





Beta-Blocker Post Myocardial Infarction: Adjunctive Therapy

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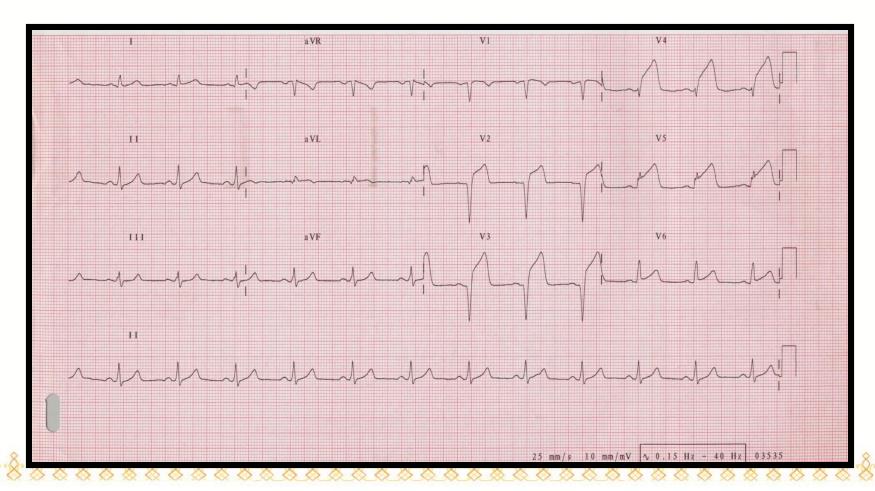
Case

- M: 52yrs
- With anterior STEMI
- PPCI of IRA (LAD) & PCI of RCA in index hospitalization
- Ticagrelor 90mg (1x2)
- Aspirin (100mg), Bisoprolol (5mg)
- Atorvastatin (80mg)
- Echo Cardiogram: EF = 45%, No mural thrombus
- The patient is stable and discharged after 4 days





ECG





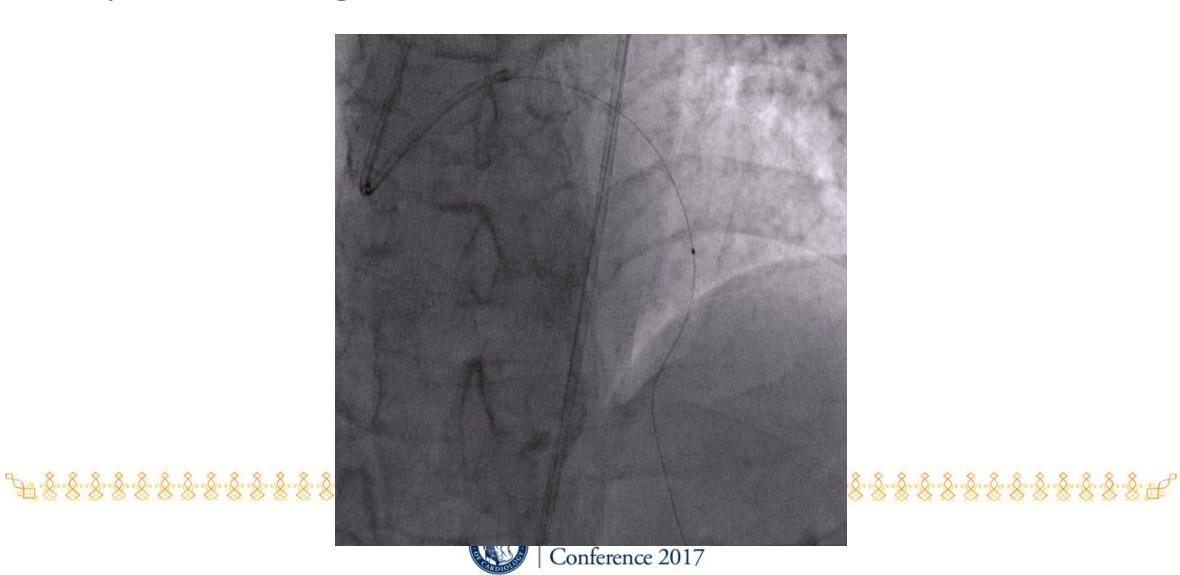
Total occlusion of LAD with big thrombus



