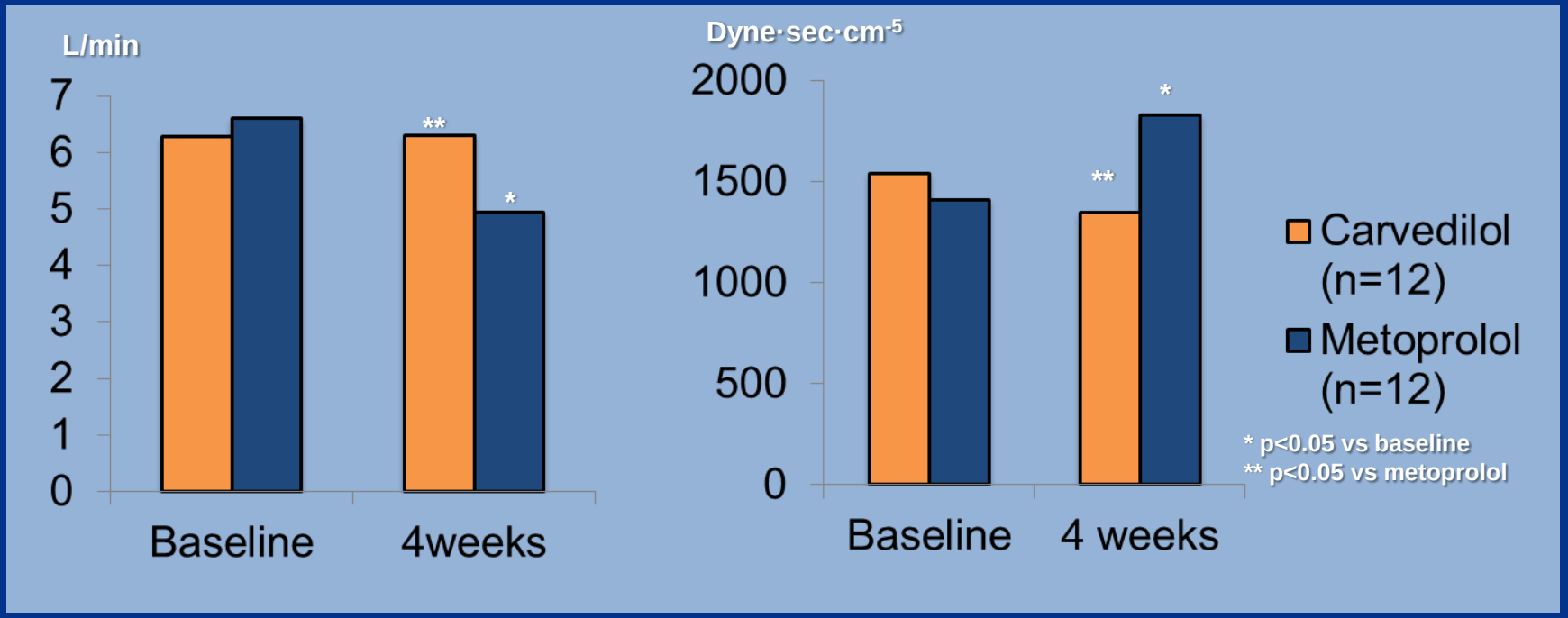
AIx, augmentation index; NC, no change; PWV, pulse wave velocity.

L Trudeau, et al. *Can J Cardiol* 2014

Vasodilating beta blockers: Central BP

- **Vasodilation**

[Cardiac output] [Systemic arterial resistance]

