STEAMI 1: Timing, Mechanical Type and Pharmacology of Reperfusion: The Three Main Challenges to Decrease Infarct Size and Increase Viability

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CONFLICTS OF INTEREST

B Ibanez has no conflicts to declare
1) Reperfusion: a paradigm shift from mortality to HF.

2) Next goal: Infarct size limitation in reperfused STEMI.

3) Ischemia/Reperfusion injury.

4) Therapies to reduce infarct size:
   - Reperfusion (PCI Vs. Lysis)
   - Delayed stenting
   - Conditioning maneuvers
   - Metoprolol

5) Impact of timing of intervention on infarct size reduction
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5) Impact of timing of intervention on infarct size reduction
STEMI: A paradigm shift

Mortality ↓↓

Heart Failure ↑↑↑

Adapted from Roger VL et al. *Circulation* 2011;123:e18-e209
Figure 2: Projected Heart Failure direct medical costs and indirect (lost productivity) costs.

Adapted from Circulation 2011; 123:933–44
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5) Impact of timing of intervention on infarct size reduction
Surrogate markers: predictors

Infarct size is a strong determinant of long-term mortality and chronic heart failure

Therapies to reduce MI size


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

Authors/Task Force Members: Borja Ibañez* (Chairperson) (Spain), Stefan James*

No therapy to reduce MI size → URGENT clinical need
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4) Therapies to reduce infarct size:
   - Reperfusion
   - + Conditioning.
   - + β-blockers.

5) Impact of timing of intervention on infarct size reduction.
Ischemia/Reperfusion injury

Ibanez, Heusch, Ovize Van de Werf. J Am Coll Cardiol 2015;65:1454-71
Microvascular Obstruction
Myocardial Healing
: critical players

State of the art review
J Am Coll Cardiol 2015;65:1454-71
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5) Impact of timing of intervention on infarct size reduction
Head to head PCI >> Thrombolysis (Up to 120 min PCI-delay)

Do early presenters without immediate PCI benefit from Lysis?

STREAM trial (STEMI ≤3 hours evolution) → No differences between transfer to PCI and immediate thrombolysis

PCI when STEMI diagnosis to PCI ≤120 min... even for early presenters

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 (ESC)

Authors/Task Force Members: Borja Ibanez* (Chairperson) (Spain), Stefan James*
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DEFER Stenting

High thrombus burden → risk of embolization and microvascular obstruction

Is there a role of deferred stenting (under intense antithrombotic therapy)?

SOTA Review on reperfusion injury
J Am Coll Cardiol 2015;65:1454-71
Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): an open-label, randomised controlled trial


Lancet 2016; 387: 2199–206

N= 1215

Primary outcome: “death, HF admission, re-MI, unplanned TVR” median F-Up 42 months
Myocardial Damage in Patients With Deferred Stenting After STEMI

A DANAMI-3-DEFER Substudy

Jacob Lønborg, MD, PhD, DMSæ, Thomas Engstrøm, MD, PhD, DMSæ, Kiril Aleksov Ahtarovski, MD, PhD, Lars Nepper-Christensen, MD, Steffen Helqvist, MD, DMSæ, Niels Vejlstrup, MD, PhD, Kasper Kyhl, MD, Mikkel Malby Schoos, MD, PhD, Ali Ghotbi, MD, Christoffer Göransson, MD, Litten Bertelsen, MD, Lene Holmvang, MD, DMSæ, Frants Pedersen, MD, PhD, Erik Jørgensen, MD, Karl Saunamäki, MD, DMSæ, Peter Clemmensen, MD, DMSæ, Ole De Backer, MD, PhD, Lene Klavgaard, RN, Dan Eik Hafsten, MD, PhD, Lars Keber, MD, DMSæ, Henning Kellbaek, MD, DMSæ, for the DANAMI-3 Investigators

J Am Coll Cardiol 2017;69:2794-804

N=510 (out of 1215)
2 CMR (predischarge, 3 months)

Infarct size

MVO
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Preinfarction angina confers protection

Ischemic preconditioning protect the heart
Remote Ischemic Conditioning

Gerd Heusch, MD,* Hans Erik Bøtker, MD, PhD,† Karin Przyklenk, PhD,‡ Andrew Redington, MD,§ Derek Yellon, PhD, DSc‖

Brief episodes of occlusion/reperfusion in a distant organ protects the heart
Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial

Hans Erik Bøtker, Rajesh Kharbanda, Michael R Schmidt, Morten Böttcher, Anne K Kaltoft, Christian J Terkelsen, Kim Munk, Niels H Andersen, Troels M Hansen, Sven Trautner, Jens Flensted Lassen, Evald Haj Christiansen, Lars R Krusell, Steen D Kristensen, Leif Thuesen, Søren S Nielsen, Michael Rehling, Henrik Toft Sørensen, Andrew N Redington, Torsten T Nielsen

