Opportunities and challenges in translating cardioprotection to the clinic

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Barcelona
Why cardioprotection?


Infarct size and prognosis in primary PCI

[Graph showing infarct size quartiles and associated mortality and heart failure hospitalization rates over time.]

- Infarct Size Quartile 1: 0% - ≤8.0%
- Infarct Size Quartile 2: >8.0% - ≤17.9%
- Infarct Size Quartile 3: >17.9% - ≤29.8%
- Infarct Size Quartile 4: >29.8%

- All-cause Mortality or Heart Failure Hospitalization (%)
- Time (Months)
OPPORTUNITIES
Treatment opportunities

Before, during and after ischemia

- Ischemic injury
- Reperfusion
- Reperfusion salvage
- Reperfusion injury

Infarct size vs. time

- Coronary occlusion
- Ischemia

Ischemic injury
Adjunct cardioprotective interventions in STEMI patients

Mechanical cardioprotection (ischemic conditioning)
- Ischemic post-conditioning
- Remote ischemic conditioning

Pharmacological cardioprotection
- Mitochondrial -targeted
- β-blockers
- ANP
- Exenatide
Mechanical cardioprotection (ischemic conditioning)
- Ischemic post-conditioning
- Remote ischemic conditioning

Pharmacological cardioprotection
- Mitochondrial -targeted
- Beta-blockers
- Adenosine
- Antiplatelet agents
- ANP
- Exenatide
Ischemic Post-Conditioning: experimental data

Zhao et al, Am J Physiol 2003

Experimentally has robustly shown to limit infarct size

Vilahur et al Eur Heart J 2012
Heusch et al Circ Res 2011
Bodi et al Int J Cardiol 2014

Ovize et al Cardiovasc Res 2010
Hausenloy D. Thrombosis Haemost 2009
Ischemic Post-Conditioning: in the clinical arena

- The optimal protocol algorithm for cardioprotection by conditioning has not yet been defined

- Direct stenting?

- Exclusion of patients with >6 hours of symptom onset to protect

- Consider the presence of co-morbidities or co-medications

Ferdinandy et al. Pharmacol Rev 2014
Remote ischemic post-conditioning: basic concepts

**Circulating humoral factors**
- Adenosine
- NO
- miRNA
- NO

**Activation of efferent neural pathways**
- Hormones
- Neuropeptides
- Cytokines/chemokines
- RNAs
- Brainstem is involved?
- Which levels of the spinal cord are mandatory?

**RECEPTOR ACTIVATION**
G-protein coupled receptors

**SIGNALING**
RISK, SAFE pathways

**MITOCHONDRIA**
(mPTP)

**CARDIOPROTECTION**

Remote ischemic post-conditioning: Clinical arena

But in cardiac surgery..

Phase III trial

Remote ischemic conditioning

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONDI</td>
<td>Bøtker (2010)</td>
</tr>
<tr>
<td>RIPC</td>
<td>Prunier (2014)</td>
</tr>
<tr>
<td>LIPSIA</td>
<td>Eitel (2015)</td>
</tr>
<tr>
<td>ERIC-LYS</td>
<td>Yellon (2015)</td>
</tr>
</tbody>
</table>

Meybohm et al N Eng J Med 2015

Hausenloy et al N Eng J Med 2015
Co-morbidities / Co-medications

STEMI patients are under medication known to exert cardioprotection.

STEMI is linked to CV risk factors and co-morbidities which reduces IPost-C cardioprotection.

- **Postconditioning**
  - Ischemia
  - Reperfusion
  - Confounders
    - Age
    - Loss of cardioprotective signalling
    - Co-morbidities
      - Hypercholesterolemia, diabetes, obesity, hypertension, LV hypertrophy
    - Medication
      - ß-blockade, statins, anti-diabetic drugs
  - Protection

- **Control**
  - Ischemia
  - Reperfusion through residual stenosis
  - Medication
    - Adenosine, nitroglycerin, ß-blockers, ACE inhibitors, AT1-blockers, statins, opioids, ivabradine, dronedarone
  - Protection

Ferdinandy et al. *Pharmacol Rev* 2014

Heusch et al. *Eur Heart J* 2012
HDL and cardioprotection: impact of CV risk factors
Cardio-vascular protective effects of HDL

ISCHEMIA/REPERFUSION DAMAGE

O₂

HDL

ANTIOXIDANT

ANTI-INFLAMMATORY

EC REPAIR

ANTITHROMBOTIC

LDL

Monocytes

IDL

VLDL

Nascent HDL

RCT

HDL 3

HDL 2

Liver

LDL-R

Badimon L & Vilahur G. N Y Acad Sciences 2012
Ability of HDL to protect the heart in the setting of ischemia/reperfusion is altered by CV risk factors (hypercholesterolemia)?