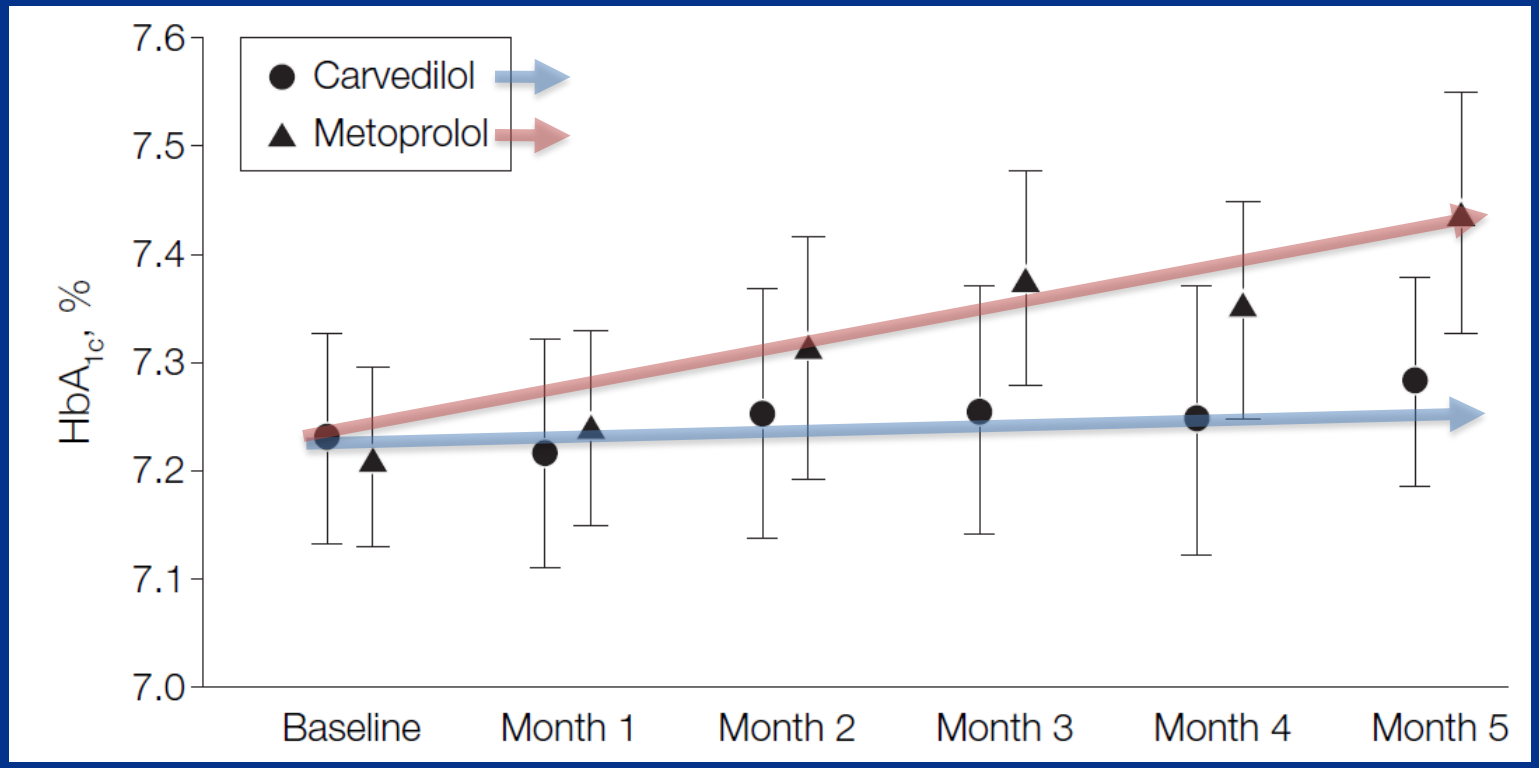


- Traditional β-blockers, such as atenolol, metoprolol, bisoprolol and propranolol, lower BP primarily by reducing cardiac output.
- By contrast, vasodilatory β-blockers, such as carvedilol, lower BP partly by reducing systemic vascular resistance.

K. Weber, et al. *Cardiovasc Drugs Ther* 1996
GC Fonarow, et al., *Expert Rev Cardiovasc Ther* 2009

Vasodilating beta blockers: Metabolic Effects

- **Metabolic effect**
  - **Carvedilol (GEMINI study)**



- **Carvedilol treatment did not increase HbA1c levels (0.02%; p = 0.65), whereas metoprolol treatment significantly increased HbA1c levels from baseline (0.15%; p < 0.001).**

GL Bakris, et al. *JAMA* 2004

Vasodilating beta blockers: Metabolic Effects

- **Metabolic effect**
  - **Nebivolol**

Parameter	Baseline	12 wk	
Fasting plasma glucose, mg/dL			
Nebivolol	101.5±10.5	99.7±9.9	
Metoprolol	99.5±10.7	101.6±9.3	
Fasting insulin, mU/L			
Nebivolol	5.55±3.12	6.04±3.21	
Metoprolol	4.91±2.73	6.04±3.41	0.048
AIRg, mU/L · min			
Nebivolol	241.1±213.7	236.8±177.6	
Metoprolol	278.1±212.0	279.5±177.9	
ISI, $10^{-4} \times min^{-1}$ per mU/L			
Nebivolol	5.41±2.41	5.35±2.36	
Metoprolol	6.42±2.92	4.89±2.06	0.007
Disposition index, U			
Nebivolol	1345.1±1400.0	1302.1±1282.2	
Metoprolol	1335.6±725.1	1285.6±1049.2	