Export cath. for aspiration thrombectomy



Aspiration again

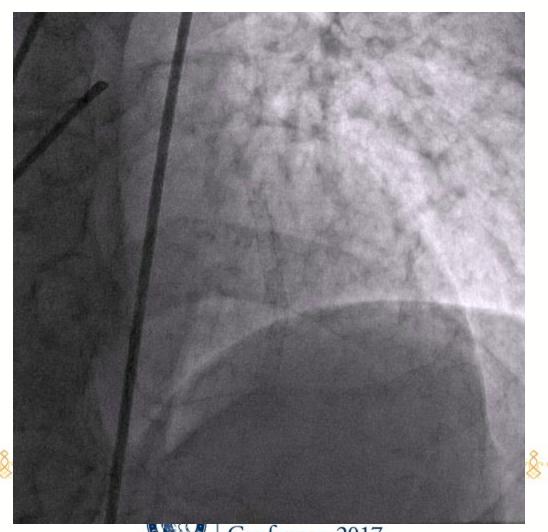


After final aspiration



DES 3/38mm



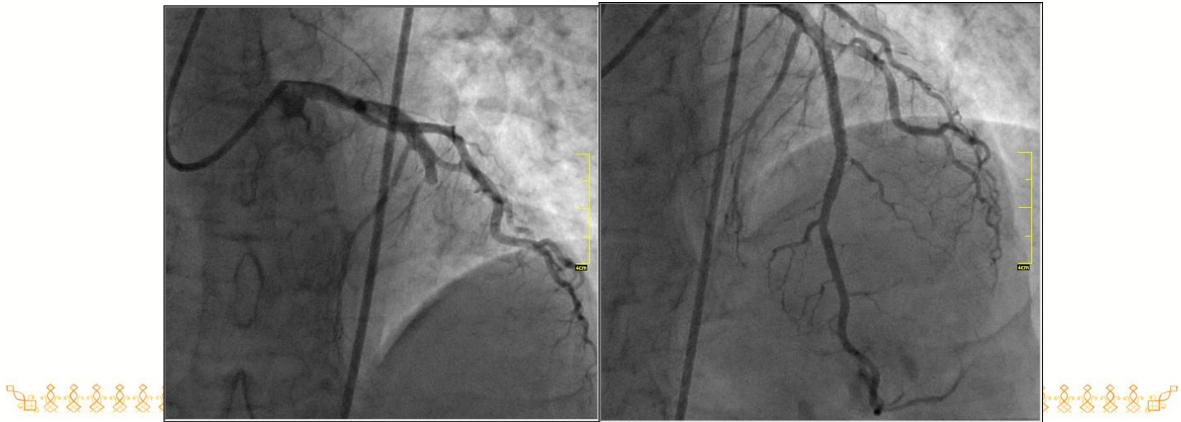






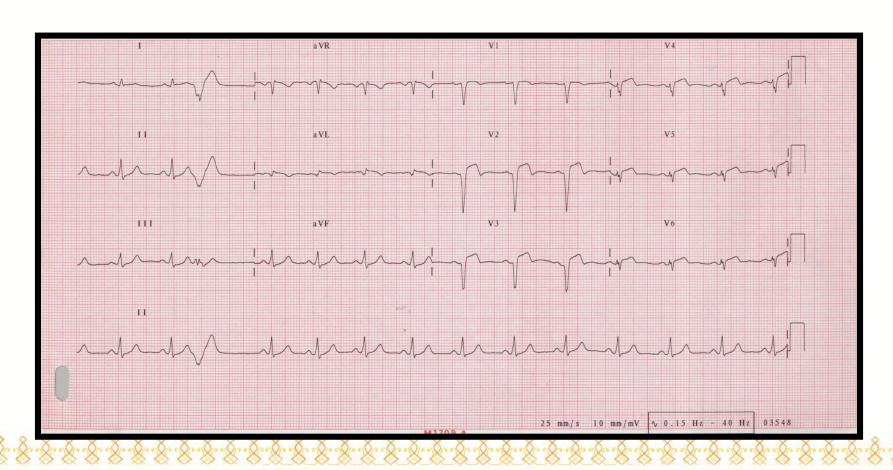
Conference 2017

Before After





ECG post PCI





Management of cardiogenic shock in ST-elevation myocardial infarction (continued)



Recommendations	Class	Level
Fibrinolysis should be considered in patients presenting with cardiogenic shock if a primary PCI strategy is not available within 120 min from STEMI diagnosis and mechanical complications have been ruled out.	lla	С
Complete revascularization during the index procedure should be considered in patients presenting with cardiogenic shock.	lla	C
Intra-aortic balloon pumping should be considered in patients with haemodynamic instability/cardiogenic shock due to mechanical complications.	lla	С
Haemodynamic assessment with pulmonary artery catheter may be considered for confirming diagnosis or guiding therapy.	IIb	В

Š.







Before hospital discharge PCI RCA was done





PCI RCA (DES)



Agenda

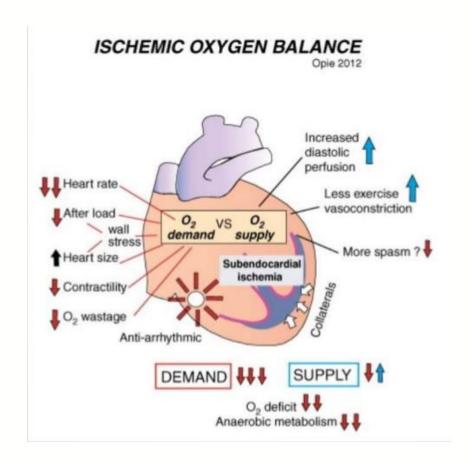
- Protective Effect of Beta-blockers
- Role of Beta-blockers in different eras
- What did the AHA recommend?
- Choice of Beta-blockers
- Long-term therapy
- Recent Guidelines of Beta-blockers in STEMI



Protective effects of beta blockers

- ↓ HR and contractility
- ↓ VO₂

- ↓ apoptosis signalling
- Anti-ischemic and antiarrhythmic effects - ↓ VF
- Anti-inflammatory
- Increase synthesis of myocardial proteins
- Shift from FFA to glucose metabolism
- Peripheral antioxidant effect
- Reduce catecholamine





Protective effects of beta blockers in ischemia

- Reduce the myocardial oxygen demand via
 - negative inotropic action
 - reduction of heart rate
 - blood pressure decrease
- Increase coronary blood flow via
 - increase in diastolic perfusion time by reducing heart rate
 - augmentation of collateral blood flow and
 - redistribution of blood flow to ischemic areas
- Alter the myocardial substrate utilization
- Decrease the microvascular damage
- Stabilize the cell and lysosomal membranes





Types of Beta Blockers

- Non Cardioselective Acebutolol, Propranolol
- Partially Cardioselective Atenolol, Metoprolol
- Highly Cardioselective Nebivolol, Bisoprolol



Role In STEMI: Thrombolytic Era

- TIMI IIB¹
 - Assessed the effects of immediate versus deferred β blockers therapy in patients receiving i.v rTPA.
 - Immediate beta-blockade produced no improvement in LVEF, nor reduced mortality (in both invasive and non-invasive treatment arms) at hospital discharge.
 - However, reduced re-infarction rate and recurrent chest pain noted
- Gusto I Post Hoc analysis²
 - Oral atenolol conferred a 5-fold lower mortality risk
 - Associated with decreased stroke, shock and arrhythmias
 - Increased recurrent ischemia and re-infarction



^{2.} Pfisterer M, Cox JL, Granger CB, et al. Atenolol use and clinical outcomes of extremololysis for acute myocardial infarction: the GUSTO-I experience. Global Utilization of Streptokinase and TPA [alteplase] for Occluded Coronary Arteries. J in Conference 2017

Role In STEMI: Thrombolytic Era

- 2004 STEMI guidelines (AHA/ACC) recommended the use of early IV β blockers in those undergoing fibrinolytic treatment
- Doubt was raised from a review of the GUSTO I trial (atenolol)
- 2007 issued new guidelines, took into account the COMMIT study of metoprolol





COMMIT/CCS-2 Study

Conclusions

- Metoprolol (15 mg IV, then 200 mg oral daily) in acute MI patients did not significantly reduce in-hospital mortality.
- It reduced the absolute risks of re-infarction by 5 per 1000 (P = .001) and of VF by 5 per 1000 (P < .001) from Day 2.
- Overall, metoprolol increased the risk of cardiogenic shock by 11 per 1000 (P
 < .00001), chiefly during the first day of hospitalization.
- In acute MI, it may be better to start beta-blocker therapy when the patient is stable (and then continue long-term therapy).





So what did the AHA recommend?

