PCI IN LATECOMERS WITH STEMI

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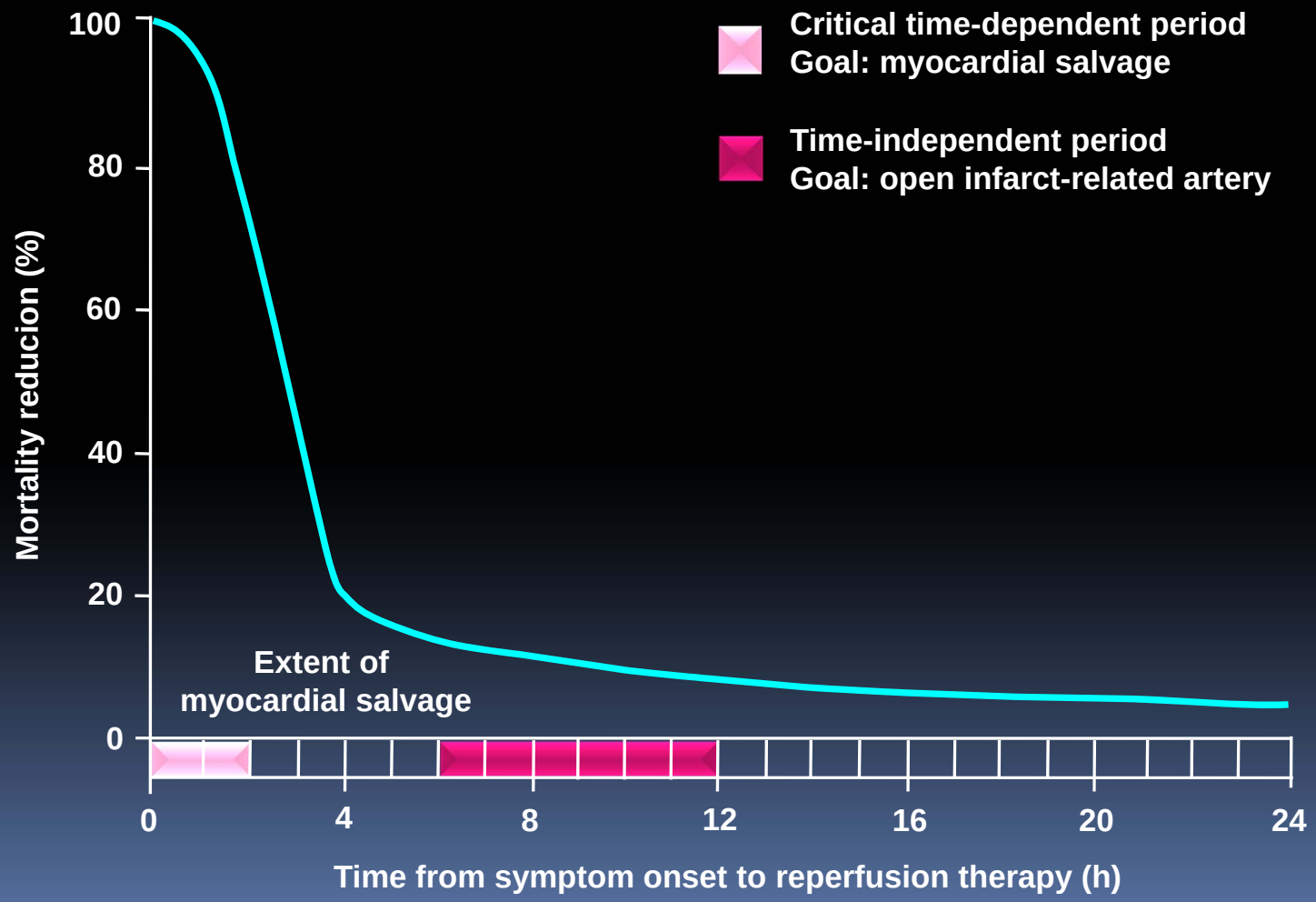
Relationship Between Duration Of Symptoms Of AMI Before Reperfusion Therapy, Mortality Reduction And Extent Of Myocardial Salvage



Introduction

- Major benefit of revascularization of the infarct-related artery (IRA) when the time from the onset of symptoms is less than 12hrs.
- ***In clinical practice, proportion of latecomer (>12hr) is high***
  - ***GRACE study ; 12%***
  - ***TETAMI study ; 40%***
- ***'Open artery hypothesis'*** proposes that late (>12hr) reperfusion, beyond the window for myocardial salvage, also reduces LV remodeling and decrease mortality.
- ***Experimental and observational data suggest that late achieving reperfusion (>12h) may confer benefit that are necrosis-independent and partially time-independent. However, large RCT trials failed to show mortality benefit. The clinical benefit of late reperfusion is controversial !***