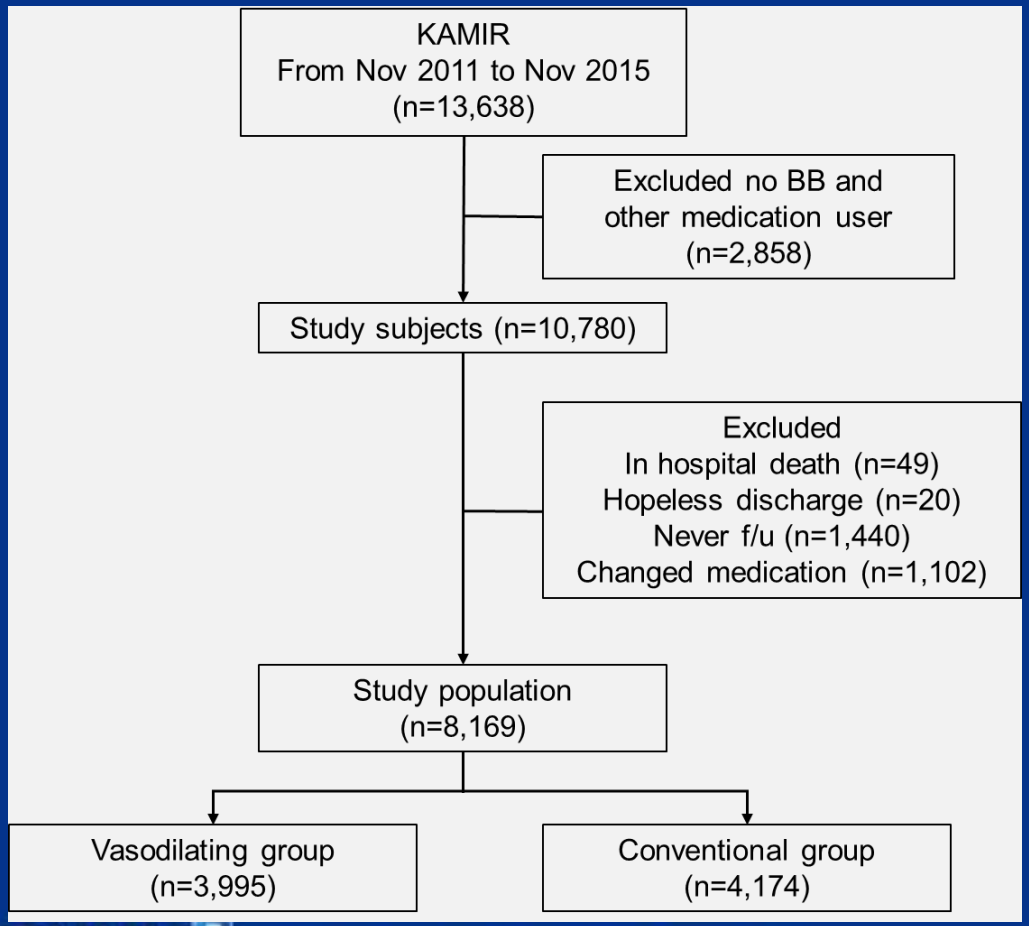
AIRg indicates acute insulin response to glucose; ISI, insulin sensitivity index.

- **Nebivolol did not affect insulin sensitivity**
- **The change in insulin sensitivity index differed significantly in the metoprolol and nebivolol treatment groups (p=0.03)**

K Ayers, et al. *Hypertension* 2012

Vasodilating BB vs. Conventional BB for AMI: from KAMIR

To investigate the benefit of vasodilating BB over conventional BB in patients with AMI



- **Crude population**
  - Carvedilol n=3,674 (45.0%)
  - Nebivolol n=321 (3.9%)
  - Bisoprolol n=4,022 (49.2%)
  - Metoprolol n=152 (1.9%)
- **PS matched population**
  - Carvedilol n=2,833 (45.7%)
  - Nebivolol n=268 (4.3%)
  - Bisoprolol n=2,972 (47.9%)
  - Metoprolol n=129 (2.1%)

JH Jung, JK Han et al. (unpub.)

Patient Characteristics

	Vasodilating BB (n=3995)	Conventional BB (n=4174)	P-value
Age	62.46±12.43	63.71±12.40	<0.001
Male	3042 (76.2%)	3047 (73.0%)	0.001
Killip class	1.27±0.71	1.38±0.78	<0.001
HTN	2023 (50.6%)	2197 (52.6%)	0.071
DM	1074 (26.9%)	1256 (30.1%)	0.001
Dyslipidemia	480 (12.0%)	440 (10.5%)	0.035
Previous MI	297 (7.4%)	297 (7.1%)	0.579
Previous angina	344 (8.6%)	354 (8.5%)	0.834
Previous HF	55 (1.4%)	57 (1.4%)	0.959
Previous CVD	260 (6.5%)	305 (7.3%)	0.155
Smoking hx.	2445 (62.5%)	2406 (58.7%)	<0.001
Family hx.	260 (6.7%)	261 (6.4%)	0.542
GFR(MDRD)	89.46±37.10	87.96±39.81	0.077
Total cholesterol	179.90±44.01	179.27±46.28	0.537
HDL	43.13±11.62	42.62±13.38	0.078
LDL	112.69±37.61	113.36±49.67	0.520
CCB	202 (5.1%)	201 (4.8%)	0.615
ACEi/ARB	3274 (82.0%)	3700 (88.6%)	< 0.001
Statin	3794 (95.0%)	3912 (93.7%)	0.015
STEMI	2104 (52.7%)	1974 (47.3%)	<0.001
LV EF	51.47±10.88	52.58±10.62	<0.001