- Administer iv β blockers on Day 0 -1 if
 - There is hypertension
 - Sinus tachycardia or AF (provided bedside echo shows normal LV function)
- Avoid early oral β blockers if
 - Signs of heart failure +
 - Increased risk of Cardiogenic Shock
 - Relative contraindications are present
 - 1st degree AV block (or any other block)
 - Active asthma
- If early contraindications are present, then re-evaluate suitability after 24 hours.





So what did the AHA recommend?

- From Day 2, benefit is seen on re-infarction and VF reduction rate
- Start with Metoprolol 50 mg 6 hourly (can go up to 200 mg/day)
- Long term use strongly recommended

METOCARD CNIC Trial — Conclusions

- Pre PCI iv β blockers reduce infarct size (by ~20%)
- Lesser infarct size means better LV function post MI/PCI
- However, it only studied anterior infarcts, not others
- The authors say –

'although important and encouraging, the results of the METOCARD-CNIC trial are probably not strong enough to warrant a change in the clinical practice of the use of 8-blockade in patients with STEMI'





Post PCI Role

- BEAT AMI Trial
 - Single blinded
 - Enrolled only patients within 6 hours of symptom onset who had Killip class I or II STEMI
 - Randomly allocated to receive heart rate control with IV esmolol for 24 hours (target of 60 bpm) or placebo.
- Result
 - Lesser troponin rise
 - Lesser CK rise
 - Lesser NT pro-BNP rise
- Infarct size not assessed with CMR





Post STEMI Role

- Well established for oral β blockers
- CAPRICORN Carvedilol in post MI patients with LVSD





Choice of beta blocker

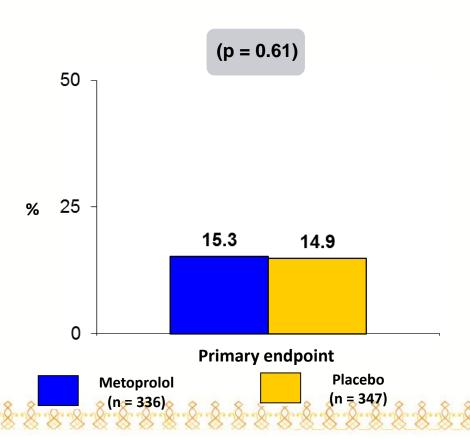
- Use a cardioselective one either metoprolol (preferred) or atenolol
- Start low, go slow
- If ongoing ischemia before PPCI, some groups recommend iv metoprolol, atenolol or esmolol.
- Watch for bradycardia or hypotension
- If hypertension present, better to use iv NTG instead to reduce BP.





EARLY-BAMI

Trial design: Patients presenting with STEMI with a plan for primary PCI, and without evidence of cardiogenic shock, were randomized to either intravenous bolus metoprolol 5 mg x 2 or matching placebo. They were followed for 30 days.



Results

- Primary endpoint, infarct size on delayed enhancement CMR at 30 days, for metoprolol vs. placebo: 15.3% vs. 14.9%, p = 0.61
- LVEF on CMR: 51% vs. 51.7%, p = 0.68
- Severe bradycardia: 1.5% vs. 0.6%, p = 0.28; cardiogenic shock: 0.6% vs. 0.3%, p = 0.62; ventricular arrhythmia: 3.6% vs. 6.9%, p = 0.05

Conclusions

- Early routine administration of intravenous metoprolol is not beneficial in reducing infarct size in patients presenting with STEMI and undergoing primary PCI, similar to what has been observed in other trials
- Small study, but no clear safety signal with early administration of intravenous beta-blockers





Relevance to My Daily Practice



- Early intravenous metoprolol dosing appears safe among patients with STEMI without acute pulmonary edema or shock.
- Potential benefit in reduction of infarct size in anterior STEMI (especially with higher metoprolol dosing).
- Reduction in malignant arrhythmias during hospitalization (3.6% vs. 6.9%).
- Most important aspect is long term secondary risk reduction.

Long term therapy – How long?

- The optimal duration of treatment is not very clear.
- Evidence supports total duration of treatment of 3 years; not much for longer than that
- When stopping, taper the dose
- REACH registry data showed no difference in benefit between beta blocker and no beta blocker groups at 2 years.
- Maybe better for those with higher risk of LVSD and chronic kidney disease
- In high risk patients, longer duration of treatment is acceptable





Long term therapy – How much

- Clinical trials suggest doses of 200 mg/day of metoprolol
- Not practical, not used in clinical practice
- Best policy Start Low, Go Slow
- Better to use longer acting preparation





Targets

- Recommendation
 - Heart Rate < 70 bpm
 - SBP > 90 mmHg
- Avoid if
 - SBP low / shock
 - Severe bronchospasm
 - Bradycardia / heart block
 - Acute heart failure
- Can be given in
 - Controlled COPD mortality benefit seen
 - Controlled heart failure carvedilol
 - Peripheral vascular disease





Closing Remarks

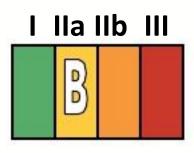
- The role of 'very early' β blockers in managing STEMI is not clearly defined.
- However, its role in preventing arrhythmias post MI is established.
- \bullet Careful assessment of patients must be before starting β blockers follow AHA guidelines
- \bullet Start β blockers within 24 hours if patient stable and no contraindication present
- Beta blockers after STEMI reduce overall mortality, non fatal MI and SCD
- As always, we need more data.





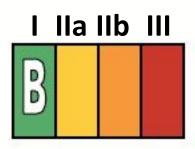
Recommendations of Beta-Blockers in STEMI

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.

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

Seung-Jae Joo1, Jae-Geun Lee1, Hyung-Yoon Kim1, Joon-Hyouk Choi1, Song-Yi Kim1, Ki-Seok Kim1, Seung Woon Rha2, Jin-Ok Jeong3, Shung Chull Chae4, Dong-Ju Choi5, Young Jo Kim6, Kwon-Bae Kim7, Jei Keon Chae8, Myung Ho Jeong9 and other KAMIR-NIH investigators

