Reperfusion injury in STEMI. Therapeutic opportunities
David Garcia-Dorado. Barcelona. Spain

1. The problem
2. Reperfusion injury after acute coronary occlusion
3. Ischemic conditioning
4. Pharmacological approaches
5. Combination therapy
6. Future research
Progression of cell death secondary to acute coronary occlusion
Progression of cell death secondary to acute coronary occlusion
Progression of cell death secondary to acute coronary occlusion.

- **Ischemia**
- **Reperfusion**

- **No reperfusion**
- **Thrombolytics, PCI**
The importance of delaying reperfusion depends on previous duration of ischemia.

**Figure 1. Duration of Ischemia and Infarct Size.**

Shown is a typical relationship between the duration of ischemia and infarct size (as a percentage of the area at risk) in patients with STEMI, with a rapid phase of increase in size as reperfusion is delayed, followed by a plateau. The effect of a delay (arrow) on infarct size may be large (A) or small (B), depending on the total ischemic time.
1. The problem

- IHD is the leading cause of death (1.8 million/year worldwide)
- Heart failure consumes 1 - 2% of health resources (60 billion € in Europe)
- STEMI remains the main responsible for both in the era of reperfusion
Reperfusion injury in STEMI. Therapeutic opportunities

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6. Future research
Myocardial reperfusion injury: cell death preventable by interventions applied upon reperfusion *
Myocardial reperfusion injury: cell death preventable by interventions applied upon reperfusion *
Mechanism of reperfusion injury in STEMI
Mechanism of reperfusion injury in STEMI
Necrosis during the initial minutes of reflow

24 h reperfusion

28 days reoerfusion

Inserte et al., Submitted
Mechanism of reperfusion injury in STEMI

**REPERFUSION**

- Ca$^{2+}$ overload
- ATP
- pH correction
- ROS

**Sercoplasmic Reticulum**

- Ca$^{2+}$ oscillations

**Cardiomyocyte DEATH**

- Garcia-Dorado Circulation. 1992
- Piper Am J Physiol 1993
- Barrabés JA Pflugers Arch. 1996
- Garcia-Dorado Cardiovasc Res. 1997
- Garcia-Dorado Circulation. 1997
- Ruiz-Meana Circ Res. 1999
- Ruiz-Meana Exp Physiol. 2000
- Ruiz-Meana Basic Res Cardiol. 2007
Mechanism of reperfusion injury in STEMI

**Ca\textsuperscript{2+}** oscillations

**Reperfusion**

**Ca\textsuperscript{2+}** overload  ATP  pH correction  ROS

**Calpain proteolysis**

**Sercoplasmic Reticulum**

**Ca\textsuperscript{2+}** oscillations

**Cardiomyocyte DEATH**

References:
- Inserte J. Br J Pharmacol. 2015
- Garcia-Dorado D. Rev Esp Cardiol. 2014
- Inserte J. J Mol Cell Cardiol. 2011
- Inserte J. Antioxid Redox Signal. 2011
- Hernando V. J Mol Cell Cardiol. 2010
- Garcia-Dorado D. Cardiovasc Res. 2006
- Inserte J. Cardiovasc Res. 2006
- Inserte J. Circ Res. 2005
- Inserte J Cardiovasc Res. 2004
Mechanism of reperfusion injury in STEMI

- REPERFUSION
  - Ca$^{2+}$ overload
  - ATP
  - pH correction
  - ROS

- Calpain proteolysis
- Sercoplasmic Reticulum
- Mitochondria
- Ca$^{2+}$ oscillations
- Cardiomyocyte DEATH

- MPT

Authors: Crompton, Halestrap, Griffiths, Bernerdi, DiLisa, Weiss, Ovize, Hausenloy
Mechanism of reperfusion injury in STEMI

**REPERFUSION**

- Ca\(^{2+}\) overload
- ATP
- pH correction
- ROS

- Calpain proteolysis
- Sarcoplasmic Reticulum
- Mitochondria

- Ca\(^{2+}\) oscillations

- Cardiomyocyte DEATH

**References**

- Fernandez-Sanz Cell Death Dis 2014
- Ruiz-Meana Bas Res Cardiol 2011
- Ruiz-Meana Cardiovasc Res 2010
- Ruiz-Meana Am J Physiol H 2009
Mechanism of reperfusion injury in STEMI