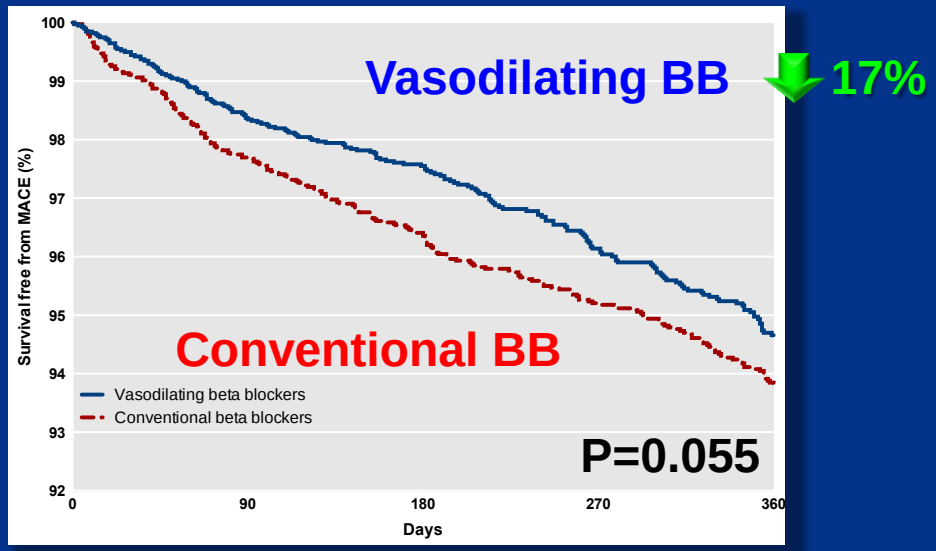
JH Jung, JK Han et al. (unpub.)

Angiographic and Procedural Characteristics

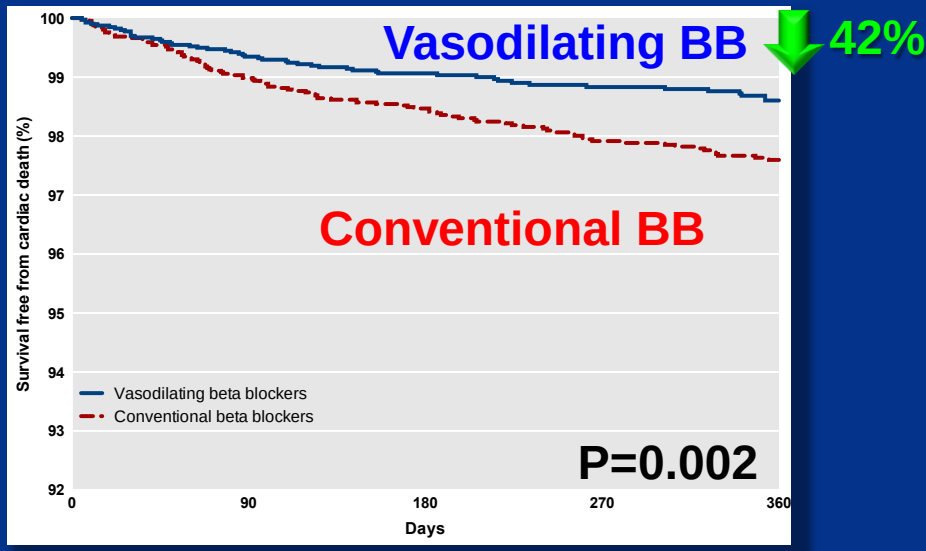
	Vasodilating BB (n=3995)	Conventional BB (n=4174)	P-value
Thrombolysis	61 (1.5%)	37 (0.9%)	0.008
CABG	68 (1.7%)	25 (0.6%)	<0.001
PCI	3713 (92.9%)	3886 (93.1%)	0.778
Target lesion (LM or LAD)	1877 (50.2%)	1909 (49.0%)	0.274
LM	70 (1.9%)	81 (2.1%)	
LAD	1807 (48.3%)	1828 (46.9%)	
LCX	639 (17.1%)	680 (17.4%)	
RCA	1222 (32.7%)	1310 (33.6%)	
Target lesion type (B2/C lesion)	2522 (86.7%)	2753 (85.6%)	0.204
Pre TIMI flow of target vessel	1.24±1.31	1.23±1.26	0.639
Post TIIMI flow of target vessel	2.97±0.23	2.97±0.22	0.778
Mean involved vessel number	1.68±0.78	1.62±0.77	0.001
1VD	1869 (46.8%)	2030 (48.6%)	
2VD	1298 (32.5%)	1366 (32.7%)	
3VD	722 (18.1%)	641 (15.4%)	

JH Jung, JK Han et al. (unpub.)