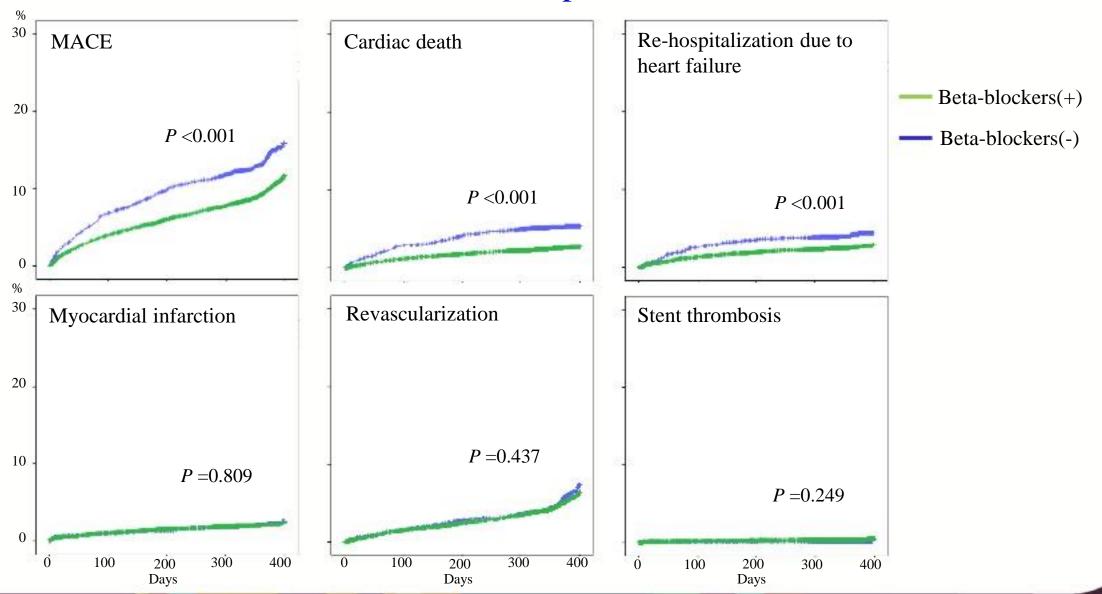
Department of Cardiology, Jeju National University Hospital, 2Department of Cardiology, Korea University Guro Hospital, Seoul, 3Department of Cardiology, Chungnam National University Hospital, Daejeon, 4Department of Cardiology, Kyungpook National University Hospital, Daegu, 5Department of Cardiology, Seoul National University Bundang Hospital, Seongnam, 6Department of Cardiology, Yeungnam University Hospital, Daegu, 7Department of Cardiology, Keimyung University Hospital Dongsan Medical Center, Daegu, 8Department of Cardiology, Chonbuk National University Hospital, Jeonju, 9Department of Cardiology, Chonnam National University Hospital, Gwangju, Korea, Republic of

The KAMIR-NIH Registry

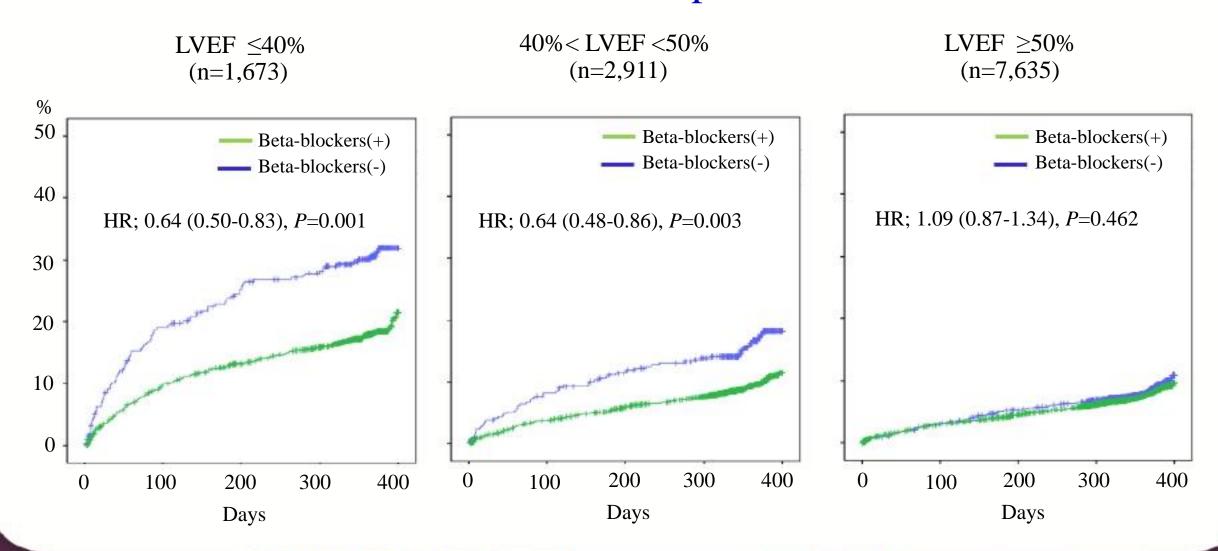


*KAMIR-NIH; Korea Acute Myocardial Infarction Registry-National Institute of Health

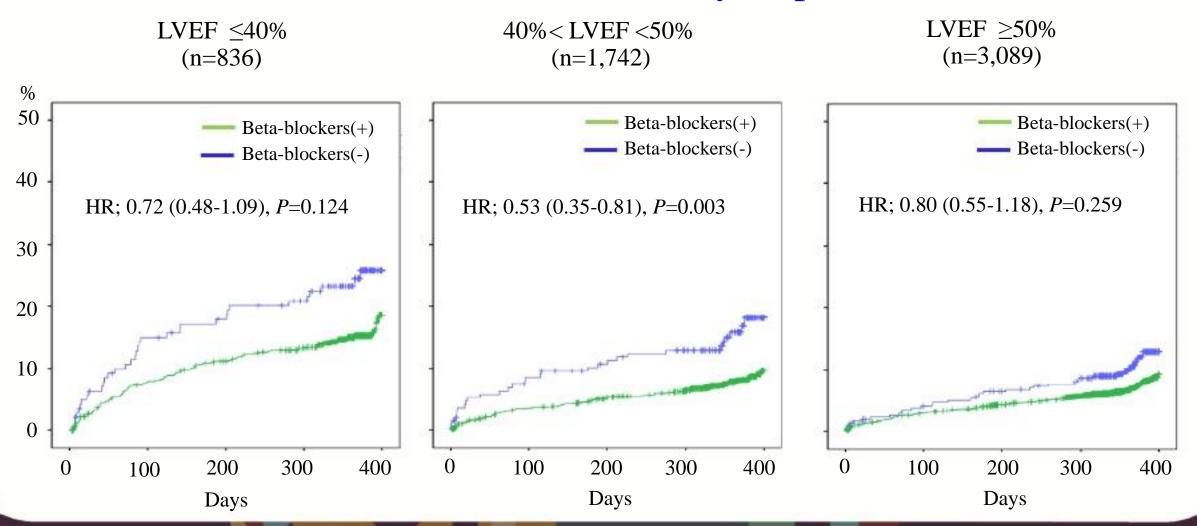
Beta-blockers reduced cardiac death and re-hospitalization due to heart failure