333 patients with first STEMI. RIC (4 cycles arm cuff inflation) or regular PCI

Conclusions

Patients treated with remote ischaemic conditioning had a lower rate of persistent late gadolinium enhancement than those receiving regular PCI (18.3% vs 22.6%, p=0.033). RIC was associated with an improvement in myocardial salvage compared with PCI alone, as measured by late gadolinium enhancement.
Letters

Remote Ischemic Conditioning Reduces Myocardial Infarct Size in STEMI Patients Treated by Thrombolysis

N=519
No access to PCI at all

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Patient Characteristics and AUC Cardiac Enzymes</th>
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<tbody>
<tr>
<td></td>
<td>Control (n = 258)</td>
</tr>
<tr>
<td>Enzymatic MI size, ng.h/ml</td>
<td></td>
</tr>
<tr>
<td>24-h AUC CK-MB</td>
<td>2,894 ± 2,306</td>
</tr>
<tr>
<td>2381 (980-4,690)</td>
<td>1,928 (780-3,289)</td>
</tr>
<tr>
<td>24-h AUC Troponin T</td>
<td>105.9 ± 69.5</td>
</tr>
<tr>
<td>109.0 (41.1-162.7)</td>
<td>74.6 (28.5-149.0)</td>
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</tbody>
</table>
RIC large trial

CONDI-2 trial, Denmark, Spain, Serbia.

- 2,000 STEMI patients
- conventional PCI vs. RIC+PCI
- Combined end-point:
  all-cause mortality / heart failure @ 2 years

ONGOING TRIAL
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5) Impact of timing of intervention on infarct size reduction
i.v. metoprolol before pPCI $\rightarrow$ ↓↓↓↓ infarct size
EARLY METOPROLOL

Mean LVEF (6 mo CMR): 48.7±9% vs. 45.0±11%

Fisher’s exact test (p=0.026)
Linear-by-Linear Association test (p=0.006)

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>i.v. metoprolol (N=101)</th>
<th>Control (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF&gt;50%</td>
<td>46.5%</td>
<td>38.6%</td>
</tr>
<tr>
<td>40%&gt;LVEF≤50%</td>
<td>32.3%</td>
<td>19.8%</td>
</tr>
<tr>
<td>35%&gt;LVEF≤40%</td>
<td>10.1%</td>
<td>14.9%</td>
</tr>
<tr>
<td>30%&gt;LVEF≤35%</td>
<td>6.1%</td>
<td>14.9%</td>
</tr>
<tr>
<td>LVEF≤30%</td>
<td>5.1%</td>
<td>11.9%</td>
</tr>
</tbody>
</table>
Metoprolol reduces Microvascular Obstruction in STEMI patients.

Cellular mechanism

Metoprolol stuns neutrophils to protect the heart

García-Prieto et al
Nature Commun 2017
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The longer the “on board” metoprolol duration at reperfusion, the higher the cardioprotection

Garcia-Ruiz et al *J Am Coll Cardiol* 2016;67:2093-104
Window β-blk admin in trials

STEMI diagnosis

PCI (reperfusion)

METOCARD-CNIC
(-53 min to PCI)
15mg metoprolol

EARLY BAMI
(-54 & -14 min to PCI)
10mg metoprolol

Lytic therapy
---- reperfusion

COMMIT
(+? min from Urokinase)

TIMI IIB
(+45 min from rtPA)

Van de Werf
(immed before rtPA)
10mg atenolol

STEMI diagnosis
Timing of RIC initiation

Remote ischaemic conditioning and healthcare system delay in patients with ST-segment elevation myocardial infarction

Kasper Pryds, Christian Juhl Terkelsen, Astrid Drivsholm Sloth, Kim Munk, Søren Steen Nielsen, Michael Rahbek Schmidt, Hans Erik Bøtker, CONDI Investigators


![Graph showing the relationship between healthcare system delay (min) and myocardial salvage index. The graph compares pPCI alone versus RIC+pPCI, with different regression lines indicating the correlation between the variables. The R-squared values and p-values are provided for each comparison.]
1) Timely reperfusion widespread use has resulted in a massive reduction of acute mortality during STEMI.
2) The next goal is to reduce infarct size to reduce chronic post-MI HF
3) Reperfusion injury reduction is a relevant target. Preserve microvascular integrity!
4) Metoprolol and remote ischemic conditioning are promising therapies
5) Timing of administration of therapies to reduce infarct size seem to play a critical role in its ability to protect from ischemia/reperfusion.
STEMI 1: Timing, Mechanical Type and Pharmacology of Reperfusion: The Three Main Challenges to Decrease Infarct Size and Increase Viability

New York Cardiovascular Symposium

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