Revascularization of the IRA: Different Scenarios

Duration of the Occlusion	Indications of PCI
<3 months	
Early (12 h) **Late (12 h to 3 months)**	**All patients (primary PCI)** **“Open Artery Hypothesis”**
>3 months	
Chronic total occlusion	**Symptoms / Ischemia / Viability guided revascularization**

Guideline Recommendations Of PCI For STEMI Latecomers

- **ESC *2008'***
  - Patients with STEMI with onset of symptoms more than 12h
    - Clinical and electrocardiographic evidence of ongoing ischemia (Class IIa, LOE: C)
    - Stable patients with STEMI (12-24h) (Class IIb)
- **ACC / AHA / SCAI *2007'***
  - **PCI for latecomers (Class I or IIa)**
    - **Reinfarction**
    - **Evidence of spontaneous or inducible ischemia**
    - **Cardiogenic shock or hemodynamic instability**
    - **Evidence of LVEF less than 40%**
    - **Heart failure or serious ventricular arrhythmia**
  - PCI in stable patients presenting more than 24h without evidence of ischemia is not recommended (Class III, LOE: B)

ACC/AHA/SCAI and ESC Guidelines for Patients

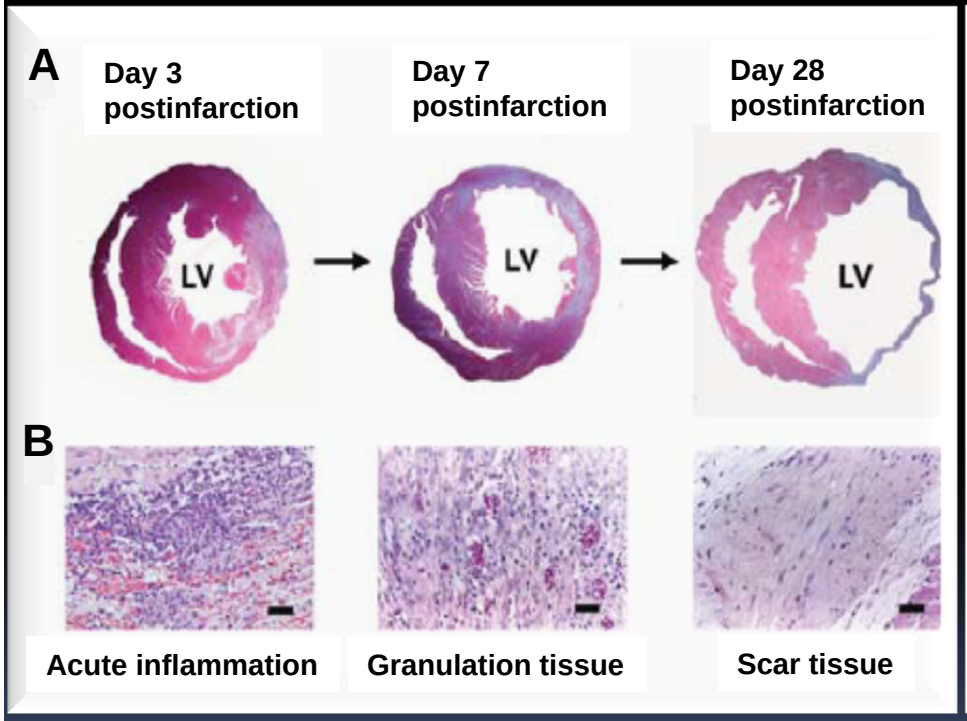
After Successful Fibrinolysis and for Patients Not Undergoing Primary Reperfusion (Latecomers)