Theilmeier et al *Circulation* 2006
Vilahur et al *J Am Col Cardiol* 2015
HDL ability to protect against Ischemia/reperfusion is found to be impaired under dislipidemic conditions

**FUNCTIONAL PARAMETERS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vehicle</th>
<th>NC&lt;sub&gt;HDL&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular ejection fraction</td>
<td>43.7±2.2</td>
<td>48.0±2.7</td>
</tr>
<tr>
<td>Left ventricular end diastolic volume</td>
<td>100.1±5.5</td>
<td>85.4±1.2*</td>
</tr>
<tr>
<td>Left ventricular end systolic volume</td>
<td>56.8±4.6</td>
<td>44.3±2.3*</td>
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**ANATOMICAL PARAMETERS**

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<tr>
<td>Area-at-risk (g left ventricle)</td>
<td>21.3±1.4</td>
<td>18.1±1.2</td>
</tr>
<tr>
<td>Mass left ventricle (g)</td>
<td>73.2±2.9</td>
<td>74.7±2.7</td>
</tr>
<tr>
<td>Infarct size (% of left ventricle)</td>
<td>23.3±1.8</td>
<td>13.8±1.3*</td>
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<td>Infarct mass (g LV)</td>
<td>17.4±1.2</td>
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<tr>
<td>Myocardial salvage</td>
<td>3.9±0.5</td>
<td>7.8±0.9*</td>
</tr>
<tr>
<td>Myocardial salvage index</td>
<td>0.18±0.02</td>
<td>0.43±0.04*</td>
</tr>
<tr>
<td>Hemorrhage (g LV)</td>
<td>2.0±0.3</td>
<td>2.0±0.4</td>
</tr>
<tr>
<td>No-reflow (g LV)</td>
<td>2.5±0.2</td>
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HDL ability to protect against Ischemia/reperfusion is found to be impaired under dislipidemic conditions

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<th>3T-CMR (Day 3 post-MI)</th>
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<th>HyperNC_HDL</th>
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G. Vilahur et al. *J Am Coll Cardiol* 2015
LGE (Infarct) T2-STIR (Edema) LGE (Infarct) CMR (merge)

Vehicle

NC_{HDL}

HyperC_{HDL}

G. Vilahur et al. J Am Col Cardiol 2015
Raising HDL cholesterol in secondary prevention does not prevent CVD

In 2nd prevention higher HDL-cholesterol levels do not reduce CV events rate beyond statins

Keene D et al BMJ 2014

Compared to healthy subjects, HDL from patients with manifest CVD ...↓ Cholesterol efflux capacity
↓ Anti-oxidant properties
↓ Anti-inflammatory effects

Sigruener et al (LURIC) PLOS one 2014
Riwanto et al JLipRes 2013
Kontush A & Chapman MJ. Pharmacology Rev 2006
HDL lose their ability to protect the heart in the setting of ischemia/reperfusion in hypercholesterolemia.
Chances for cardioprotection in STEMI patients...

Ischemic conditioning
- Post-conditioning
- Remote ischemic post-conditioning

Pharmacological conditioning
- Cyclosporine
- Beta-blockers
- Statins
- Adenosine
- Antiplatelet agents
- Etc..

Multiple drugs have shown to reduce infarct size in experimental animal models ....
PHASE-II trials: not all have been beneficial

Gerd Heush  *Comp Physiol* 2015
**In the bench,**
cardioprotective therapies are effective

At the bedside,
not all have demonstrated to be beneficial

**NONE HAS DEMONSTRATED CLINICAL BENEFIT IN PHASE III TRIALS**
The prevailing notion on the translation of cardioprotective strategies to clinical practice is disappointment. In fact, there is (yet) no single randomized clinical trial which has unequivocally demonstrated a better clinical outcome for patients experiencing an acute myocardial infarction or undergoing cardiovascular surgery when receiving an adjunct cardioprotective agent/intervention before or at reperfusion.

