2016 Annual Spring Scientific Conference of the KSC Apr., 15, 2016

Revisit of Beta-blocker in AMI

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β-blockers for Myocardial Infarction



 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 <u>during and after</u> <u>hospitalization for all patients with STEML</u> and with no contraindications to their use. (*Level of Evidence: B*)
- 3. Patients with <u>initial contraindications</u> to the use of beta blockers in the first 24 hours after **STEMI** should be <u>reevaluated</u> 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.	lla	В
Oral treatment with beta-blockers is indicated in patients with heart failure or LV dysfunction.	I	А
Intravenous beta-blockers must be avoided in patients with hypotension or heart failure.	ш	В
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.	lla	B

- The <u>benefit of long-term treatment</u> with beta-blockers after STEMI is well established, although <u>mostly from</u> trials pre-dating the advent of modern reperfusion therapy and pharmacotherapy...
- In contemporary trials utilizing primary PCI, betablockers have <u>NOT</u> been investigated, although it is not unreasonable to extrapolate their benefit to this setting.
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What guidelines tell us

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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





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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. \rightarrow 100mg po for 7days
 - Mortality benefit for 7days, even for 1yr

Meta-analysis: β-blockers for MI

Short term trials: no mortality benefit!

N. Freemantle, et al. *BMJ* 1999 Long term trials: 33% mortality benefit!

Trial Van de Werf 1993 ^{w43} Yusuf 1980 ^{w48} ISIS-1 Collaborative Group 1986 ^{w17} Atenolol pooled Heber 1987 ^{w14} Labetalol pooled	Weight (%) Odds ratio (95% Cl) 0.3 0.23 (0.00 to 2.37) 2.8 0.74 (0.44 to 1.24) 71.1 0.94 (0.86 to 1.03) 74.2 0.93 (0.85 to 1.02) 0.4 1.84 (0.62 to 5.81) 0.4 1.84 (0.62 to 5.81)	Trial Boissel 1990w ⁵¹ Acebutolol pooled Reynolds 1972 ^{w72} Ahlmark 1974 ^{w49} Wilhelmsson 1974 ^{w79} Andersen 1979 ^{w50}	Weight (%) Odds ratio (95% Cl) 2.9 0.49 (0.25 to 0.93) 2.9 0.49 (0.25 to 0.93) 0.3 1.03 (0.13 to 8.21) 0.8 0.58 (0.15 to 1.94) 1.2 0.48 (0.16 to 1.33) 4.3 0.96 (0.62 to 1.47) 6 0.82 (0.59 to 1.17)
Von Essen 1982 ^{w44} TIMI IIB Study Group 1989 ^{w40} MIAMI Trial Research Group 1985 ^{w25} Metoprolol pooled CPRG 1981 ^{w6} Fuccella 1968 ^{w11} Wilcox 1980b ^{w46} Lombardo 1979 ^{w22}	Drug β Blockers Angiotensin converting enzyme	Number needed to treat* 42 No long term trials in unselected	0.1 1.02 (0.48 to 2.16) 1.5 1.00 (0.01 to 86.25) 1.6 1.02 (0.52 to 1.99) 0.3 0.62 (0.05 to 5.61) 0.3 0.62 (0.05 to 5.61) 0.7 0.56 (0.11 to 2.53) 1.4 1.91 (0.76 to 5.05) 2.4 0.55 (0.21 to 1.36)
Oxprenolol pooled Owensby 1984 ^{w31} Pindolol pooled Evemy 1978 ^{w9} Johansson 1980 ^{w18} Thompson 1970 ^{w39}	Antiplatelet agent ²² Statin ²⁹	153 94	4.6 0.73 (0.39 to 1.35) 5.4 0.76 (0.49 to 1.18) 7.9 0.92 (0.67 to 1.27) 0.5 0.62 (0.40 to 0.96) 23.1 0.80 (0.66 to 0.96) 1.0 1.33 (0.87 to 2.04)