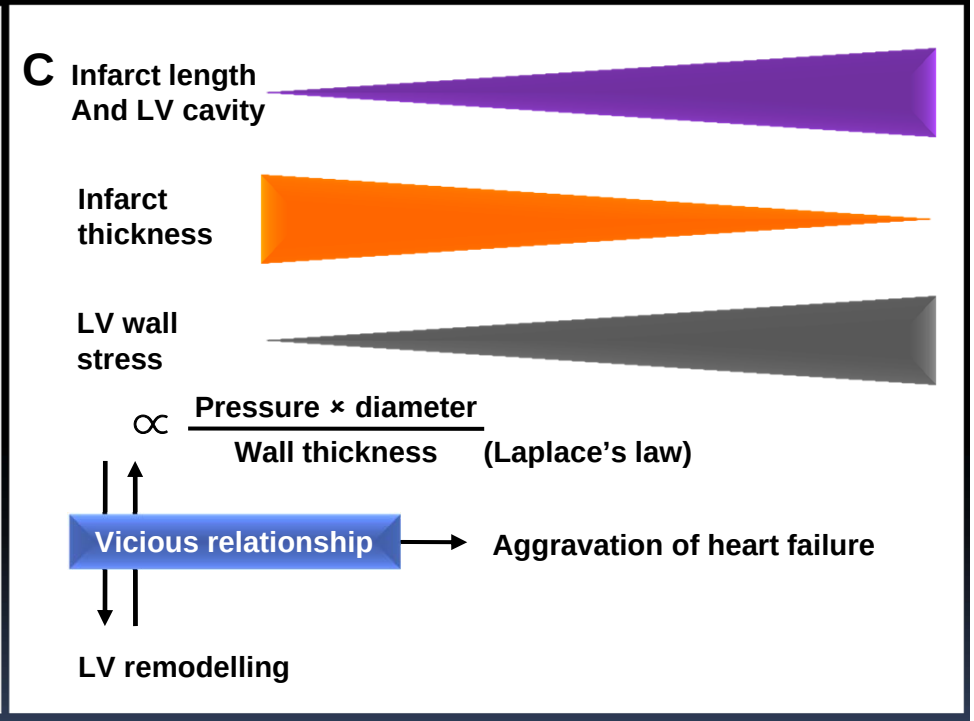
Clinical Condition	ACC/AHA/SCAI	ESC
After successful fibrinolysis (up to 24 h) independent of angina and/or ischemia	< 12 h; Routine angiography and PCI if applicable; Class I, LOE: A 12 h - 24 h; No recommendation	Routine angiography and PCI if applicable; Class I, LOE: A
Patients not undergoing reperfusion (latecomers) or after fibrinolysis with residual moderate-to-severe ischemia (beyond 24 h)	PCI if applicable; Class I, LOE: B	PCI if applicable; Class IIa, LOE: C
Latecomers (12 to 24 h) asymptomatic and stable	No recommendation	PCI if applicable; Class IIb, LOE: B
Latecomers (>24 h) with hemodynamically significant stenosis in a patent IRA	PCI may be considered part of an invasive strategy (Class IIb, LOE: B)	No recommendation
Latecomers (>24 h) asymptomatic and stable with totally occluded IRA, without evidence of ischemia	PCI not recommended (Class III, LOE: B)	PCI not recommended (Class III, LOE: B)

Background of Open Artery Hypothesis

- Gradual recovery of myocardial blood flow (2-fold) in ischemic region at 96 h after experimental coronary occlusion
- The wave-front phenomenon; a gradient of flow reduction
- Anaerobic glycolysis and FFAs metabolism ; 20% of coronary blood flow
- Intermittent patency of IRA on coronary angiogram : up to 30% (<12h), about 50% (12-48h)
- Low-flow ischemia ; **stunned or hibernated myocardium**
  : Stuttering course of AMI
  : The presence of collateral circulations
  : Ischemic preconditioning
- ***The infarcted myocardium is a highly dynamic tissue, which is not simply dead, nor is it inert.***

Effect Of The Post-MI Healing Process On Cardiac Geometry And Its Relation To Wall Stress And Heart Failure





Proposed Mechanisms Underlying The Beneficial Effects Of Late Reperfusion

1. Effect on infarct tissue

1) Acceleration of infarct healing:
   Absorption of myocardial debris
   Acceleration of collagen synthesis
2) Retention of hematic scaffolding:
   Hemorrhage, edema, and contraction band necrosis
3) Reduction of collagen degradation
4) Preservation of the non-myocyte cell component :
   Acceleration of proliferation of granulation tissue cells
   Suppression of apoptosis of granulation tissue cells

2. Effect on salvaged cardiomyocytes

1) Awakening hibernating myocardium:
   Mitigation of cardiomyocyte degeneration
2) Reduction of cardiomyocyte apoptosis

Randomized Clinical Studies Of Late Reperfusion More Than 24 H After The Onset Of AMI