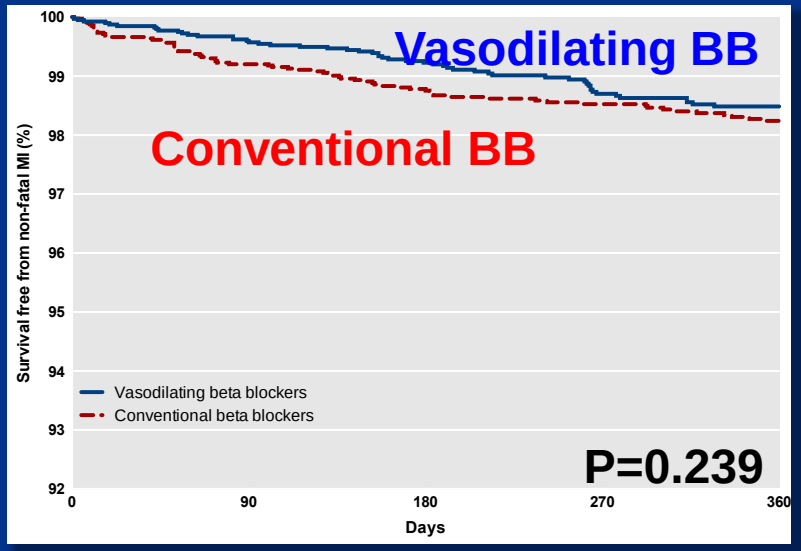
MACE



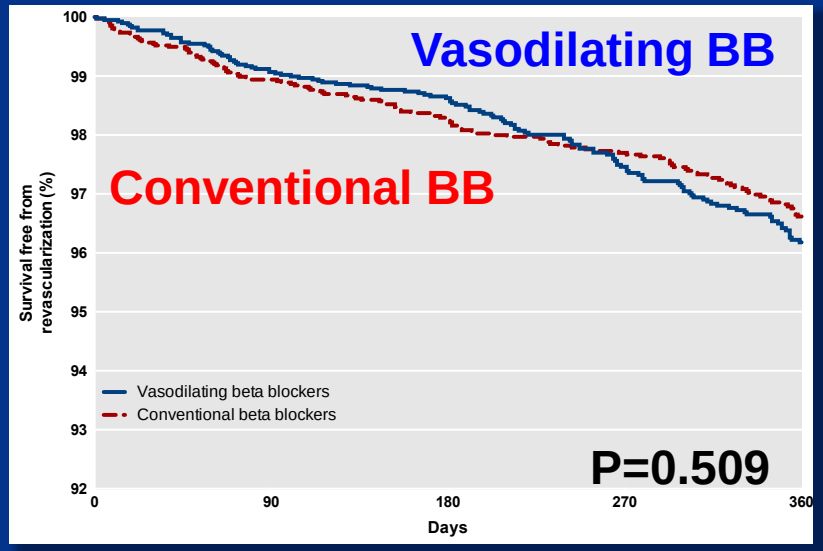
Cardiac death



Non-fatal MI



Any revascularization



SNUH Cardiovascular center

JH Jung, JK Han et al. (unpub.)

Clinical Outcomes: Crude population

	Vasodilating BB (n=3995)	Conventional BB (n=4174)	HR (95% CI)	P-value
MACE	182 (4.6%)	237 (5.7%)	0.827 (0.682-1.004)	0.055
Cardiac death	50 (1.3%)	92 (2.2%)	0.579 (0.410-0.817)	0.002
MI	52 (1.3%)	69 (1.7%)	0.806 (0.562-1.155)	0.239
Revascularization	125 (3.1%)	125 (3.0%)	1.087 (0.848-1.393)	0.509
Rehospitalization	80 (2.0%)	98 (2.3%)	0.867 (0.645-1.165)	0.343

JH Jung, JK Han et al. (unpub.)

Patient Characteristics: PS matching

	Vasodilating BB (n=3101)	Conventional BB (n=3101)	P-value
Age	62.82±12.28	62.91±12.54	0.763
Male	2328 (75.1%)	2331 (75.2%)	0.930
Killip class	1.30±0.75	1.28±0.67	0.463
HTN	1574 (50.8%)	1585 (51.1%)	0.780
DM	861 (27.8%)	854 (27.5%)	0.842
Dyslipidemia	345 (11.1%)	356 (11.5%)	0.659
Previous MI	197 (6.4%)	219 (7.1%)	0.264
Previous angina	256 (8.3%)	250 (8.1%)	0.781
Previous HF	39 (1.3%)	37 (1.2%)	0.813
Previous CVD	207 (6.7%)	198 (6.4%)	0.644
Smoking hx.	1887 (60.9%)	1859 (59.9%)	0.634
Family hx.	192 (6.4%)	202 (6.7%)	0.658
GFR(MDRD)	89.83±37.55	90.21±41.27	0.704
Total cholesterol	180.13±43.58	180.18±45.96	0.968
HDL	42.90±11.34	42.88±12.40	0.955
LDL	112.76±37.33	114.20±51.47	0.224
CCB	149 (4.8%)	134 (4.3%)	0.361
ACEi/ARB	2690 (86.7%)	2706 (87.3%)	0.546
Statin	2953 (95.2%)	2970 (95.8%)	0.298
STEMI	1597 (51.5%)	1590 (51.3%)	0.859
LV EF	52.15±10.68	52.15±10.45	0.991