Gerd Heush  *Circulation Research 2017*
CHALLENGES
Barriers / challenges to translating experimentally successful interventions into clinical therapies

**Preclinical Level:**

1. The **MECHANISMS** of I/R injury and protection need to be **FULLY UNRAVELLED**

2. Lack of **ROBUST PRECLINICAL DATA**

3. Use of **HEALTHY** and **YOUNG** animal models that do not approximate the clinical setting

4. Failure to disseminate **NEGATIVE RESULTS**
Barriers / challenges to translating experimentally successful interventions into clinical therapies

**Clinical Level:**

1. Lack of **PHASE-II** clinical trials (dosing and timing)
Metoprolol in cardioprotection

2007

Circulation

Early Metoprolol Administration Before Coronary Reperfusion Results in Increased Myocardial Salvage: Analysis of Ischemic Myocardium at Risk Using Cardiac Magnetic Resonance

Borja Ibanez, Susanna Prat-González, Walter S. Speidl, Gemma Vilahur, Antonio Pinero, Giovanni Cimmino, Mario J. García, Valentin Fuster, Javier Sanz and Juan J. Badimon

2011

International Journal of Cardiology

The cardioprotection granted by metoprolol is restricted to its administration prior to coronary reperfusion

Borja Ibanez, Giovanni Cimmino, Susanna Prat-González, Gemma Vilahur, Randolph Hutter, Mario J. García, Valentin Fuster, Javier Sanz, Lina Badimon, Juan J. Badimon

Cardiac Function (MRI)

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<th>Placebo</th>
<th>Metoprolol</th>
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<td>LVEF: 35% vs 35%</td>
<td>LVEF: 37% vs 43%</td>
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Salvaged Myocardium

- Pre-reperfusion: Metoprolol vs Placebo
- Post-reperfusion: Metoprolol vs Placebo

% of Area at Risk

- Pre-reperfusion: Metoprolol vs Placebo
- Post-reperfusion: Metoprolol vs Placebo

Salvaged Myocardium

- Pre-reperfusion: Metoprolol vs Placebo
- Post-reperfusion: Metoprolol vs Placebo

Salvaged Myocardium

- Pre-reperfusion: Metoprolol vs Placebo
- Post-reperfusion: Metoprolol vs Placebo
**Metoprolol & cardioprotection in the clinical setting**

**2013**
- B. Ibáñez et al. V. Fuster. Circulation 2013

**2016**
- Roovink V et al. J Am Col Cardiol 2016

**Metoprolol i.v. pre-reperfusion**
- Dose: 15mg
- Timing: <6h
- Anterior infarcts (21% IS)
- No β-blockers
- 1st STEMI
- PPCI
- All infarcts (15.3% IS)
- On β-blockers 19%
- Control

**7 days after STEMI**
- Reduced infarct size

**6 months after STEMI**
- Improved LVEF

**Graphs:**
- 336 patients: 10 mg metoprolol
- Significant improvement with metoprolol?
  - Baseline characteristics
  - Infarct size
  - Peak and area under creatine kinase (CK) curve
  - Left ventricular ejection fraction
  - Incidence of adverse events
  - Incidence of malignant arrhythmias

- 346 patients: placebo
- 683 patients

**Statistics:**
- 3.6% vs. 6.9%
Barriers / challenges to translating experimentally successful interventions into clinical therapies

Clinical Level:

1.- Lack of **PHASE-II** clinical trials (dosing and timing)

2.- Lack of **SOLID CONSISTENT** experimental evidence
TRO40304 inhibits the opening of the mitochondrial permeability transition pore.

**RATIONALE:** TRO40304 has been shown to reduce infarct size by 50% in rat and mouse models and to improve LVEF at 24h and 1 month in these models.