Filosof 198 Fractolol pooled Mueller 1980 ^{w26} Peter 1978 ^{w32} Ledwich 1968 ^{w20} Gupta 1982 ^{w12}	Calcium channel blockers (diltiazem) ³⁰ Thrombolysis and aspirin for 4 weeks ¹⁶	∞ 24	2.4 0.16 (0.02 to 0.79) 3.8 0.53 (0.26 to 1.06) 4.6 0.92 (0.61 to 1.41) 11.8 0.91 (0.71 to 1.17) 3.6 0.96 (0.60 to 1.55) 3.6 0.96 (0.60 to 1.55) 2.0 0.97 (0.51 to 1.50)
Sloman 1967 ^{w37} Dotremont 1968 ^{w8} Kahler 1968 ^{w19} Barber 1976 ^{w3} Bath 1966 ^{w27} Balcon 1966 ^{w2} Norris 1984 ^{w30}	*Number needed to avoid death in 2 year after myocardial infarction.	rs of treatment in unselected patients	2.5 0.07 (0.59 to 1.03) 11.0 0.78 (0.59 to 1.03) 13.9 0.80 (0.63 to 1.02) 2.4 1.00 (0.12 to 8.31) 0.2 0.44 (0.11 to 1.43) 1.5 0.86 (0.40 to 1.84) 2.3 1.07 (0.59 to 1.93) 2.1 0.40 (0.19 to 0.83)
Clausen 1966 ^{w5} Roberts 1984 ^{w35} Norris 1968 Propranolol pooled Tonkin 1981 ^{w41} Comphell 1984 ^{w41}	1.0 0.89 (0.39 to 2.04) 1.2 1.25 (0.62 to 2.54) 1.5 1.35 (0.74 to 2.50) 8.7 1.00 (0.77 to 1.28) 0.1 1.10 (0.01 to 88.04) 0.1 0.01 to 0.11 0.01 to 1.01 to 0.11 0.01 to 0.	A toniow 1992 w ⁶⁰ Hansteen 1982 ^{w60} BHAT Trial Research Group 1982 ^{w57} Propranolol pooled ↓ Julian 1982 ^{w62} Sotalol pooled ↓	16.0 0.65 (0.37 to 1.5) 16.0 0.65 (0.37 to 1.5) 1.0 0.72 (0.56 to 0.91) 26.6 0.71 (0.59 to 0.85) 5.3 0.81 (0.54 to 1.21) 5.3 0.81 (0.54 to 1.21) 5.3 0.81 (0.54 to 1.51)
Ranganathan 1988 ^{w34} ICSG 1984 ^{w16} UKCSG 1983 ^{w42} Timolol pooled Fixed effects pooled	0.1 0.45 (0.01 to 9.51) 0.2 0.35 (0.01 to 4.57) 0.3 0.72 (0.10 to 4.43) 0.3 0.77 (0.14 to 3.81) 1.0 0.72 (0.32 to 1.60) 100 0.95 (0.88 to 1.02)	Hoque 1987*** Norwegian Multicentre Study Group 1981**68 Timolol pooled Darasz 1995**69 Xamoterol pooled Fixed effects pooled	1.0 0.53 (0.17 to 1.54) 12.6 0.60 (0.45 to 0.79) 13.6 0.59 (0.46 to 0.77) 0.1 3.45 (0.25 to 188.83) 0.1 3.45 (0.25 to 188.83) 100 0.77 (0.70 to 0.84)
Full random effects pooled Heterogeneity Q=21.0, df=50, P=1.0	100 0.96 (0.85 to 1.08) 0.01 0.1 0.2 0.5 1 2 5 10 100	Full random effects pooled Heterogeneity Q=39.7, df=32, P=0.16 0.01 0.1 0.2 0.5 1 2 5 10	100 0.77 (0.69 to 0.85) 100

What guidelines tell us

β-blockers in pre-reperfusion era

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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%

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Z. Chen, et al. Lancet 2005

COMMIT trial: early IV, then oral metoprolol

	Metoprolol (n=22 929)	Placebo (n=22 923)	Odds ratio (95% Cl)	Absolute difference per 1000 (SE)	р
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)	< <mark>0.0001</mark>
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)	< <mark>0.000</mark> 1
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

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

	Metoprolol (n=22 929)	Placebo (n=22 923)	Odds ratio (95% Cl)	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