Recent reviews on mechanisms:
Garcia-Dorado CVR 2012 (Ca2+), REC 2014
J Mol Cell Cardiol 2011 (edema),
Inserte, CVR 2012 (Calpains), ARS 2011 (pH)
Rodriguez-Sinovas (Cx43), BBA 2012, Ruiz-Meana CVR 2011, BRC 2011(Mito-SR), Inserte (cGMP), BJP 2014
Reperfusion injury in STEMI. Therapeutic opportunities

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Strategies to limit reperfusion injury in STEMI

Conditioning

- Ischemic post-conditioning
- Remote ischemic conditioning
- Other

Pharmacological treatments
Ischemic postconditioning: brief periods of ischemia at the onset of reperfusion
Mechanism of reperfusion injury in STEMI

**REPERFUSION**

- Ca²⁺ overload
- ATP
- pH correction
- ROS

**Calpain proteolysis**

**Sarcoplasmic Reticulum**

**Ca²⁺ oscillations**

**Mitochondria**

**MPT**

**Cardiomyocyte DEATH**

References:
- Piper Basic Res Cardiol 1996
- Agulló Am J Physiol H 2000
- Ruiz-Meana J Physiol 2004
- Sarri Biochem J 2006
- Inserte Cardiovasc Res 2008
- Inserte Cardiovasc Res 2009
- Rodríguez-Sinovas A, Basic Res Cardiol 2009
Ischemic Post-Conditioning

↓ Wахsout rate

Delayed pH recovery

Delayed & reduced Ca2+ oscillations, calpain activation
Less hypercontracture and MPT

Inserte et al. JMCC 2011, JAHA2013, CVR 2014
Ischemic Post-Conditioning

↓ ROS

↑ NO

↑ sGC

↑ cGMP

PKG

↓ NHE

Delayed pH recovery

↓ Washout rate

Delayed & reduced Ca2+ oscillations, calpain activation
Less hypercontracture and MPT

Inserte et al. JMCC 2011, JAHA2013, CVR 2014
Ischemic Post-Conditioning

↓ ROS
↑ NO
↓ GC
↑ GMP

↓ CaMKII Thr287
↓ SERCA
↓ PKA
↓ PLB
↑ PDE2
PKG

↓ NHE

Delayed pH recovery

↓ Washout rate

Delayed & reduced Ca2+ oscillations, calpain activation
Less hypercontracture and MPT

Inserte et al. JMCC 2011, JAH A2013, CVR 2014
Effect of IPoCo on infarct size in patients with STEMI

Figure 2. Forest plot for infarct size, expressed as weighted standardized mean difference.

Overall fixed effect (-0.4142, p < 0.0001)

Overall random effect (-0.5837, p = 0.0024)

Laskey WK (2005)
Staat P (2005)
Ma P (2006)
Yang XC (2007)
Thibault H (2008)
Laskey W (2008)
Lømborg J (2010)
Xue F (2010)
Sörensson P (2010)
Garcia S (2011)
Freixa X (2011)
Tarantini G (2012)
Thuny F (2012)
Dwyer NB (2013)
Strategies to limit reperfusion injury in STEMI

Conditioning
  Ischemic post-conditioning
  Remote ischemic conditioning
  Other

Pharmacological treatments
Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion

K Przyklenk, B Bauer, M Ovize, RA Kloner and P Whittaker

*Circulation 1993, 87:893-899*
FORMS OF REMOTE ISCHEMIC CONDITIONING (RIC)

Remote Ischemic PRECOND       PERCOND       POSTCOND

Protected organ B (HEART)

TIME

= ischemia
FORMS OF REMOTE ISCHEMIC CONDITIONING (RIC)

Remote Ischemic PRECOND     PERCOND     POSTCOND

Organ A (LIMB)

Protected organ B (HEART)

TIME

= ischemia
Triggers, mediators and effectors of RIC

Rajesh K Kharbanda: ESC 2012
Rople of parasympathetic nerve in RIC (femoral occlusions) induced cardioprotection in isolated rabbit hearts