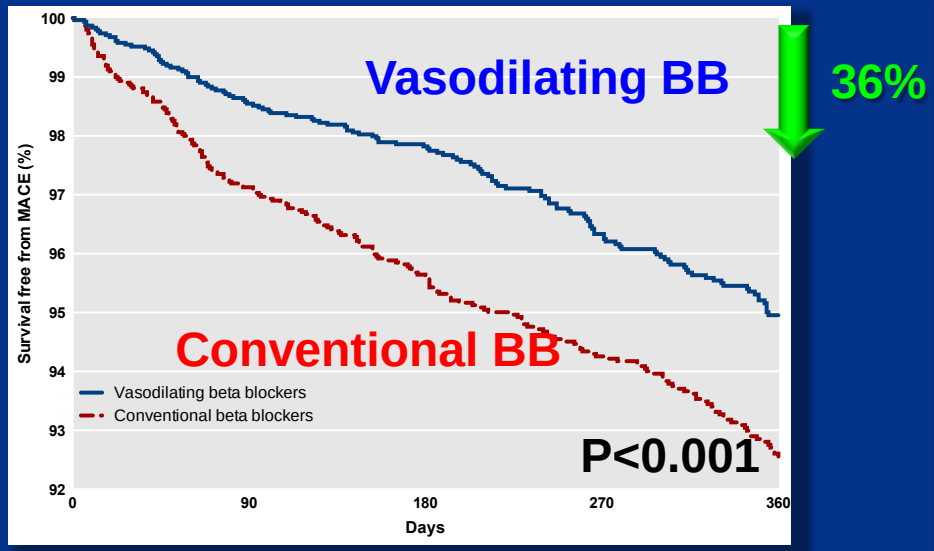
JH Jung, JK Han et al. (unpub.)

Angiographic and Procedural Characteristics: PS matching

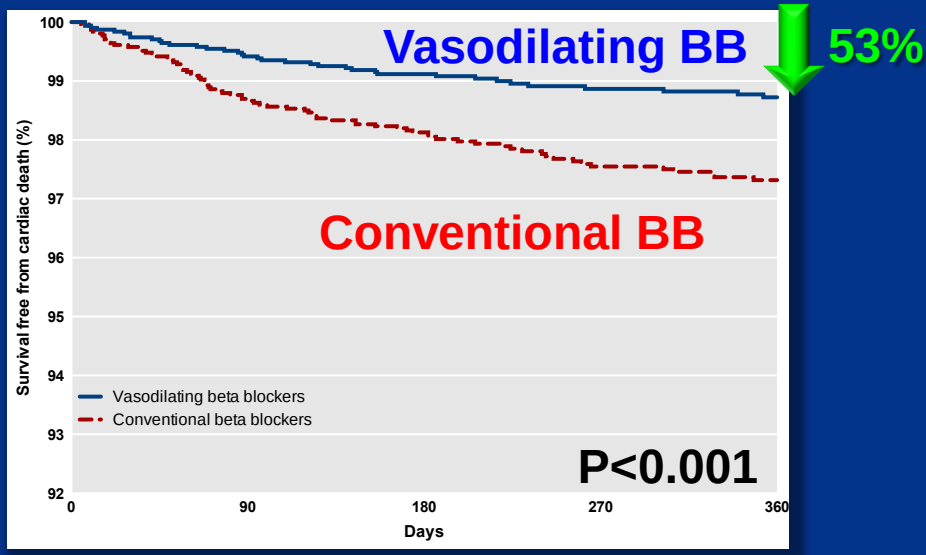
	Vasodilating BB (n=3101)	Conventional BB (n=3101)	P-value
Thrombolysis	39 (1.3%)	29 (0.9%)	0.223
PCI	2939 (94.8%)	2938 (94.7%)	0.955
Target lesion (LM or LAD)	1472 (50.1%)	1443 (49.1%)	0.465
LM	55 (1.9%)	55 (1.9%)	
LAD	1417 (48.2%)	1388 (47.3%)	
LCX	496 (16.0%)	494 (16.8%)	
RCA	971 (31.3%)	1000 (34.0%)	
Target lesion type (B2/C lesion)	2530 (86.1%)	2544 (86.7%)	0.549
Pre TIMI flow of target vessel	1.26±1.31	1.20±1.25	0.081
Post TIIMI flow of target vessel	2.97±0.22	2.97±0.21	0.466
Mean involved vessel number	1.65±0.77	1.65±0.77	0.921
1VD	1509 (48.7%)	1484 (47.9%)	
2VD	1019 (32.9%)	1042 (33.6%)	
3VD	526 (17.0%)	517 (16.7%)	

JH Jung, JK Han et al. (unpub.)