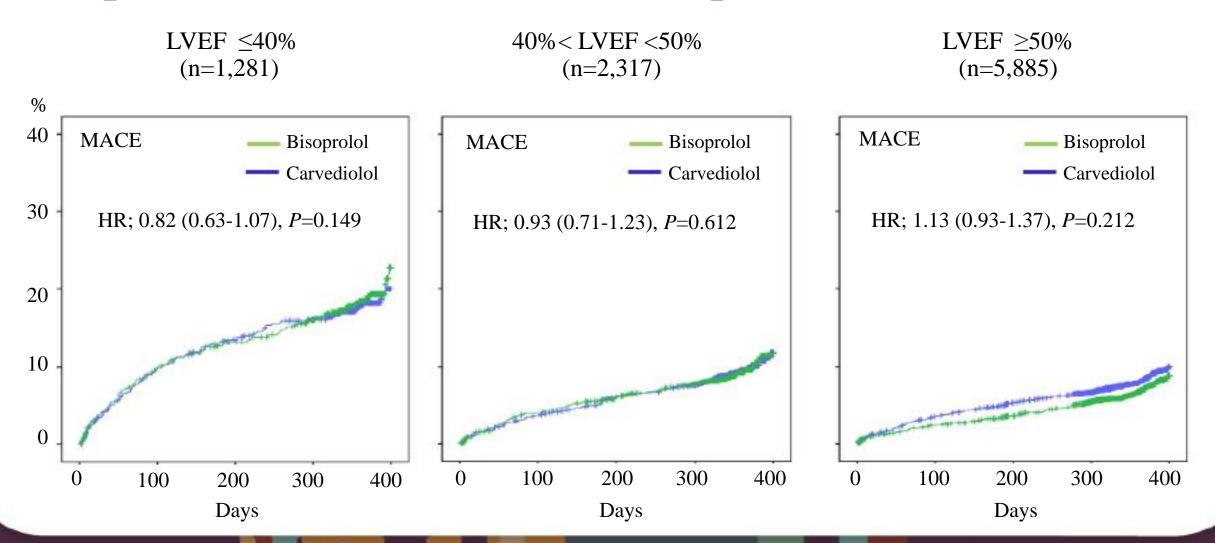
Beta-blockers did not reduce MACE in patients with LVEF ≥50%



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



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.



Can beta-blockers be stopped in patients with preserved left ventricular function after acute myocardial infarction? Five-year follow-up of FAST-MI 2005

N. Danchin 1, **E. Puymirat** 1, G. Ducrocq 2, R. Sader 3, X. De Boisqelin 4, C. Boureux 5, N. Delarche 6, J. Ferrieres 7, F. Schiele 8, T. Simon 9

(1) AP-HP, HEGP, Paris; (2) AP-HP, Hôpital Bichat, Paris; (3) CH de Laon; (4) Clinique La Valette, Montpellier; (5) CH de Perpignan; (6) CH de Pau; (7) CHU Rangueil, Toulouse; (8) CHU Jean Minjoz, Besançon; (9) AP-HP, Hospital Saint-Antoine, Paris, France









Background and Aim

Background

guidelines.

✓ Most RCTs of beta-blockers after AMI were led before the era
of reperfusion therapy and modern secondary prevention.

STEMI

NSTEMI

✓ Their usefulness in patients currently treated for AMI with preserved LV function is debated, leading to divergences between European and American

Aim

✓ To assess the impact of beta-blocker discontinuation on 5year mortality in the FAST-MI 2005 cohort.





ESC

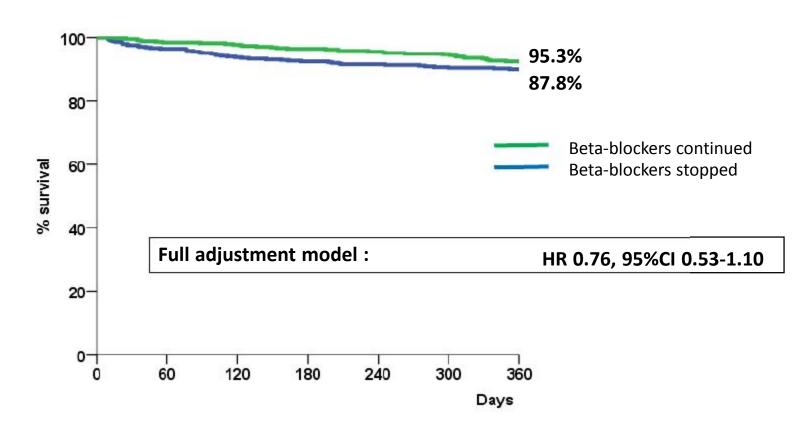
I→IIaB

IA

IA



One-year survival







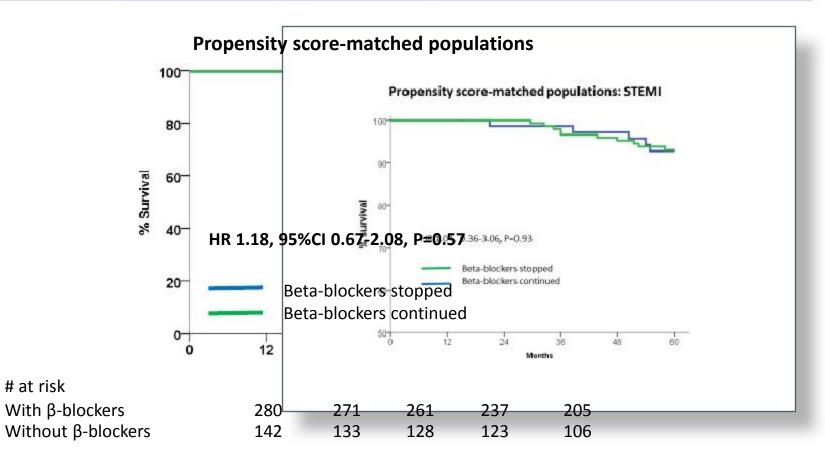
→ Beta-blockers might be useful during the first year in AMI patients with preserved LV function and no history of heart failure



at risk

Five-year outcome

	Beta-blockers ongoing	Beta-blockers stopped		AdjustedHR (95%CI)
Five-yeardeath	8.8%	13.0%	0.63(0.40-0.97)	1.01(0.59-1.73)









Conclusion

- In acute myocardial infarction patients with preserved LV function and no history of heart failure:
- \checkmark early β -blocker treatment might be beneficial;
- ✓ stopping β-blockers during the first year after discharge was not associated with increased mortality at five years.
- These results support the changes adopted in the most recent ESC guidelines.