Study	No. of patients rep.: + / -	Method for rep.	Time to rep.	Sustained patency rep.: + / -	Overall outcome
Topol et al. TAMI-6	71, 34 / 37	tPA+ / -PTCA	12–48 h	60% / 38% at 6 months	Negative (mortality, LV volume, LV systolic function at 6 months)
Dzavik et al. TOMIIS	44, 25 / 19	PTCA	5–42 days; mean, 21 days	43% / 19% at 4 months	Negative (clinical outcomes, LV size and EF at 4 months); positive in the subset (LVEF at 4 months)
Horie et al.	83, 44 / 39	PTCA	>24 h	96% / 13% at 6 months	Positive (LV volume at 6 months; death, recurrent MI, congestive heart failure at 50 months)
Yousef et al. TOAT	66, 32 / 34	Stenting	3 days–6 weeks; mean, 26 days	91% / 19% at 12 months	Greater LV dilation but improved exercise tolerance and QOL with reperfusion at 12 months
Steg et al. DECOPI	212, 109 / 103	Stenting	2–15 days	83% / 34% at 6 months	Improved LVEF but no difference in clinical outcomes at 2 years
Hochman et al. OAT	2166, 1082 / 1084	Stenting	3–28 days; median, 8 days		Negative (event-free survival at 4 years); trend toward higher reinfarction rates in reperfusion
Davik et al. TOSCA-2	381, 150 / 136	Stenting	3–28 days; median, 10 days	83% / 25% at 1 year	Negative (LVEF at 4 years); trend toward less LV dilation in reperfusion

Reperfusion PCI in latecomers

- **In the Open Artery Trial (TOAT)**
  - PCI with stenting performed 3 ds to 6 wks after ant. AMI
  - Greater LV dilatation with late reperfusion
  - 44% increase in adverse events risk
  - Improve exercise tolerance and quality of life
- **DEsobstruction COronaire en Post-Infarctus (DECOPI) trial**
  - 2–15 days after MI randomized to PCI or no PCI
  - Improve LVEF with reperfusion
  - No difference in clinical outcomes at 6 mo
  - *Pts with IRA patency, independent of randomization, showed markedly improved clinical outcomes, which suggest prevention of restenosis and reocclusion is the key to the clinical benefit of late reperfusion*

Reperfusion PCI in latecomers

- **In OAT study**
  - **: 3-28 days after AMI, 2201 stable pts randomization**
  - **: Exclusion criteria ; cardiogenic shock, NYHA III/IV HF, severe ischemia, LM or 3-vv ds**
  - ➢ Death from any cause, nonfatal reinfarction or NYHA class IV heart failure
    - 17.2% of PCI group and in 15.6% of the medical therapy group
    - Higher reinfarction rates in the PCI group
    - No difference in event free survival between groups, median f/u of 3.2 yr
    - Equal LV systolic function at 1 yr
- **In TOSCA-2**
  - ➢ No effect on LVEF
    - Pts with patent IRA had greater increases in LVEF regardless of treatment
- ➡ ***Reperfusion by use of PCI with stenting 3–28 days after STEMI***
  - ➢ ***Not associated with a mortality benefit or improvement in LVEF compared with medical therapy alone***
- ➡ ***These findings seem to refute the late open-artery hypothesis***