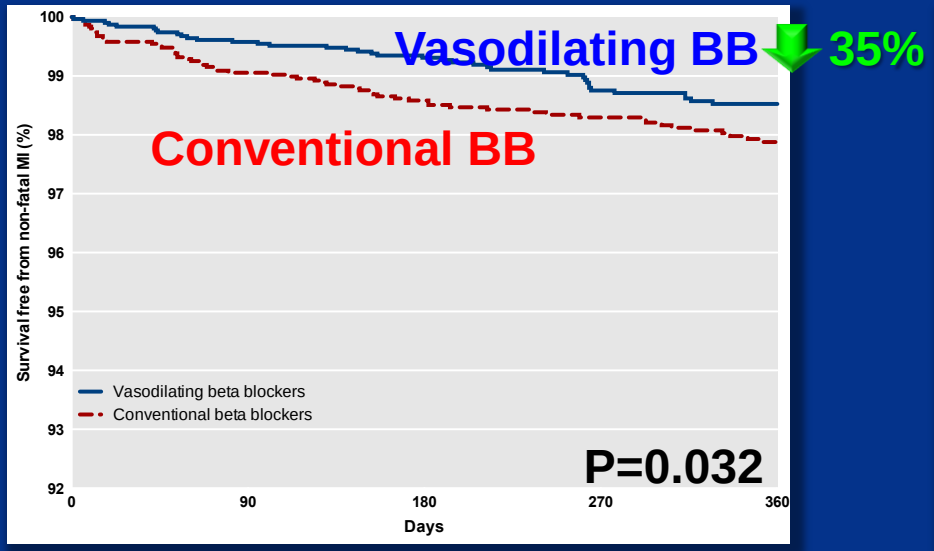
MACE



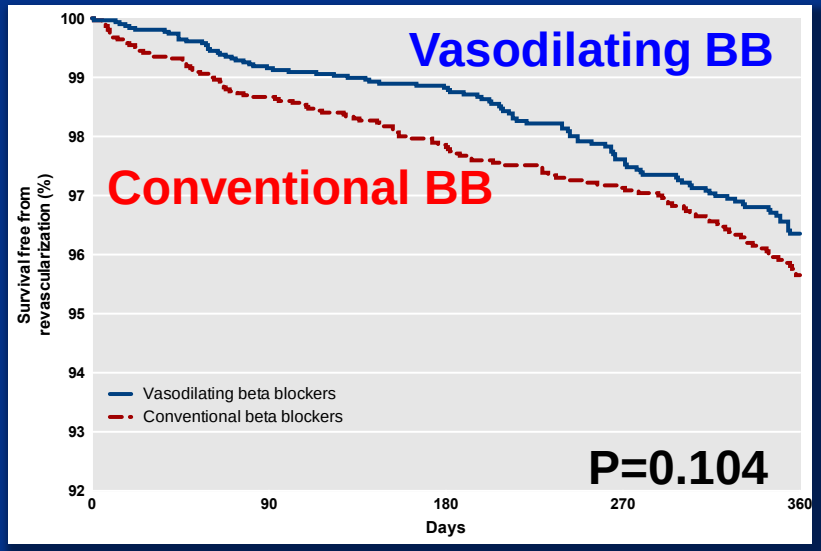
Cardiac death



Non-fatal MI



Any revascularization



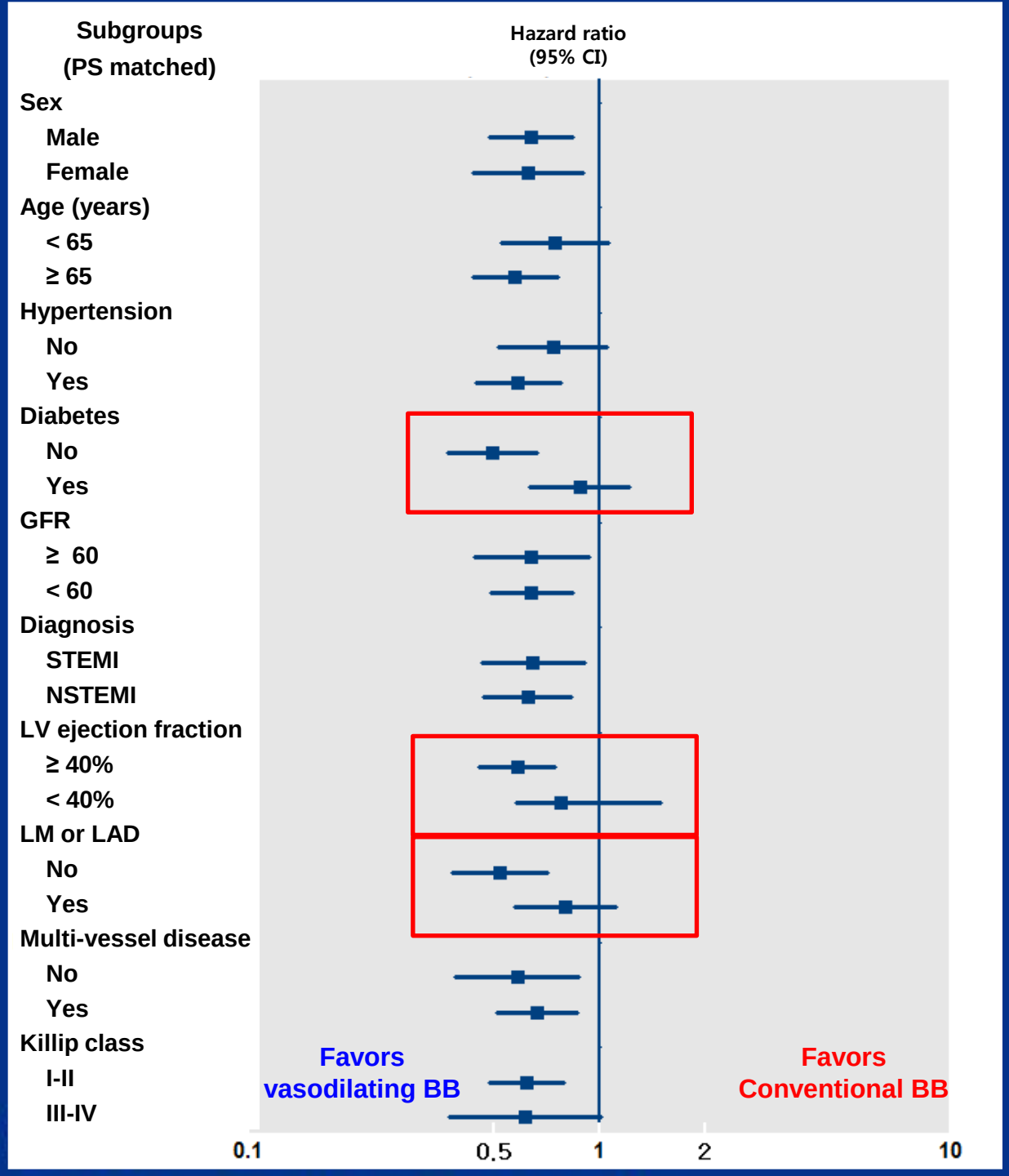
SNUH Cardiovascular center

JH Jung, JK Han et al. (unpub.)

Clinical Outcomes: PS matching

	Vasodilating BB (n=3101)	Conventional BB (n=3101)	Adjusted HR (95% CI)	P-value
MACE	133 (4.3%)	207 (6.7%)	0.639 (0.514-0.794)	<0.001
Cardiac death	36 (1.2%)	76 (2.5%)	0.470 (0.316-0.699)	<0.001
MI	39 (1.3%)	60 (1.9%)	0.646 (0.432-0.967)	0.032
Revascularization	92 (3.0%)	115 (3.7%)	0.797 (0.606-1.048)	0.104
Rehospitalization	62 (2.0%)	86 (2.8%)	0.712 (0.514-0.988)	0.041

JH Jung, JK Han et al. (unpub.)



	HR	95.0% CI	P for interaction
Male	0.641	0.486-0.844	0.928
Female	0.628	0.440-0.897	
< 65	0.749	0.525-1.068	0.256
≥ 65	0.576	0.437-0.760	
No	0.738	0.517-1.053	0.328
Yes	0.589	0.447-0.776	
No	0.498	0.371-0.669	0.012
Yes	0.880	0.632-1.225	
≥ 60	0.643	0.441-0.938	0.982
< 60	0.643	0.492-0.839	
STEMI	0.649	0.464-0.908	0.866
NSTEMI	0.626	0.470-0.834	
≥ 40%	0.584	0.457-0.747	0.091
< 40%	0.778	0.580-1.503	
No	0.524	0.384-0.716	0.063
Yes	0.805	0.578-1.120	
No	0.584	0.390-0.873	0.587
Yes	0.667	0.513-0.868	
I-II	0.624	0.489-0.796	0.949
III-IV	0.615	0.376-1.009	

JH Jung, JK Han et al. (unpub.)

Conclusion (2): vasodilating BB

- **Vasodilating β-blockers: carvedilol, nebivolol**
  - **Potential benefits: central BP, metabolic effects..**
  - **Better for MACE, cardiac death, non-fatal MI, compared with conventional BB: from KAMIR**
  - **Further RCTs are warranted**


Thank you for your attention!!!