1. Pigs (n=6)

Baseline blood extraction (1) → Post-RIC blood extraction (1)

2. Dialisate preparation

Baseline plasma (1) → 1800 rpm, 15’ → Post-RIC plasma (1) → Plasma dialisate (against 10-fold volume, 12-14 kDa cutoff, overnight, 4ºC). Storage at -80ºC

3. Mice (n=12/group)

Control group (baseline plasma dialisate, n=12)

Baseline dialisate 30’ → Ischemia 35’ → Reperfusion 60’

Post-RIC plasma dialisate (n=12)

Post-RIC dialisate 30’ → Ischemia 35’ → Reperfusion 60’ → LDH release, LVdevP → Infarct size

PLASMA FROM RIC PIGS PROTECTS ISOLATED MICE HEARTS
PLASMA FROM RIC PIGS PROTECTS ISOLATED MICE HEARTS

Alburqueque-Bejar et al. Unpublished
FORMS OF REMOTE ISCHEMIC CONDITIONING (RIC) IN STEMI PATIENTS

Remote Ischemic PRECOND  PERCOND  POSTCOND

Organ A
(limb)

Protected organ B
(HEART)

TIME

= ischemia
Remote Ischemic conditioning in STEMI: clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>N number (Control vs. RIC)</th>
<th>Clinical setting</th>
<th>RIC protocol (site of delivery)</th>
<th>Endpoint</th>
<th>Infarct size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rentoukas et al.</td>
<td>30 vs. 33</td>
<td>STEMI (pPCI) with morphine</td>
<td>4 x 5 min arm I/R (Hospital)</td>
<td>Troponin I peak</td>
<td>↓ (40%)</td>
</tr>
<tr>
<td>CONDI-1 Botker et al.</td>
<td>69 vs. 73</td>
<td>STEMI (pPCI)</td>
<td>4 x 5 min arm I/R (Ambulance)</td>
<td>SPECT myocardial salvage index</td>
<td>↓ (36%)</td>
</tr>
<tr>
<td>Munk et al.</td>
<td>33 vs. 31</td>
<td>Anterior STEMI (pPCI)</td>
<td>4 x 5 min arm I/R (Ambulance)</td>
<td>SPECT MI size (30 days)</td>
<td>↓ (56%)</td>
</tr>
<tr>
<td>RIPOST-MI Prunier et al.</td>
<td>17 vs. 18</td>
<td>STEMI (pPCI)</td>
<td>3 x 5 min arm I/R (Hospital)</td>
<td>AUC CK-MB/AAR</td>
<td>↓ (33%)</td>
</tr>
<tr>
<td>Crimi et al.</td>
<td>48 vs. 48</td>
<td>Anterior STEMI (pPCI)</td>
<td>4 x 5 min leg I/R (Hospital)</td>
<td>AUC CK-MB</td>
<td>↓ (20%)</td>
</tr>
<tr>
<td>ERIC-STEMI White et al.</td>
<td>43 vs. 40</td>
<td>STEMI (pPCI)</td>
<td>4 x 5 min arm I/R (Hospital)</td>
<td>MI size (MRI)</td>
<td>↓ (27%)</td>
</tr>
<tr>
<td>ERIC-LYSIS Hausenloy et al</td>
<td>206 vs. 208</td>
<td>STEMI (Thrombolysis)</td>
<td>4 x 5 min arm I/R (Hospital)</td>
<td>AUC CK-MB AUC Trop T</td>
<td>↓ (18%)</td>
</tr>
</tbody>
</table>
Reperfusion injury in STEMI. Therapeutic opportunities

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Reperfusion injury in STEMI: unsolved issues and limitations

Orphan targets

Coronary microcirculation

Platelet activation and P-selectin expression

Platelet adhesion

Thrombin and other

Na⁺ pump failure

Na⁺ overload

reverse NCX

Ca²⁺ overload

calpain activation

SR Ca2+ oscillations

fragility

sarcolemmal rupture

Mitochondria

repolarization & ATP availability

Mitochondria

pH_i normalization: NHE, NBS, etc

Na⁺ influx & pH normalization:

pH_i normalization:

NHE, NBS, etc

ROS

MPT

↑ contractile activation

Cell-to-cell propagation

↑ contractile activation

sarcolemmal rupture

Coronary microcirculation

Cytosol

Na⁺ overload

reverse NCX

Ca²⁺ overload

calpain activation

orphan targets

Protecting the heart against reperfusion injury:

open questions

Reperfusion injury in STEMI: unsolved issues and limitations
PKG signaling is cardioprotective

1. Hernando V et al JMCC 2011
2. Abdallha et al CVR 2006
Pharmacological increase of myocardial cGMP-PKG signaling in STEMI

Natriuretic Peptides

- ANP
- BNP
- Urodilatin
- CNP

pGC

sGC

cGMP

PKG

NO

NO donors
- L-arginine
- BH4
- NOS protectors

sGC activators
- (ataciguat...)

MEMBRANE
Stimulation of cGMP synthesis with ANP prevents reoxygenation-induced hypercontracture
Hempel et al. Am J Physiol 1997;273: H244-9

Hypoxia and acidosis impair cGMP synthesis in coronary endothelium and cardiomyocytes
L-arginine limits reperfusion injury by a cGMP-dependent mechanism

Urodilatine at reperfusion limits necrosis in rat hearts

Pretreatment with intravenous of L-arginine limits infarct size in pigs

I.v. urodilatin at the time of coronary reperfusion limits infarct size

I.v. ataciguat reduces infarct size secondary to transient LAD occlusion in rats
Clinical trials potentially involving PKG activation

- Delayed pH recovery
- PKG signaling
- Ca²⁺ hypercontracture/fragility
- PLB
- MPT
- Reperfusion arrhythmias
- CELL DEATH
Clinical trials potentially involving PKG activation

Postconditioning
Thibault H et al. *Circulation* 2008

- Delayed pH recovery
- PKG signaling
- PLB
- Ca\(^{2+}\) hypercontracture/fragility
- MPT
- CELL DEATH