Reperfusion With PCI In 'Early' Latecomers

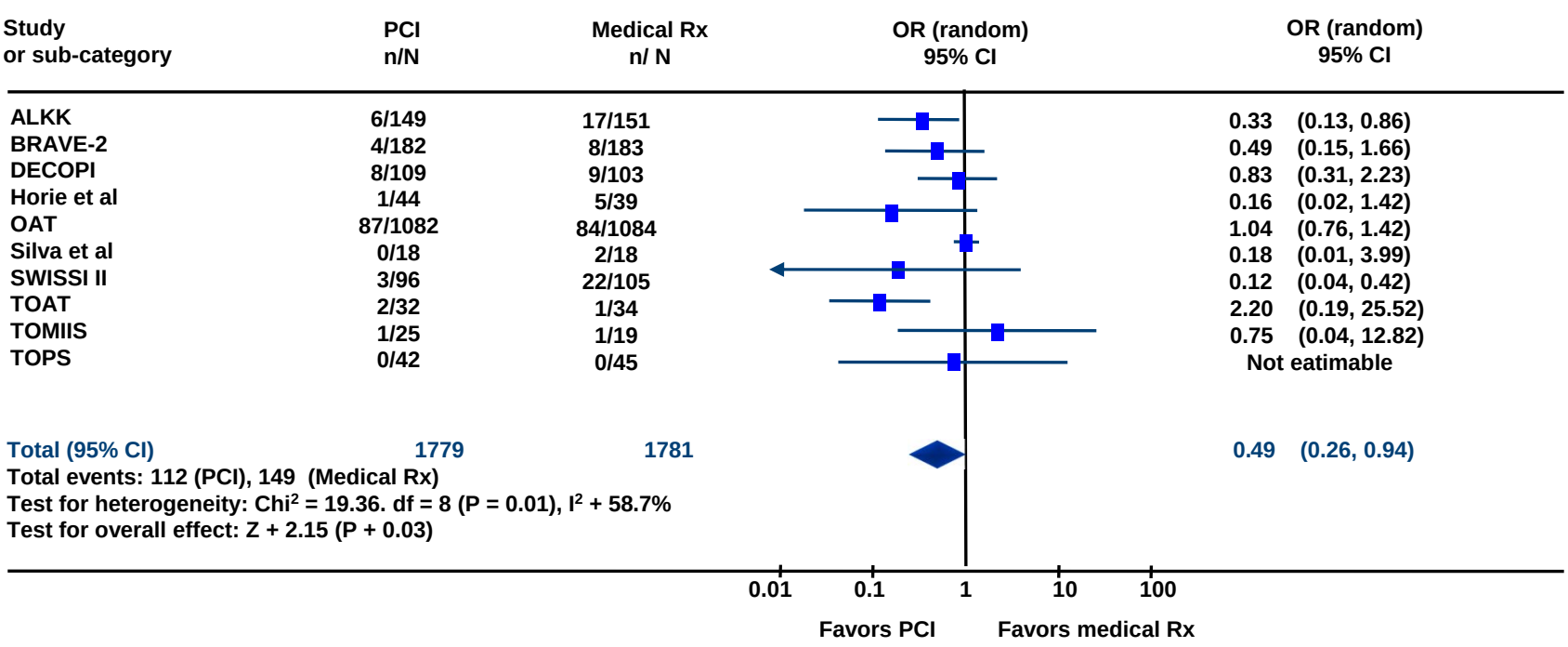
- **BRAVE -2**
  - 365 pts without symptoms 12~48 h after onset of STEMI
  - Significant reduction of infarction size
    : PCI vs. Medical treatment – 8% vs. 13%
  - No significant difference in clinical end point
    but favorable 33% relative risk reduction at 30 days
  - ***50% had some antegrade flow of IRA,***
    44% collaterals among no antegrade flow
    Only 27% had TIMI 0 flow and no collaterals
  - ***Better initial TIMI grade or patency of IRA was a significant predictor of smaller infarct size and of the better efficacy of PCI in 'early' latecomers***