**NO EFFECT**

Dan Antar et al *Eur Heart J* 2013

Hansson et al *Eur J Pharmacol* 2015
CIRCUS: CICLOSPORINE

CONSISTENT DATA ON

Argaud et al  J Mol Cel Cardiol 2005

INCONSISTENT DATA ON

Sheu et al  Int J Cardiol 2011
De Paulis et al  Basic Res Cardiol 2013
Karlsson et al  J Cardiovasc Pharmacol Ther 2010

Reperfusion NECROSIS

Ciclosporine

ARGAUD ET AL

British Journal of Pharmacology

REVIEW

Cyclosporin variably and inconsistently reduces infarct size in experimental models of reperfused myocardial infarction: a systematic review and meta-analysis

WY Lim1, CM Mesnow2 and C Berry3

1HRI Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK. 2Department of Endocrinology, University of Glasgow, Glasgow, UK. 3Division of Cardiology, University of Glasgow, Glasgow, UK.
**The only PHASE III clinical trial so far in cardioprotection...**

**FAILED**

**POTENTIAL EXPLANATIONS:**

- 12h symptoms CIRCUS vs 4h Phase II - (any viable tissue left at 12h?)
- Higher use of P2Y12 inhibitors CIRCUS (cardioprotective)
- Vehicle used: cremophor vs intralipid (CIRCUS) which reduces infarct size as much as Ciclosporine

Barriers / challenges to translating experimentally successful interventions into clinical therapies

Clinical Level:

1. Lack of **SOLID CONSISTENT** experimental evidence
2. Lack of **PHASE-II** clinical trials (dosing and timing)
3. Which **CLINICAL SCENARIO** and **OPTIMAL PATIENT** should be considered
The optimal patient and clinical scenario

- TOTALLY OCCLUDED LAD: LARGE INFARCTS
- NO COLLATERALS
- ADMITTED PREFERABLY <6h AFTER SYMPTOM ONSET
- TIMI FLOW 0 PRIOR PRIOR-PPCI
- TIMI FLOW >2 POST PPCI
- NO PRE-INFARCTION ANGINA
FUTURE/NEW OPPORTUNITIES

Identify novel targets

Test new strategies
Identify novel targets

**Novel targets and future strategies for acute cardioprotection: Position Paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart**


**Epigenomic and transcriptomic approaches in the post-genomic era: path to novel targets for diagnosis and therapy of the ischaemic heart? Position Paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart**

Test new strategies: HMG-CoA reductase inhibitors, Statins

Acetyl-CoA → HMG-CoA inhibitors → HMG-CoA → Mevalonate → Isopentenyl-PP → Farnesyl-PP → Squalene → Cholesterol ▼

Farnesyl-PP → Geranylgeranyl-PP → Activation of Rho, Rac, Cdc42

Statin-related “pleiotropic effects”
Direct cardioprotective effects??

- Improvement endothelial function
- Atherosclerotic plaque stabilization
- Decreased inflammatory response
- Lower thrombotic risk

Badimon & Vilahur. Rev Esp Cardiol 2010
Clinical support...

Better outcomes in ACS patients when **oral** LD of statins are administered **early after revascularization** (Miracle, PROVE-IT, A to Z).

Cannon et al *N Eng J Med* 2004
Kinlay et al *Circulation* 2004
de Lemos et al *Eur Heart J* 2004

Decreased rates of peri-procedural complications in several small-scale studies where **oral** LD satins are administered **before an elective or emergent PCI**.

Patti et al *Circulation* 2006
Patti et al *J Am Col Cardiol* 2007
Di Scieascio et al *J Am Col Cardiol* 2009
Statins, do they exert cardioprotection when administered intravenously prior to reperfusion?

- **Simvastatin (P.O)**
- **β-OH-Simvastatin (I.V)**

**β-OH-SIMVASTATIN**

(Lactone form (closed))

Hydrolisis

Sodium hydroxide + heat

Hydroxiacid form (open)

**Intravenous β-OH-Simvastatin (0.3mg/kg)**

**Reperfusion**

75 min

15 min

150 min

Echocardiography

Infarct size analysis

Molecular / Histological approaches

I/R injury

Fat: 24%

20% saturated fat

2% cholesterol

1% cholic acid

Protein: 20.2%

Carbohydrates: 35.3

Fiber: 5%

Minerals: 6%

Water: 9%

Iv Statin administration prior reperfusion protects against I/R injury

**OXIDATIVE DAMAGE**

**NEUTROPHILE INFILTRATION**

**MITOCHONDRIAL FUNCTION**

**APOPTOSIS EXECUTION**

Intravenous statin administration supresses myocardial RhoA activation

HMG CoA reductase

Acetyl CoA

HMG CoA

Mevalonate

Isopentenyphyrophosphate

Geranyl geranylation

Farnesilation

RhoA

GTP

GDP

RhoA

RhoA activation

ACTIVO

INACTIVE
Intravenous statin administration reduces infarct size and improves cardiac performance.