Z. Chen, et al. Lancet 2005

β-blocker in Stable Outpatients

- From REACH registry ۲
- Age \geq 45 with CAD, CV disease, PAD, or at least 3 \bullet atherothrombotic risk factors
- Enroll: Dec., 2003 Dec. 2004, F/U: 44 mo. \bullet
- **PS** matching •



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

Known MI

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S. Bangalore, et al. JAMA 2012

Meta-analysis: β-blockers for MI All-cause mortality

		B-Blocker	Co	ntrols				
	Trial	Events N	Events	s N	IRR	(95% CI)	IRR (95% CI)	Weight
Pre-reperfusion era	Pre-Reperfusion Era Anderson et al Balcon et al Barber et al Barber et al Clausen et al Federman Fuccella et al Goteborg Heber et al Herlitz et al ICSG ISIS-1 Lombardo et al MIAMI MILIS Multicentre Norris et al Owensby Roque et al Rossi et al Salathia et al Snow Snow 1980 Thompson et al UKCSG Wilcox et al (Atenolol) Wilcox et al (propranolol Yusuf et al D+L Subtotal (I-squared		$\begin{array}{c} 64\\ 14\\ 46\\ 49\\ 29\\ 62\\ 162\\ 4367\\ 1142\\ 124\\ 4367\\ 1142\\ 1244\\ 17\\ 152\\ 77\\ 15\\ 3\\ 5\\ 19\\ 19\\ 16\\ 0 \end{array}$	242 58 53 147 57 64 51 114 697 7990 127 2901 135 95 371 225 95 371 225 95 371 225 95 371 225 95 384 55 67 71 52 887 384 55 67 233			$\begin{array}{c} 0.97 \ (0.68, 1.38)\\ 0.96 \ (0.45, 2.05)\\ 0.82 \ (0.35, 1.89)\\ 0.87 \ (0.57, 1.32)\\ 1.15 \ (0.57, 1.32)\\ 1.15 \ (0.57, 1.32)\\ 1.15 \ (0.57, 1.32)\\ 1.15 \ (0.57, 1.32)\\ 0.87 \ (0.57, 1.32)\\ 0.92 \ (0.48, 1.75)\\ 0.51 \ (0.05, 5.62)\\ 1.79 \ (0.78, 4.10)\\ 0.64 \ (0.43, 0.96)\\ 5.00 \ (0.58, 42.80)\\ 0.64 \ (0.43, 0.96)\\ 0.73 \ (0.16, 3.26)\\ 0.86 \ (0.74, 1.00)\\ 0.69 \ (0.28, 1.73)\\ 0.87 \ (0.58, 1.11)\\ 1.01 \ (0.06, 16.11)\\ 1.09 \ (0.56, 2.54)\\ 1.09 \ (0.56, 2.54)\\ 1.09 \ (0.56, 2.54)\\ 1.09 \ (0.56, 2.54)\\ 1.09 \ (0.56, 2.26)\\ 1.30 \ (0.76, 2.22)\\ 1.00 \ (0.06, 15.99)\\ 0.41 \ (0.06, 15.99)\\ 0.41 \ (0.11, 1.59)\\ 0.42 \ (0.14, 1.20)\\ 0.87 \ (0.59, 1.28)\\ 0.74 \ (0.20, 2.77)\\ 1.41 \ (0.63, 3.17)\\ 1.02 \ (0.54, 1.92)\\ 0.87 \ (0.45, 1.68)\\ 0.42 \ (0.17, 1.02)\\ 0.86 \ (0.79, 0.94)\\ 0.86 \ (0.79, 0.94)\\ 0.86 \ (0.79, 0.94)\\ \end{array}$	$\begin{array}{c} 2.25\\ 0.48\\ 0.39\\ 1.56\\ 0.66\\ 0.05\\ 0.40\\ 1.75\\ 0.06\\ 1.75\\ 0.223\\ 0.334\\ 0.04\\ 0.48\\ 0.97\\ 0.048\\ 0.97\\ 0.045\\ 0.97\\ 0.045\\ 0.25\\ 1.816\\ 0.60\\ 0.11\\ 0.16\\ 0.42\\ 0.68\\ 0.65\\ 0.35\\ 34.52 \end{array}$
Reperfusion era	Reperfusion Era Basu et al COMMIT EMIT Gardtman MEMO METOCARD-CNIC RIMA TIMI II B Tomas Van de Werf et al D+L Subtotal (I-squared I-V Subtotal	2 77 1774 22929 2 55 5 134 3 130 0 139 1 79 1 79 1 720 2 62 1 100 1 = 0.0%, p = 0.73	3 1797 4 6 1 4 17 4 4 5)	74 22923 53 128 135 131 70 714 59 94			$\begin{array}{c} 0.64 \ (0.11, \ 3.83) \\ 0.99 \ (0.92 \ 1.05) \\ 1.93 \ (0.17, \ 21.25) \\ 1.19 \ (0.32, \ 4.45) \\ 0.52 \ (0.13, \ 2.08) \\ 0.31 \ (0.01, \ 7.65) \\ 0.22 \ (0.02, \ 1.98) \\ 0.99 \ (0.51, \ 1.94) \\ 0.48 \ (0.09, \ 2.60) \\ 0.24 \ (0.03, \ 2.10) \\ 0.98 \ (0.92, \ 1.05) \\ 0.98 \ (0.92, \ 1.05) \end{array}$	0.09 64.19 0.05 0.16 0.14 0.03 0.06 0.61 0.10 0.06 65.48
	D+L Overall (I-squared I-V Overall Interaction P-value: 0.02	= 0.0%, p = 0.664)			0 0 -	0.94 (0.89, 0.99) 0.94 (0.89, 0.99)	100.00
					1	1 10		
SNILLI Com			-		Favors B-Blocker	Favors Controls		
SNUH Car	ulovascular	center				S. Banga	lore, et al. A	JM 201