Reperfusion PCI In Latecomers

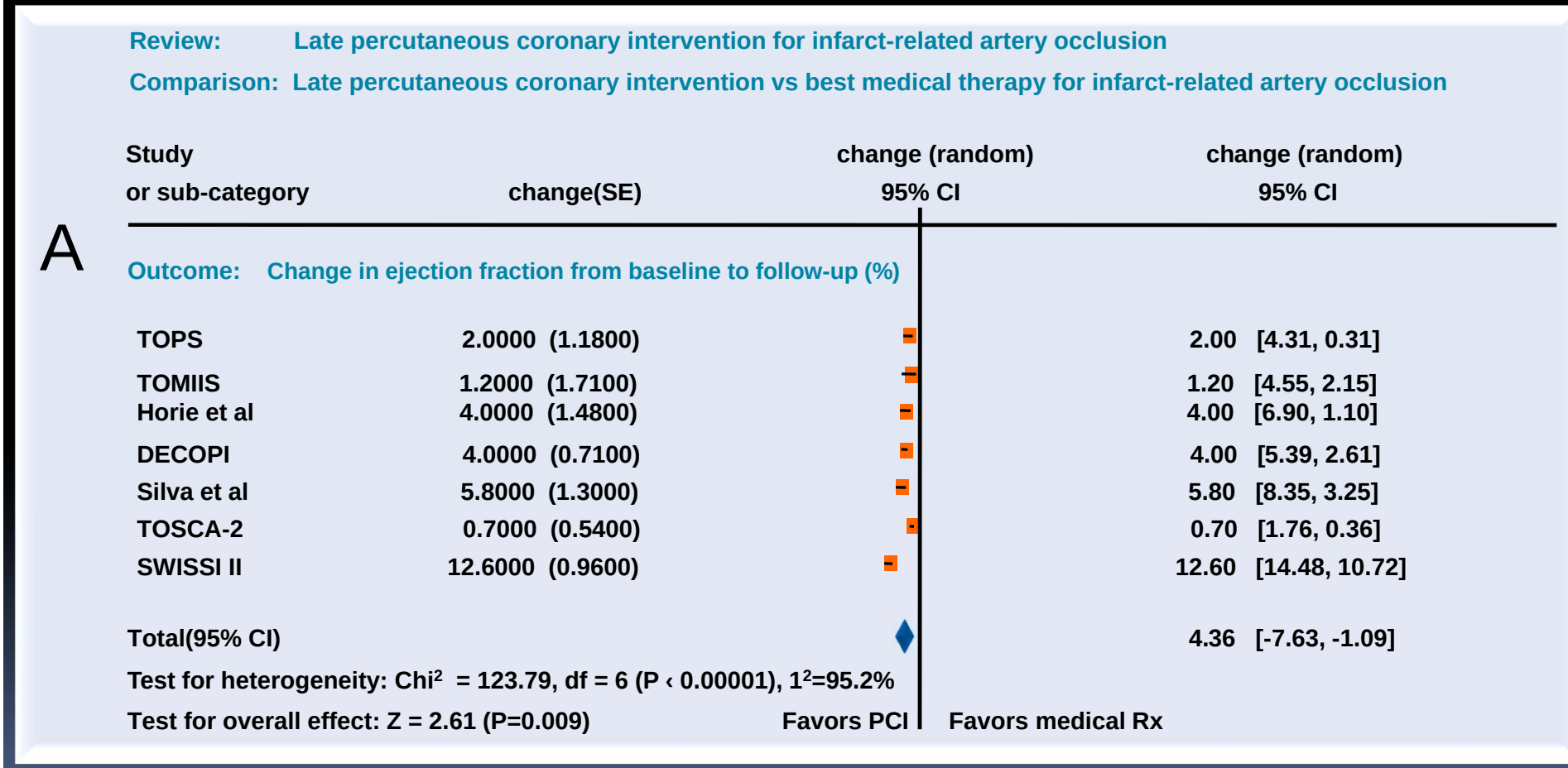
- **Meta-analysis about latecomers by Abbate et al.**
  3560 patients randomized to late PCI vs. optimal medical treatment
  - Late PCI improved survival as compared with medical treatment
    - All cause mortality reduction
      - Favorable effect on cardiac function and remodeling
    - Improvement of +4.4% of LV EF
    - Long term positive influence of PCI by preventing apoptosis of hibernating myocardium.

A

Review: Late percutaneous coronary intervention for infarct-related artery occlusion
Comparison: Late percutaneous coronary intervention vs best medical therapy for infarct-related artery occlusion
Outcome: Death



Individual And Pooled Group Differences In Changes In Cardiac Function : Meta-analysis Of RCT



Meta-analysis about latecomers by Abbate et al.

Issues To Be Resolved In Future

- ***Timing of late reperfusion***
  : reperfusion initiated 8-10 days post-MI may be too late to have a beneficial effect on remodeling
- ***Magnitude of acute myocardial infarction***
  : benefits of late reperfusion are greatly needed by pts with large transmural MI
- ***Patency of revascularized IRA***
  : rate of reinfarction due to reocclusion tends to be high in PCI group, which worsens prognosis and may negate any benefit. Clinical study designed to use DES may be a good choice.
- ***Discrepancy between experimental animal models and clinical situations***

Risk Stratification - I

- **LV ejection fraction**
  - ➢ Cardiac mortality gradually increased as LVEF decreased below 40%
  - ➢ OAT included only 21% of pts who had a LVEF of less than 40%

- **Myocardial viability**
  - ➢ Thallium-201 or technetium-99m SPECT, FDG- PET, dobutamine stress ECHO. and dobutamine stress cardiac MRI
  - ➢ Contrast-enhanced MRI
  - ➢ The Viability-Guided Angioplasty after Acute Myocardial Infarction (VIAMI) trial
    - Those with viability, demonstrated on low-dose dobutamine echo. performed 48–72 h after STEMI
    - PCI was associated with a significant reduction in ischemic event rates

  → ***Revascularization should be considered if viability is demonstrated***

Risk Stratification - II

- **Stress testing**
  - ➢ Exercise testing after STEMI
    - Useful in assessing exercise capacity, identifying persistent ischemia, risk stratification for future cardiac events
    - Submaximal exercise test (3-5 days)