**IN FARCT SIZE**

- Necrosis/AAR
- %
  - Control
  - ß-OH-S

**LVEF**

- Δ LVEF (%)
- Improvement
- Worsening
- Baseline

- 2.5h post-reperfusion vs ischemia
- Control
- ß-OH-S

Antiplatelet agents

ACS

NSTEMI & UA

STEMI
ADP-receptor antagonists: effect on infarct size

Platelet aggregation

Clopidogrel
Cangrelor
Aspirin

30min ischemia
+ 3h reperfusion

Clopidogrel Cangrelor Aspirin

Infarct size

Yang X et al J Cardiovas Pharm Therap 2013
Clinical support...

**Clopidogrel - ADP-receptor blockers**

- Barrabes et al. *Thromb & Haemost* 2010
- Yang X et al. *J Cardiovas Pharm & Therap* 2013
- Schäfer et al. *Basic Res Cardiol* 2011
- Roubille et al. *Basic Res Cardiol* 2012
- Patti et al. *J Am Col Cardiol* 2011 ARMYDA-6-MI

**Potential explanations:**

1. Improved coronary patency
2. Improved coronary flow

---

**Diagram:**

- Immediate Clopidogrel 600 mg Loading (n=100)
- PCIs according to standard center procedure (OP 1B 111a at the physician’s discretion)
- 600 mg Clopidogrel arm
- ASA (100 mg /day)
- Clopidogrel (75 mg /day)

**End-points:**

Primary: Infarct size
Secondary: TIMI flow pre-PCI

**Infarct size – 24h**

- CK-MB, Troponin I, Hb:
  - 4, 5, 12, 24, 36, 48 and 72 hours after PCI

**Graphs:**

- C-reactive protein (mg/l)
- Troponin I (ng/ml)
Effect of ticagrelor on infarct size: adenosine-related effect

**Adenosine receptors**
- A1
- A2a
- A2b
- A3

- Vasodilation
- Cardioprotection (post-conditioning)
- Modulation of inflammation

**Antiplatelet effects**
- Platelet inhibition

**TICAGRELOR**

**Red Blood Cells**
- CD39 (NTPDase-1)
- CD73
- ATP → AMP
- ADENOSINE
- Antiplatelet effects
- ENT-1
- Red Blood Cells

**Endothelial cells**
- A1
- A2a
- A2b
- A3
- Vasodilation
- Cardioprotection (post-conditioning)
- Modulation of inflammation

**Platelets**
- ADP
- P2Y12
- A2A
- GPIIb/IIIa
- Platelet inhibition
Ticagrelor exerts direct cardioprotective effects


PLACEBO
CLOPIDOGREL (LD: 600mg; MD: 75mg)
TICAGRELOR (LD: 180mg; MD: 90 mb bid)

Experimental pig model of closed-chest acute MI induction and reperfusion

2h/4h
60min
24h

3T - MRI

• Cardiac functional analysis
  • No-reflow
  • Necrosis
  • Edema
• Local cardiac effects
• Systemic effects
• Thrombosis / coagulation

Outcome
Ticagrelor reduces infarct size to a greater extent than clopidogrel

<table>
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<th>CMR analyses</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>LV mass (g)</td>
<td>Non-treated</td>
<td>70.0 [64.1-73.7]</td>
<td>Troponin (ng/mL)</td>
<td>Non-treated</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>72.2 [69.3-74.7]</td>
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<td>Ticagrelor</td>
<td>70.6 [67.9-74.4]</td>
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<td>Ticagrelor +8SPT</td>
<td>70.5 [65.0-70.2]</td>
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<td>Edema (g LV)</td>
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<td>23.4 [20.9-31.1]</td>
<td>LVEF (%)</td>
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<tr>
<td>Necrosis (% LV)</td>
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<td></td>
<td>Clopidogrel</td>
<td>20.9 [19.3-22.8]*</td>
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<td>16.4 [15.5-17.9]**†</td>
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<td>Ticagrelor +8SPT</td>
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<tr>
<td>No-reflow (gr LV)</td>
<td>Non-treated</td>
<td>4.6 [2.1-6.0]</td>
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<tr>
<td></td>
<td>Clopidogrel</td>
<td>2.0 [1.5-2.8]*</td>
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<td>2.1 [1.8-3.0]*</td>
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</table>