Meta-analysis: β-blockers for MI Cardiogenic shock

		B-BI	ocker	Cont	rols						
	Trial	Ever	nts N	Event	s N		IRR (9	5% CI)		IRR (95% CI)	Weight
Bro reportucion ora	Pre-Reperfusion Era							1			
Fre-repenusion era	Anderson et al	8	238	2	242			+ <u>·</u> ·		4.07 (0.86, 19.15	0.25
	Balcon et al	14	56	14	58			+		1.04 (0.49, 2.17)	1.08
	Briant et al	2	62	0	57			· · ·		4.60 (0.22, 95.75	0.06
	Clausen et al	5	66	8	64					0.61 (0.20, 1.85)	0.48
	Fuccella et al	3	106	3	114			•		1.08 (0.22, 5.33)	0.23
	ISIS-1	135	8037	122	7990					1.10 (0.86, 1.41)	9.92
	Lombardo et al	8	133	6	127			++		1.27 (0.44, 3.67)	0.53
	MIAMI	86	2877	93	2901		-	.		0.93 (0.70, 1.25)	6.92
	Norris et al	10	364	8	371			+		1.27 (0.50, 3.23)	0.69
	Norris et al	3	226	4	228					0.76 (0.17, 3.38)	0.27
	Salathia et al	20	416	14	384			+•		1.32 (0.67, 2.61)	1.27
	Snow	3	52	6	55		.	1		0.53 (0.13, 2.11)	0.31
	Wilcox et al	2	157	1	158			- <u>-</u>		2.01 (0.18, 22.20)	0.10
	Yusuf et al	1	244	4	233			+ <u>i</u>		0.24 (0.03, 2.14)	0.12
	D+L Subtotal (I-squared	= 0.0%	p = 0.7	40)				\Diamond		1.05 (0.89, 1.23)	22.23
	I-V Subtotal							\Diamond		1.05 (0.89, 1.23)	
								1			
Reperfusion era	Reperfusion Era		00000	005						1 29 (1 18 1 41)	77 14
	COMMIT	1141	22929	885	22923					0.80 (0.27, 2.39)	0.50
	METOCARD-CNIC	6	139	(131			1	_	0.32 (0.01 7 79)	0.06
	Iomas	0	62	1	59					6 58 (0 34 127 3	9) 0.07
	Van de Werf et al	3	100	0	94				/	1 29 (1 18 1 40)	77 77
	D+L Subtotal (I-squared	1 = 0.0%	o, p = 0.4	53)				X		1.29 (1.18, 1.40)	11.11
	I-V Subtotal							V.		1.23 (1.10, 1.40)	
	D+L Overall (I-squared	= 0.0%,	p = 0.46	8)				\diamond		1.23 (1.14, 1.33)	100.00
	I-V Overall							\diamond		1.23 (1.14, 1.33)	
	Interaction P-value: 0.03										
								1			
							1	1	10		
						Fa	avors B-Blocker	Fav	ors Controls		