      Symptom-limited exercise test (after 5 days)
  - ➢ DANAMI-I and SWISSI II trials

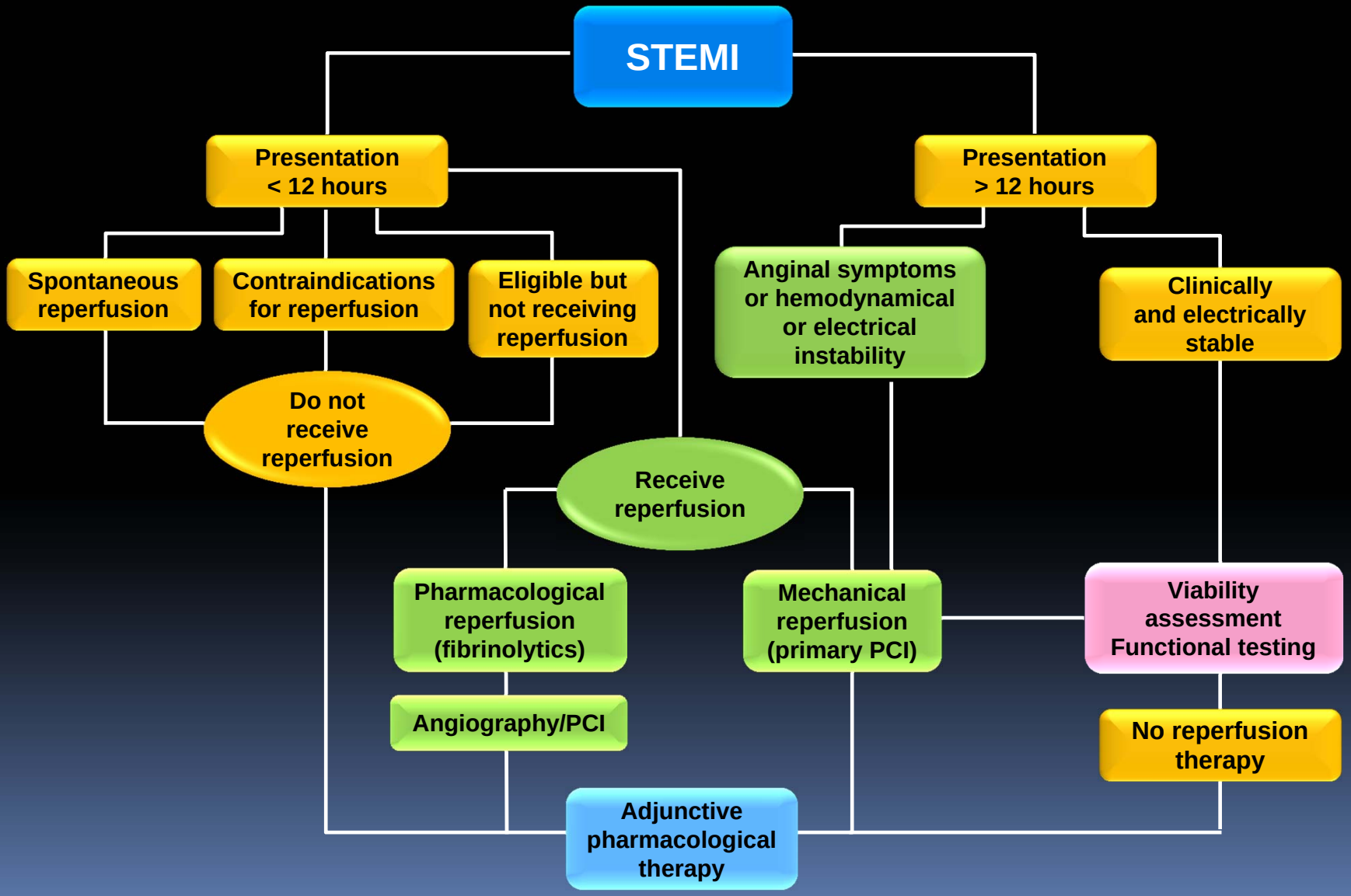
    ; Beneficial effects of PTCA performed late after MI in patients with persistent ischemia on stress testing
  - ➢ INSPIRE trial

    ; Adenosine sestamibi SPECT was effective for monitoring postinfarct ischemia
  - ➢ *Stress testing with imaging is a viable means of identifying high risk pts (severe ischemia, LM or 3-vv ds) who could still benefit from late reperfusion*

Risk Stratification - III

- **ECG and infarct-related artery status in early latecomers**
  - The predictive value of negative T wave as a marker of reperfusion is strongly considered
  - When T wave are positive, ECG discloses high probability of occluded IRA
  - Successful treatment of STEMI
    → Normalization of ST segment , accompanied T wave inversion → Marker of restored myocardial flow
  - Negative T wave in 'early' latecomers can push invasive strategy to salvage the greatest amount of residual ischemic myocardium
  - *Danish study demonstrated the patency of IRA is a major determinant of salvage of large amount of myocardium by PCI independent of its timing, on the contrary, the timing play a major role when the IRA is totally occluded according to the paradigm* ***'earlier is better'***