* p<0.05 vs placebo-control animals
† p<0.05 vs clopidogrel-treated animals

Ticagrelor reduces infarct size to a greater extent than clopidogrel and edema formation post-MI

<table>
<thead>
<tr>
<th>CMR analyses</th>
<th>Treatment</th>
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</tr>
</thead>
<tbody>
<tr>
<td>LV mass (g)</td>
<td>Non-treated</td>
<td>70.0 [64.1-73.7]</td>
<td>Troponin</td>
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<td></td>
<td>Clopidogrel</td>
<td>72.2 [69.3-74.7]</td>
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<td>Ticagrelor</td>
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<tr>
<td></td>
<td>Ticagrelor+8SPT</td>
<td>66.5 [65.0-70.2]</td>
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<td>Ticagrelor+8SPT</td>
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<tr>
<td>Edema (g LV)</td>
<td>Non-treated</td>
<td>23.4 [20.9-31.1]</td>
<td>LVEF (%)</td>
<td>Non-treated</td>
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<td>Clopidogrel</td>
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<td></td>
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<td>23.1 [20.2-24.4]**†</td>
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<tr>
<td></td>
<td>Ticagrelor+8SPT</td>
<td>24.6 [23.6-34.5]</td>
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<tr>
<td>Edema (% LV)</td>
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<td>36.2 [33.9-43.2]</td>
<td>LVEDV (mL)</td>
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<td>Infact mass (g LV)</td>
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<td>22.8 [17.3-25.8]</td>
<td>LVESV (mL)</td>
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<td>Ticagrelor+8SPT</td>
<td>2.2 [2.0-2.6]*</td>
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* p<0.05 vs placebo-control animals
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Ticagrelor reduces infarct size via adenosine-dependent mechanisms

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</table>
|              | Ticagrelor           | 16.3 [14.2-19.9] || p<0.05 vs placebo-control animals
|              | Ticagrelor+8SPT      | 24.6 [22.8-25.3] |
| Necrosis (% LV) | Non-treated        | 22.8 [17.3-25.8] |
|                | Clopidogrel          | 15.7 [14.2-16.2] |
|                | Ticagrelor           | 12.0 [10.6-12.9] || p<0.05 vs clopidogrel-treated animals
|                | Ticagrelor+8SPT      | 14.9 [14.6-16.1] |
| Necrosis (%) LV | Non-treated         | 31.1 [25.9-39.1] |
|                | Clopidogrel          | 20.9 [19.3-22.8] |
|                | Ticagrelor           | 16.4 [15.5-17.9] |
|                | Ticagrelor+8SPT      | 22.4 [21.8-23.9] |
| No-reflow (gr LV) | Non-treated        | 4.6 [2.1-6.0] |
|                | Clopidogrel          | 2.0 [1.5-2.8] |
|                | Ticagrelor           | 2.1 [1.8-3.0] |
|                | Ticagrelor+8SPT      | 2.2 [2.0-2.6] |
| Troponin (ng/mL) | Non-treated        | 19 [16.5-21.7] |
|                | Clopidogrel          | 13.4 [13.0-14.0] | *p<0.05 vs placebo-control animals
|                | Ticagrelor           | 10.9 [9.3-11.4] | **p<0.05 vs clopidogrel-treated animals
|                | Ticagrelor+8SPT      | 14.2 [12.2-16.1] |
| LVEF (%)      | Non-treated          | 43.0 [42.0-43.6] |
|                | Clopidogrel          | 47.2 [45.4-48.2] |
|                | Ticagrelor           | 47.2 [45.4-48.1] |
|                | Ticagrelor+8SPT      | 48.7 [46.6-51.0] |
| LVEDV (mL)    | Non-treated          | 93.0 [87.6-98.1] |
|                | Clopidogrel          | 73.7 [68.9-81.3] |
|                | Ticagrelor           | 77.4 [71.8-89.2] |
|                | Ticagrelor+8SPT      | 84.4 [76.9-86.8] |
| LVESV (mL)    | Non-treated          | 54.0 [49.2-55.5] |
|                | Clopidogrel          | 39.5 [36.3-41.9] |
|                | Ticagrelor           | 39.2 [37.3-46.0] |
|                | Ticagrelor+8SPT      | 44.2 [40.4-45.7] |
Edema reduction