MPT

PKG signaling
Clinical trials potentially involving PKG activation

Postconditioning
Thibault H et al. *Circulation* 2008

Delayed pH recovery

Ca\(^{2+}\)
hypercontracture/fragility

PKG signaling

ANPeptide

PLB

MPT

CELL DEATH
Clinical trials potentially involving PKG activation

Postconditioning
Thibault H et al. *Circulation* 2008

Delayed pH recovery

PKG signaling

ANPepptide

GIK-IMMEDIATE
Selker P et al *JAMA* 2012

Exenatide
Lonborg J et al *Circ Cardiovasc Interv* 2012

Early ICoronary Adenosine
Garcia-Dorado et al *IJC* 2014

Ca^{2+}

hypercontracture/fragility

PLB

MPT

CELL DEATH
Clinical trials aiming at MPT: Direct MPT inhibition

- **Postconditioning**
  - Thibault H et al. *Circulation* 2008

- **Delayed pH recovery**

- **PKG signaling**

- **ANPeptide**

- **GIK-IMMEDIATE**
  - Selker P et al. *JAMA* 2012

- **Exenatide**

- **Early ICoronary Adenosine**
  - Garcia-Dorado et al. *IJC* 2014

- **Cyclosporine A**

- **Ca\(_2+\)**
  - Hypercontracture/fragility

- **PLB**

- **MPT**

- **CELL DEATH**
<table>
<thead>
<tr>
<th>Cardioprotective Therapy</th>
<th>Independent Clinical Trials – Number of Patients</th>
<th>Therapeutic intervention</th>
<th>Clinical Outcome</th>
<th>General Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Natriuretic Peptide</td>
<td>J-WIND-ANP* (N=569)</td>
<td>IV capetide 72h infusion started after reperfusion</td>
<td>15% reduction in 72 h AUC- total and 2.0% absolute Increase in the LVEF</td>
<td>Pharmacological cardioprotection</td>
</tr>
<tr>
<td>Glucose-insulin-potassium before pPCI (GIK)</td>
<td>IMMEDIATE* (N=357)</td>
<td>Iv GIK infusion for 12 h started by paramedics in ambulance—prior to reperfusion</td>
<td>No difference in progression to MI Reduction in the MI size and less in-hospital mortality and cardiac arrest</td>
<td>Pharmacological cardioprotection Positive and negative results Only 1 study.</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>METOCARD-CNIC* (N=270)</td>
<td>iv metoprolol three-5 mg boluses administered in ambulance prior to pPCI</td>
<td>Reduction in MI size (5–7 days by CMR)</td>
<td>Pharmacological cardioprotection Inconsistent preclinical data Only 1 Study.</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Piot et al. * (N=58)</td>
<td>IV CsA (2.5 mg/kg) 10 min prior to PPCI</td>
<td>44% decrease in MI size (72 h AUC total CK) 20% decrease in MI size (CMR in subset of 27 patients) 28% decrease in MI size and smaller LVESV on CMR at 6 months</td>
<td>Pharmacological cardioprotection Two independent clinical trials Controversial results Ongoing trials: CIRCUS (NCT01502774) CYCLE (NCT01650662)</td>
</tr>
<tr>
<td></td>
<td>Ghaffari et al. * (N=101)</td>
<td>IV bolus injection of 2.5 mg/kg of CsA prior to thrombolysis</td>
<td>Administration of CsA show no reduction MI size or any improvement in clinical outcomes</td>
<td></td>
</tr>
</tbody>
</table>
## EXENATIDE STUDIES IN STEMI

<table>
<thead>
<tr>
<th>Study</th>
<th>N number (Control vs. Exenatide)</th>
<th>Clinical setting</th>
<th>Administration (site of delivery)</th>
<th>Endpoint</th>
<th>Infarct size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nikolaidis et al. (7^5)</td>
<td>10 vs. 11</td>
<td>AMI and LVEF &lt;40%</td>
<td>72 hr infusion of GLP-1 after primary angioplasty (Hospital)</td>
<td>LVEF improvement (26% in treatment group)</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Lonborg et al. (4^7)</td>
<td>85 vs. 87</td>
<td>STEMI (Thrombolysis and pPCI)</td>
<td>IV 15 min before intervention (Hospital)</td>
<td>Myocardial salvage index (CMR, 90 days)</td>
<td>↓ (23%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ (30%) (^{4^8})</td>
</tr>
<tr>
<td>Woo et al. (5^0)</td>
<td>40 vs. 18</td>
<td>STEMI (Thrombolysis and pPCI)</td>
<td>10 µg subcutaneous and intravenous bolus 10 µg 5 min prior to pPCI 10 µg subcutaneous twice per day injection for 2 days (Hospital)</td>
<td>AUC Troponin I CK-MB (72h) CMR (30 days) Echocardiography (6 months)</td>
<td>↓ (46%)</td>
</tr>
<tr>
<td>Bernink et al. (4^9)</td>
<td>19 vs. 20</td>
<td>STEMI (Thrombolysis and pPCI)</td>
<td>IV infusion exenatide - 5 µg- started 30 min prior to pPCI continuous infusion for 72h -20 µg/24h- (Hospital)</td>
<td>Safety and feasibility of high dose exenatide</td>
<td>Not Applicable</td>
</tr>
</tbody>
</table>

* Follow-up study to Lonborg et al. 2012 \(^{4^7}\)
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Combination of RIC + insulin therapy

Rationale of combined therapy

1. Different mechanisms of action, additive effects
2. Lower doses, less side effects
3. Potentially different modulation by age, sex, comorbidities

Selection of treatments

a) Consistent, strong preclinical evidence, as essential previous step to clinical translation.
b) At least two positive and independent proof-of-concept clinical trials.
c) No neutral clinical study.
Combination therapy against myocardial reperfusion injury in PIGS

**METHODS**

Transient coronary occlusion (40 min, LAD)

Study protocol: 3 treatments

A) **RIC:** 5’ Isq/5’Rep, Right femoral artery (during ischemia)
B) **GIK** or glucose 5% (from 10 min after ischemia onset)
C) **Exenatide** (from min 25)

<table>
<thead>
<tr>
<th>RIC</th>
<th>GIK</th>
<th>Exenatide</th>
<th>No treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>No</td>
<td>11</td>
<td>11</td>
<td>14</td>
</tr>
</tbody>
</table>