Class effect of beta-blockers in survivors of ST-elevation myocardial infarction

: A nationwide cohort study using insurance claims database

Ting-Tse Lin₁; K. Arnold Chan, Sc.D.,₂Ho-Min Chen,³ Mei-Shu Lai,^{3,4} Chao-Lun Lai,¹

Background

Beta-blocker therapy is the standard treatment for ST-elevation myocardial infarction (STEMI). The evidence supporting the benefit of beta-blockers has been obtained primarily from predating randomized trials. However, whether beta-blockers exert a class effect remains controversial in the modern PCI era.

Methods

We identified all patients who had the first ST-elevation MI through 2003 to 2010 from the NHI claims database in Taiwan. We compared patients prescribed with carvedilol, bisoprolol or

propranolol. The study outcome included all-cause death, cardiovascular death and recurrence of MI. Treating the carvedilol group as the reference, simultaneous three-group comparison

approach using Cox regression model with adjustment for age, sex and the propensity score was used to compare the relative risks of different outcomes.

Declaration of Interest

There is no conflict of interest or financial support concerning this presentation.

Table 1. Basic characteristics

		Bisoprolo					
	- <u>c</u>	arvedilo	<u>l</u> l	CD:	Propranc		
	Variable			SD•		SD+	
	Patients (n)	7591	5934		3311		
	Female (%)	21.7	19.7	0.05	20.8	0.02	
	Age (years, Mean)	62.1	60.7	0.10	60.6	0.11	
	Comorbidities (%)						
	Congestive Heart failure	6.9	5.2	0.07	4.3	0.12	
	Cerebrovascular disease	9.7	8.8	0.03	8.2	0.06	
	Chronic pulmonary disease	8.6	7.7	0.03	7.7	0.03	
1	Dementia	1.4	1.1	0.03	1.3	<0.01	
	Diabetes without chronic complication	24.7	23.8	0.02	20.9	0.09	
	Diabetes with chronic complication	8.4	6.1	0.09	5.5	0.12	
	Liver disease	5.2	5.0	0.01	5.5	0.01	
	Pepticulcer disease	9.6	9.6	< 0.01	10.2	0.02	
	Renal disease	5.6	4.4	0.06	4.1	0.07	
	Prescriptions at discharge (%)						
	Aspirin	96.7	97.5	0.05	96.3	0.02	
	Clopidogrel	88.7	92.7	0.14	78.1	0.29	
	Warfarin	3.6	2.3	0.08	2.7	0.05	
	CCBs	23.1	24.3	0.03	24.6	0.04	
	ACEIs	75.6	72.6	0.07	72.4	0.07	
	ARBs	20.1	23.3	0.08	13.1	0.19	
	Loop diuretics	44.5	33.0	0.24	26.9	0.37	
	Spironolactone	13.6	9.6	0.13	5.5	0.28	
	Statins	53.9	63.4	0.19	46.0	0.16	
	Amiodarone	16.2	12.4	0.11	10.0	0.18	

Results

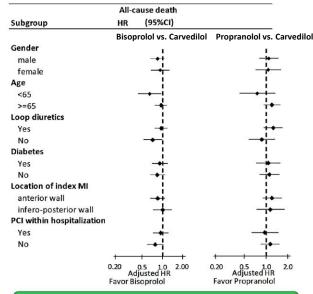
Table 2. Clinical outcomes in different beta-blocker groups

-		Total (Carvedilol	Bisoprolol	<u>Propranolo</u> l
-	n	168	36	7591	3 593 4
	Follow-uptime(years) Mean(SD) All-causedeath,n(%)	1.0(1 624 (3.		1.0(1.3) 5 (4.5%) 1	0.8(1.9) 938 (3 (3%6)%)
	CVdeath,n(%)	309 (1.8	3%) 174	(2.3%)	9 \$15.71%1%)
	RecurrenceofMI,n(%)	1229 (7.	3%) 564		122 23.5%)
	Abbreviations:CV cardiovascula	ar·MI myor	ardialinfar	ction·SD star	ndarddeviatio

Table 3. Relative risks of different clinical outcomes between three beta-blocker groups.

		All-cause death			CV death			Recurrence of N	II
Crude results									
Drug	HR	95% CI	р	HR	95% CI	р	HR	95% CI	р
Carvedilol	1			1			1		
Bisoprolol	0.62	(0.52-0.74)	<0.001	0.64	(0.50-0.82)	<0.001	0.92	(0.81-1.04)	0.18
Propranolol	0.81	(0.64-1.03)	0.08	0.66	(0.46-0.9	5) 0	.024	1. 1.7 .96-1.31)	0.16
Simultaneous	three-grou	ıp comparison ap	proach wi	th adjustn	nent for the p	ropensity :	score*		
Drug	HR	95% CI		p	HR 9	5% CI	р	95%ICI	р
Carvedilol	1				1			1	
Bisoprolol	0.87	(0.72-1.05)	0.14	0.87	(0.68-1	13)	0.30	9.07 85-1.10)	0.63
Propranolol	1.07	(0.84-1.36)	0.58	0.92	(0.64-1	.32)	0.64	1(·1)!97-1.33)	0.12
Pairwise contro	ast approd	ach with adjustm	ent for the	propensit	ty score†				
HR	95% CI	р	н	IR 95	% CI	р	HR	95% CI	р
Carvedilol	1				1			1	
Bisoprolol	0.88	(0.73-1.06)	0.17	0.88	3 (0.68-1	13)	0.31	9.886-1.12)	0.76
Propranolol	1.06	(0.83-1.36)	0.62	0.90	(0.62-1	.31)	0.58	1(-10295-1.31)	0.18
Pairwise contr	ast approd	ach with stratific	ation on th	e quintile:	s of the prope	ensity score	e‡		
Drug	HR	95% CI		р	HR 9	5% CI	р	95 ∜ि ।	р
Carvedilol	1				1			1	
Bisoprolol	0.86	(0.72-1.04)	0.11	0.87	(0.67-1	13)	0.29	9.986-1.12)	0.77
Propranolol	1.04	(0.81-1.33)	0.77	0.89	(0.61-1	.29)	0.53	1(-10396-1.33)	0.14

Figure 1. Subgroup analyses



Conclusion

After adjustment for baseline characteristics, there was no difference in risks of all-cause death, cardiovascular death and recurrence of MI between carvedilol, bisoprolol and propranolol.

In a real-world population-based setting in Taiwan, the present study suggests that the choosing a specific beta-blocker for STEMI patients will have little influence on clinical outcomes, supporting the concept of class effect of beta-blockers.

