

# Effect of remote ischaemic conditioning on clinical outcomes in patients with STEMI undergoing primary PCI

## The CONDI-2/ERIC-PPCI - trial

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On behalf of the CONDI-2 – ERIC-PPCI Investigators



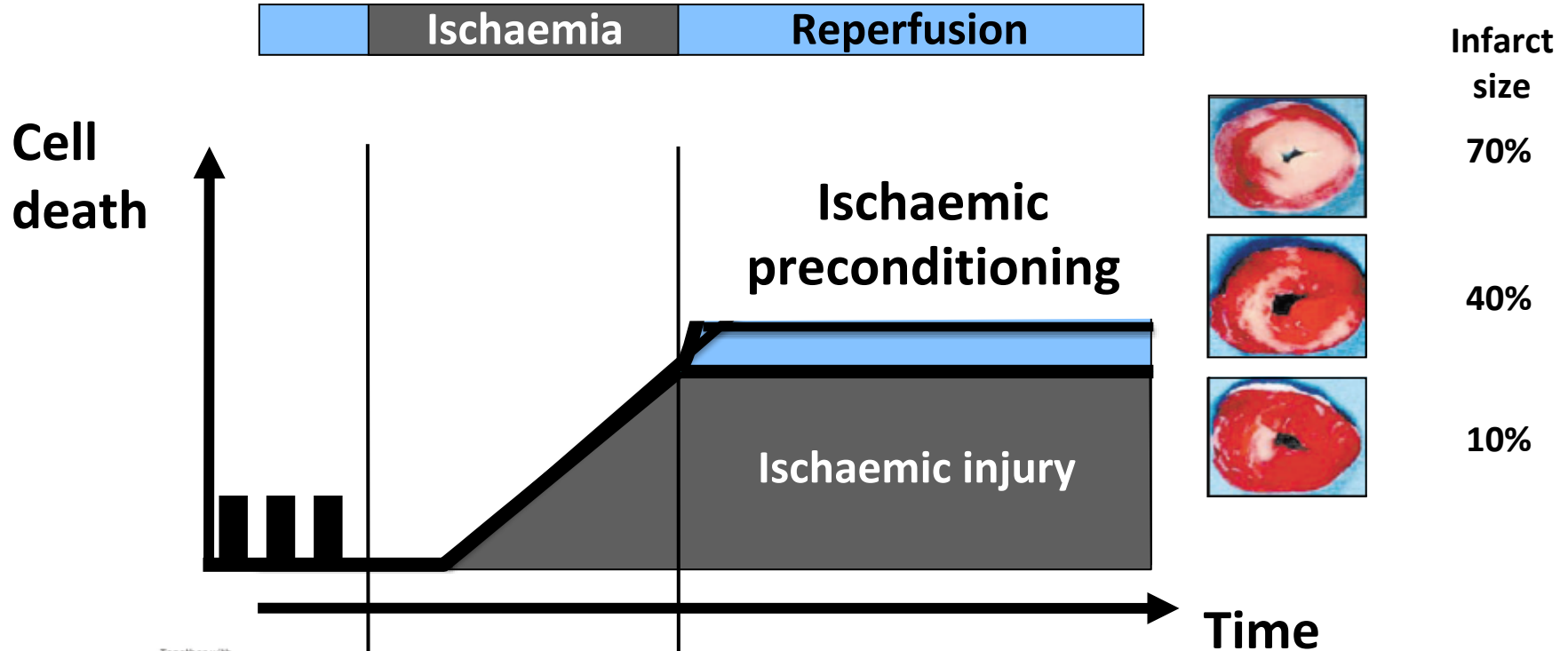
# Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Shareholder CellAegis Inc)



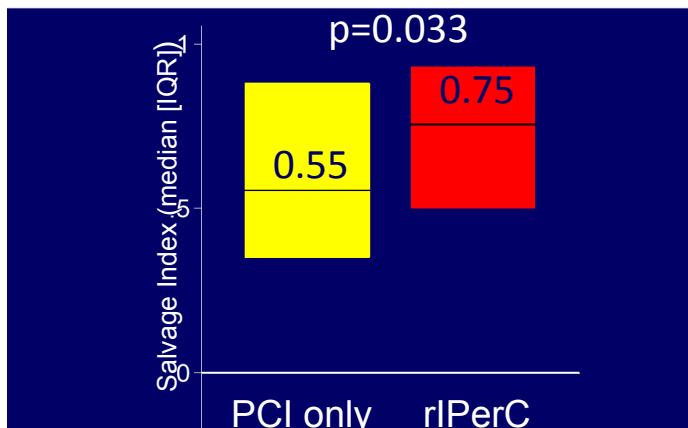
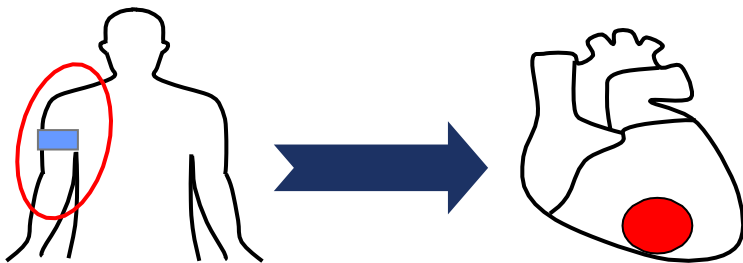
# Background