<table>
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<tr>
<th>Necrosis (DE)</th>
<th>Edema (T2 STIR)</th>
<th>Histopathology (TTC)</th>
</tr>
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<tbody>
<tr>
<td>Placebo-control</td>
<td>Clopidogrel</td>
<td>Ticagrelor</td>
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Adenosine contributes to cardioprotection by ischemic conditioning which, in turn, has shown to reduce edema formation in man.
TAKE HOME MESSAGE: Opportunities and Challenge to successfully translate cardioprotection

Networks and procedures in analogy
Selection of agents with consistent preclinical/experimental data

Heush et al. *Circulation Res* 2017
X. Rossello & D. Yellon *Circulation* 2016

1. Reductionist models either in small or large animals
2. Animal models on a background of co-morbidities and/or medications
3. Proof-of-concept clinical trials (infarct size)
4. Clinical outcomes trials (heart failure and mortality)

Perform Phase II dose-finding studies
Selecting the optimal patient
Thank You

Prof. Lina Badimon
Dr. Laura Casani
Dr. Teresa Padró
PhD Soumaya Ben-Aicha
Dr. Esther Peña
Dr. Oriol Juan-Babot
Dr. Sandra Camino
Dr. Gemma Arderiu
Pablo Catalina
Mª. Angeles Cánovas
Fco. Javier Rodríguez
Josep Moreno
Sergi Lopez

Dr. Manuel Gutiérrez
Dr. Antoni Capdevila
Dr. Alberto Hidalgo
Dr. Lluís Carreras
Dr. Guillem Pons-Llado
Therapies that show promise... mild hypothermia

Severe hypothermia (20° C-28° C)
Moderate hypothermia (28° C-32° C)
Mild hypothermia (32° C-35° C)

Metabolic slowing
Erk activation (RISK)

The CHILL-MI Trial

Hale et al J Cardiovas Pharmacol 2011
Tissier et al Basic Res Cardiol 2010
Yang et al Basic Res Cardiol 2011

D. Erlinge et al JACC 2014
Atorvastatin, given at reperfusion, attenuates reperfusion injury *ex vivo* through multiple prosurvival signaling pathways.

30 min global ischemia + 30 min reperfusion

Bell & Yellen, *J Am Col Cardiol* 2003

Aquaporin proteins are transmembrane channels critically involved in cellular water balance closely related to edema.

Aquaporin-4 (AQP-4)?

- Aquaporin-4 is responsible or cerebral ischemia (Yao et al. 2014)
- Aquaporin-4 increases after myocardial ischemia and is involved in myocyte swelling and infarct size (Rutkovskiy A et al. 2012; Warth et al. 2007)
- Adenosine signaling regulates aquaporin-4 expression (Lee et al. 2013)
- Aquaporin-4 expression is found to be reduced in ENT-1** mice (Hinton et al. 2014)
Ticagrelor reduces aquaporin-4 transcription and protein levels.
AMPK: a critical component of myocardial metabolism


[ATP] ↑ \→ [ATP] ↓ , [AMP, ADP] ↑

**ISCHEMIA**

*Active AMPK*

ATP-consuming pathways
- Fatty acid synthesis
- Cholesterol synthesis
- Glycogen synthesis
- Protein synthesis

ATP-producing pathways
- Glycolysis
- Glucose uptake
- FA - β-oxidation

*Inactive AMPK*

Consume less ATP

Produce more ATP
AMPK exerts cardioprotective properties

G. Heusch *Circulation Research* 2015

Ischemia-reperfusion

$\text{AMPK} \rightarrow K_{\text{ATP}}$

- eNOS
- ER Stress
- ROS production
- mPTP opening

Cardioprotective signal transduction in conditioning

Castañares-Zapatero D et al. 2013

AMPK$^{-/-}$ mice: AMPK prevents ventricular edema formation
Ticagrelor increases AMPK signaling activation.