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S. Bangalore, et al. AJM 2014

Meta-analysis: β-blockers for MI

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

•	Multicenter ranc
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- 1,959 Pts. with A
- Mean F/U: 1.3yr

1.0-

0.9-

0.8

0.7-

0.6-

0.5-

0.4

0.3

0.2-

0.1-

0.

0

Proportion event-free



Carvedilol group

Placebo group

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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



Malignant ventricular arrhythmia Any ventricular arrhythmia Atrial flutter or atrial fibrillation Any supraventricular arrhythmia

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Risk reduction (%)²⁾

J. McMurray, et al. *JACC* 2005

Cardiovascular center 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.





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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



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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, nonβ-blocker 1,325
- Median F/U: ≈ 1 yrs.

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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)

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J. Yang, et al. JACC CVI 2014

Consistent Outcomes across the subgroups

Subgroups	Number of patients		Hazard ratio	95% CI	p for interaction
Age					
< 75 years	3061		0.98	0.46-1.28	0.26
275 years	914 —	-	0.52	0.32-0.04	
Sex					
Male	2903 —	-	0.50	0.27-0.95	0.53
Female	1072 —	⊢	0.68	0.45-1.04	0.00
Diabetes					
No	2968		0.66	0.37-1.17	0.07
Yes	1007	<u> </u>	0.60	0.14-2.51	0.97
	3073		0.56	0 20-1 07	
≤ 40%	902	<u> </u>	0.48	0.19-1.22	0.96
Killip class on admis	sion				
1-11	3390	_	0.50	0.27-0.93	0.12
111-17	585		0.70	0.39-1.26	
Multivessel disease					
No	1946		0.52	0.22-1.21	0.35
Yes	2029 —	■┼─	0.71	0.34-1.47	0.00
Infarct related arten	,				
Non-LAD	1898		0.63	0.25-1.62	0.64
LAD	2077	<u> </u>	0.58	0.26-1.28	0.04
DC metek	0.1 0.5	1 2	10		
rs matche	Favors β-blocker	Favo	ors no β-blocker		

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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%)

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E. Choo, et al. Heart 2014

	linica		No beta blocker	Beta blocker		HR (95% CI)	P for interaction		tion
		All patients	10.7(63/591)	6.3(37/591)		0.58(0.39-1.93)		Ula	
		Age<65	4.3(13/299)	3.7(11/297)		- 0.87(0.30-0.78)	0.227		
		Age≥65	17.1(50/292)	8.8(26/294)		0.49(0.42-1.22)			
		Male	7.8(32/411)	5.6(23/411)		0.71(0.23-0.82)	0.238		
		Female	17.2(31/180)	7.8(14/180)		0.43(0.34-1.26)			
		No HTN	7.5(23/305)	5.0(15/299)		0.66(0.31-0.89)	0.599		
		HTN	14.0(40/286)	7.5(22/292)		0.53(0.14-1.45)			
		SBP<100	16.1(9/56)	7.1(4/56)		- 0.45(0.39-0.92)	0.636		
		SBP≥100	10.1(54/535)	6.2(33/535)		0.60(0.26-3.06)			
		HR<50	11.9(5/42)	10.9(5/46)		0.89(0.35-0.84)	0.456		
		HR≥50	10.6(58/549)	5.9(32/545)		0.55(0.25-0.82)			
		NSTEMI	13.4(34/253)	6.4(16/251)		0.46(0.41-1.26)	0.266		
		STEMI	8.6(29/338)	6.2(21/340)		0.72(0.46-1.54)			
		Single vessel	8.1(23/285)	6.7(19/282)		- 0.84(0.25-0.75)	0.115	Choo, e	t al. <i>Heal</i> 201
	Table 5 Cumulativ	Multivessel	13.1(40/306)	5.8(18/309)		0.43(0.38-1.29)			
		Culprit: LM/LAD	10.6(25/235)	7.3(17/233)		- 0.69(0.29-0.86)	0.433	95% CI)	p Value
	All cause death Cardiac death	Culprit: RCA/LCX	K 10.7(38/356)	5.6(20/358)		0.50(0.20-0.71)	•••-		0.008
	Stroke	no ACEi/ARB	17.0(35/206)	6.8(13/190)		0.37(0.49-1.45)	0.056		0.209
	Ischaemic stroke Myocardial infarction	ACEi/ARB	7.3(28/385)	6.0(24/401)		- 0.84(0.00-0.00)			0.123 0.844
5	Any revascularisation PS, propensity score.			Beta l	0.1 1 olocker better	10 No beta blocker better			0.903