Spectrum Of Clinical Scenarios And Therapeutic Options In STEMI



Additional Clinical Recommendations

- *Adjuvant criteria propose for urgent coronary angioplasty and PCI for patients not undergoing primary reperfusion (latecomers > 12 to 72 h)*

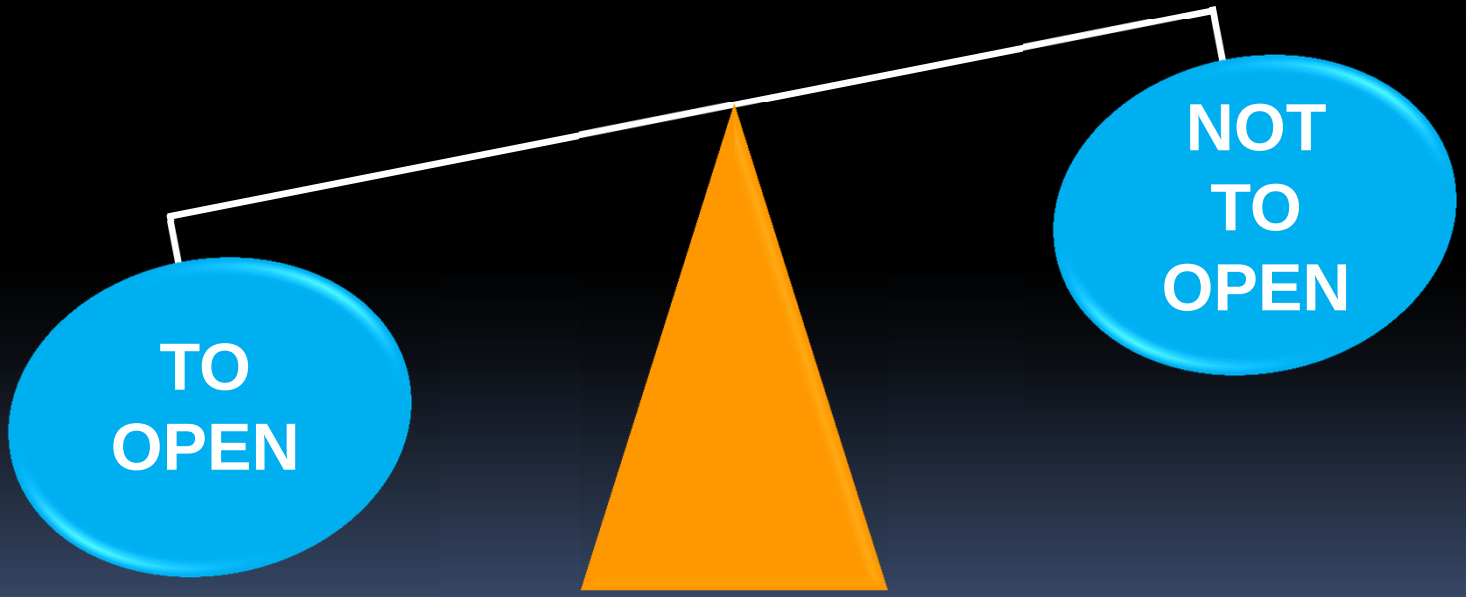
Clinical condition	Recommendation
Patients not undergoing reperfusion in latecomers with :	
Stuttering course of MI	
Ischemic preconditioning in the previous 12-24h	Urgent angiography and PCI if applicable
New bundle branch block	
Negative T waves in the infarct-related leads	
Positive T wave in the infarct-related leads	Emergent angiography and PCI if applicable

Conclusion

- Many aspects of reperfusion therapy in 'early‘ latecomers with STEMI are still subject to debate and several ‘ad-hoc' trials are desirable.
- The guidelines suggest primary PCI for late pts with clinical and/or ECG evidence of ongoing ischemia, reinfarction, cardiogenic shock, hemodynamic instability, heart failure, documented EF less than 40% and serious ventricular arrhythmias.
- Some adjunctive clinical aspects, such as the stuttering course of MI, the chance of an existing coronary collateral circulation, the ischemic preconditioning and the IRA status, should be taken into consideration for 'early‘ latecomers with STEMI.

Take Home Message

Never too late to do PCI well !




경청해 주셔서 감사합니다!