Intravenous Beta-Blocker Therapy in ST-Segment Elevation Myocardial Infarction

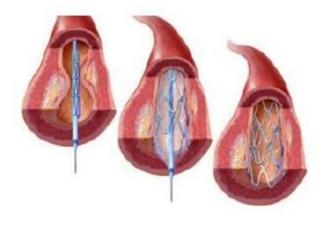
Dworeck C, Redfors B, Haraldsson I, Angerås O, Odenstedt J, Ioanes D, Petursson P, Völz S, Albertsson P, Råmunddal T,Omerovic E

Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden

Potential benefits

Background

Benefits and danger of i.v. pretreatment with beta blockers with STEMI



- Reduce infarct size
- Reduce malignant ventricular arrhythmias
- Improve LV finction
- Improve survival

IV beta blockade





- Higher risk for cardiogenic shock
- Higher risk for mortality

What is SWEDEHEART? SWEDE



Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

- § National registry of coronary artery disease care and valvular interventions
- § Effects:
 Improves quality of care
 Improves outcome
 Powerful tool for research
 Improves cost-effectiveness



SWEDEHEART

SCAAR

Angiography and PCI 1998

RIKS HIA

Acute coronary care 1995

Thoracic surgery

SEPHIA

Secondary prevention 2005

TAVI

Transcatheter Aortic Valve Implantation 2010

SWEDEHEART



- Annual enrolment: 80 000 cases
 - 20 000 myocardial infarctions
 - 10 000 unstable angina
 - 25 000 with other causes to their symptoms
 - 40 000 coronary angiography or angioplasty
 - 7 000 Heart surgery
 - 6 000 secondary prevention
- 1000 variables

BARCELON

2737 users (mainly doctors and nurses)

ESC CON(◆ At a given time: ~ 60 simultaneous users

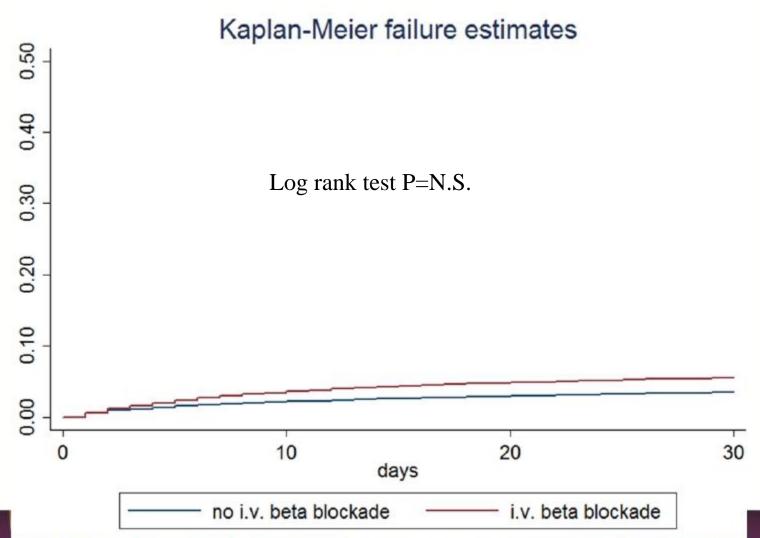
RIKS-HIA

SCAAR

Heart surgery registry

SEPHIA

Results



Conclusions

- In our study, the use of IV beta-blockade in patients with STEMI was not associated with
 - increased risk of death at 30-days
 - increased risk of in-hospital cardiogenic shock.

2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation



The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology

Chairpersons: Borja Ibanez (Spain), Stefan James (Sweden).

Authors/Task Force Members: Stefan Agewall (Norway), Manuel J. Antunes (Portugal), Chiara Bucciarelli-Ducci (UK), Héctor Bueno (Spain), Alida L. P. Caforio (Italy), Filippo Crea (Italy), John A. Goudevenos (Greece), Sigrun Halvorsen (Norway), Gerhard Hindricks (Germany), Adnan Kastrati (Germany), Mattie J. Lenzen (The Netherlands), Eva Prescott (Denmark), Marco Roffi (Switzerland), Marco Valgimigli (Switzerland), Christoph Varenhorst (Sweden), Pascal Vranckx (Belgium), Petr Widimský (Czech Republic).







.escardio.org/guidelines 2017 ESC Guidelines for the Management of AMFSTEM I (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx095)

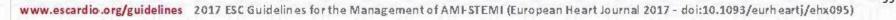
Routine therapies in the acute, subacute and long-term phases



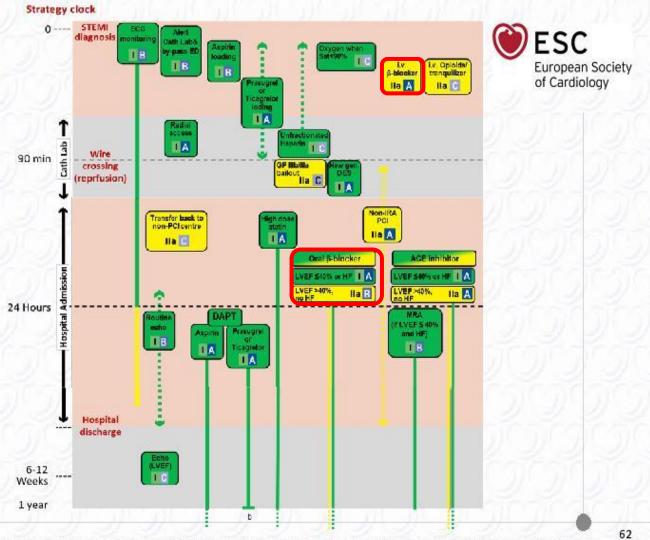
Recommendations	Class	Level				
Beta-blockers						
Oral treatment with beta-blockers is indicated in patients with heart failure or LVEF ≤40% unless contra-indicated.	11)	А				
Intravenous beta-blockers should be considered at the time of presentation in patients undergoing primary PCI without contraindications, with no signs of acute heart failure, and with an SBP >120 mmHg.	lla	А				
Routine oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all patients without Contra-indications.	lla	В				
Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure or AV block or severe bradycardia.	M	В				

& & & ...