-

Conclusion (1): pre- vs. repersuiion era

- β-blockers in pre-reperfusion era
 - Extensive myocardial scarring: a substrate for reentrant 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. repersuiion 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 Indepen	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 H	Hg)	0.119										
Brachial PP (/10 mm H	<u> </u>			0.063								
Carotid SBP (/10 mm H	g)				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% Cls)	HR (95% Cls)	HR (95% Cls)	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)‡					

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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}	$\downarrow \\ \downarrow \leftrightarrow$	
Beta-blockers ^{2,61–63,63,23,103,106,107}	$\uparrow\uparrow$	
Calcium channel blockers ^{61–63,96} Diuretics ^{61–63,100,102} Nitrates ^{68,70,71,74}	$\begin{array}{c}\downarrow\leftrightarrow\\\leftrightarrow\\\downarrow\downarrow\end{array}$	

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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	NČ	
Labetalol	Improvement	Improvement	
Carvedilol	Improvement	Improvement	
Nebivolol	Improvement	Improvement	
Alexandration index NC and shares DW/V mules more relative			

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

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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.

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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).

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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 $ imes$ 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	
AlBa indicates acute insulin res	nonea to alucasa. K	SL inculin consitivity	index

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 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



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
ССВ	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

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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%)	

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Cardiac death





Any revascularization





Non-fatal MI



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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

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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
ССВ	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

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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%)	

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Cardiac death

53%



Non-fatal MI



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Any revascularization



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

P<0.001

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

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Subgroups		Hazard ra	tio	
(PS matched)		(95% CI)	
Sex				
Male				
Female				
Age (years)				
< 65			-	
≥ 65				
Hypertension				
Νο			-	
Yes				
Diabetes	Г			
Νο				
Yes			_	
GFR	L			
≥ 60				
< 60				
Diagnosis				
STEMI				
NSTEMI				
LV ejection fraction	_			
≥ 40%				
< 40%				
LM or LAD				
No		_		
Yes			_	
Multi-vessel disease	L			
Νο				
Yes				
Killip class	Ferrers			Ferrers
I-II				Favors Conventional PP
III-IV	vasoullating			
0.1	1	0.5 1	2	10

HR	95.0% CI	P for interaction
0.641	0.486-0.844	0 028
0.628	0.440-0.897	0.320
0.749	0.525-1.068	0.050
0.576	0.437-0.760	0.256
0.738	0.517-1.053	
0.589	0.447-0.776	0.328
0.498	0.371-0.669	
0.880	0.632-1.225	0.012
0.643	0.441-0.938	
0.643	0.492-0.839	0.982
0.649	0.464-0.908	
0.626	0.470-0.834	0.866
0.584	0.457-0.747	
0.778	0.580-1.503	0.091
0.524	0.384-0.716	
0.805	0.578-1.120	0.063
0.584	0.390-0.873	
0.667	0.513-0.868	0.587
0.624	0.489-0.796	
0.615	0.376-1.009	0.949
JH Jı	ing, JK Han e	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!!!