Total: 69 patients

Combination therapy against myocardial reperfusion injury in PIGS

METHODS

Transient coronary occlusion (40 min, LAD)
Study protocol: 3 treatments

A) RIC: 5’ Isq/5’Rep, Right femoral artery (during ischemia)
B) GIK or glucose 5% (from 10 min after ischemia onset)
C) Exenatide (from min 25)

GIK: 30% glucose, 50 U/L insulin, 80 mEq KCl: 1.5 ml/kg
(IMMEDIATE: JAMA 2012)

Exenatide (10µg or 40µL of Byetta 10 in 100mL of saline)
72mL/h 15’ before reperfusion
26mL/h since reperfusion, during 2 hours.
(Lonborg et al EHJ 2012)
Signaling pathways. 5 min reperfusion (n=4 per group)

**Control region**
- Control
- GIK
- RIC
- GIK + RIC
- Exenatide
- Exen + RIC

**Area at risk**
- Control
- GIK
- RIC
- GIK + RIC
- Exenatide
- Exen + RIC

**Protein Blot Analysis**
- p-Akt (Ser473)
- Akt (total)
- OxPhos CII

**Graphical Data**
- **p-Akt/Akt**
  - **Control region**
  - **Area at risk**

**Stepwise regression analysis**
- GIK p < 0.0001
- Region p = 0.032
- RIC p = 0.033

Signaling: H1 NMR metabolomics in myocardium

A) Pattern recognition

- Control
- GIK or exenatide
Signaling: H1 NMR metabolomics in myocardium

A) Pattern recognition

- Control
- GIK or exenatide

B) Validation:

- RIC
Signaling pathways: AKT – eNOS activation with GIK

Signaling pathways: different in RIC, GIK and EXE

RIC → PoCo → REPERFUSION → \( \text{O}_2^- \) → \( \text{ONOO}^- \) → S. Reticulum ↔ Mitochondria → CELL DEATH

\( \text{eNOS BH}_2 \) → \( \text{BH}_4 \)NOS → NO → PKG → S. Reticulum ↔ Mitochondria → CARDIOPROTECTION

INSULIN → Akt → Glucose uptake → Metabolic shift

EXENATIDE → Glucose uptake → Metabolic shift

RESULTS: INFARCT SIZE
2 hours of reperfusion (n= 7-10 per group)

COMBination Therapy in Myocardial Infarction: The COMBAT-MI Trial

ClinicalTrials.gov  NCT 04376

SPONSOR: H.U. Vall d’Hebron Research Institute, Spain

PARTICIPANTS: HUVH, Barcelona; HUGTP, Barcelona; Spain
                Hatter Cardiovascular Institute, London, GB

TREATMENTS: Exenatide i.v., RIC, both or neither

PATIENTS: Included > 16y with STEMI receiving pPCI < 6h
           Excluded confused, TIMI > 1, Shock > 48h, c.i. CMRI

Primary ENDPOINT: Infarct Size (CMRI 2 -7 days after pPCI)

SAMPLE SIZE: 360 pts

DESIGN: Double blind, placebo controlled

STATISTICS: Factorial 2 x 2

START - END: Sept 15, 2015 - February 2017
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Future research

1) The mechanisms of R-induced cell death are only partially understood
2) The mechanism of RIC needs to be elucidated
3) PKG interventions need to be further explored in IS trials
4) Combination therapies to be developed and clinically tested
5) Extending reduction of RI into prevention of adverse post-infarct remodeling
6) Translation to clinical outcome trials (death, heart failure)
7) Social need: lot of work for cardiovascular scientists and clinical investigators
Reducing Myocardial Injury Secondary to Coronary Artery Disease (REMIND)

Program 2, Cardiovascular Research Network of the ISCiii
Coordinating group: Sevicio de Cardiología HUVH-VHIR, UAB

VHIR cardiovascular cooperative project
Neurovascular, Diabetes, Hepathology, Nephrology
THANK YOU!

Cardiovascular Research Group
Vall d’Hebron University Hospital and Research institute
Universitat Autònoma de Barcelona. SPAIN