"Do not forget"
interventions in STEMI
patients undergoing a
primary PCI strategy





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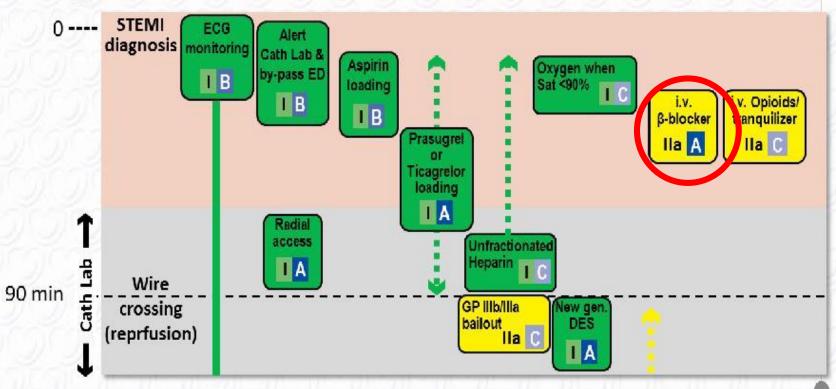




"Do not forget" interventions in STEMI patients undergoing a primary PCI strategy



Strategy clock



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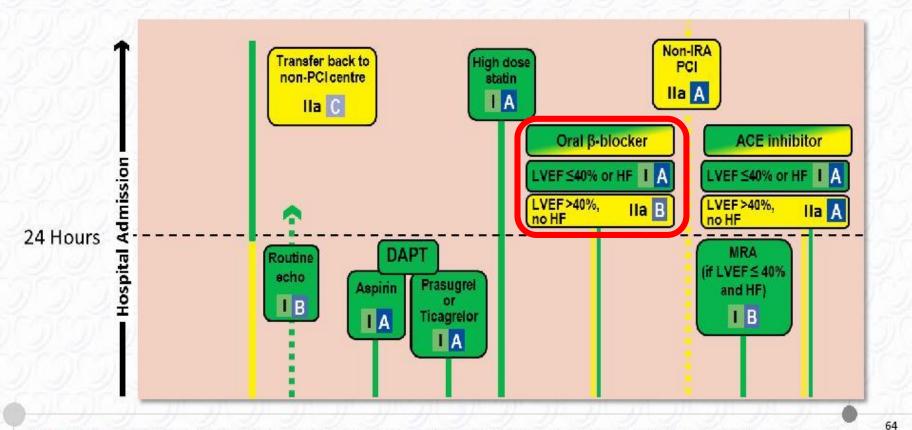


63



"Do not forget" interventions in STEMI patients undergoing a primary PCI strategy





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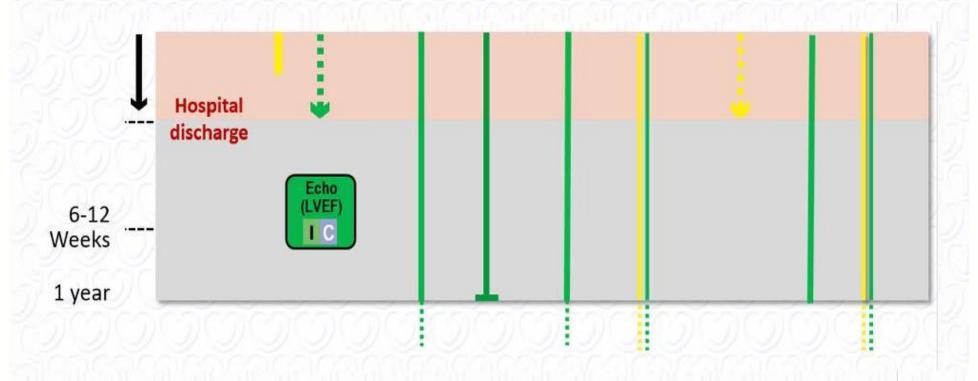






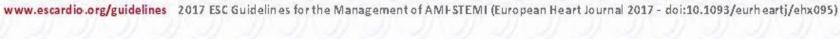
"Do not forget" interventions in STEMI patients undergoing a primary PCI strategy





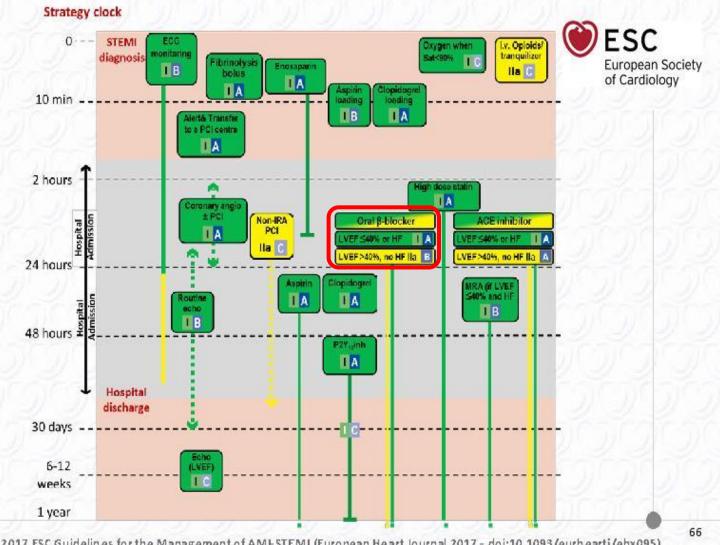








"Do not forget" interventions in STEMI patients undergoing a successful fibrinolysis strategy







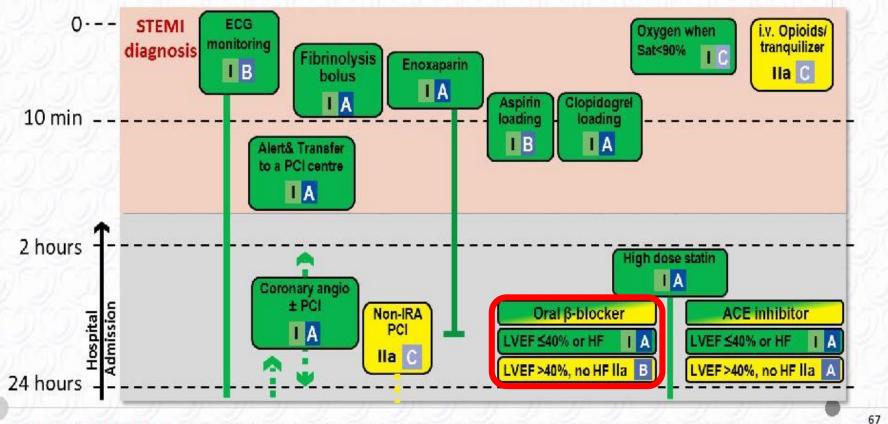




"Do not forget" interventions in STEMI patients undergoing a successful fibrinolysis strategy



Strategy clock





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