ERIC-PPCI





# Remote ischaemic conditioning



Bøtker et al. *Lancet* 2010; 373: 727-34

| Study                    | No of patients (Control/RIC) | Endpoint                                  | Result                                                        |
|--------------------------|------------------------------|-------------------------------------------|---------------------------------------------------------------|
| Rentoukas et al. 2010    | 30/33                        | ST-segment resolution                     | 20% increase in patients achieving full ST-segment resolution |
| Crimi et al. 2013        | 50/50                        | CK-MB (AUC 72 h after PCI)                | 20% reduction                                                 |
| Prunier et al. 2014      | 17/18                        | CK-MB (AUC 72 h after PCI)                | 31% reduction                                                 |
| Yellon et al. 2015       | 258/261                      | TnT (AUC 24 h after PCI)                  | 17% reduction                                                 |
| Eitel et al. 2015 LIPSIA | 232/232/232                  | Salvage index (MRI)                       | 23 % increase                                                 |
| White et al. 2015        | 40/43                        | Myocardial edema (MRI)                    | 27 % reduction                                                |
| Verouhis et al 2016      | 46/47                        | Salvage index (MRI)                       | No effect                                                     |
| Ladejobi et al. 2017     | 58/92                        | Admission for heart failure<br>NT-pro-BNP | 78% reduction<br>61% reduction                                |
| Gaspar et al. 2018       | 217/231                      | Cardiac death and HHF                     | 65% reduction                                                 |



# Aim

ERIC-PPCI

- To investigate whether remote ischaemic conditioning, as an adjunct to primary PCI, can reduce cardiac death or hospitalisation for heart failure at 12 months



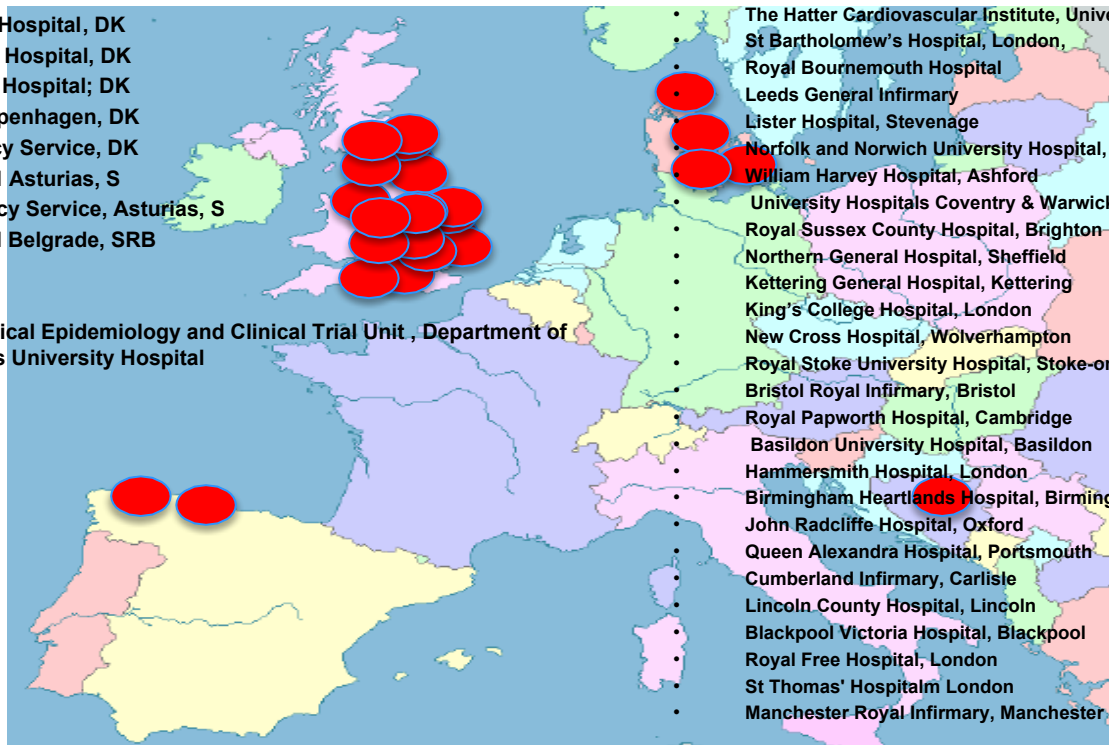
# Organization and participating centres



## • CONDI-2:

- Aarhus University Hospital, DK
- Aalborg University Hospital, DK
- Odense University Hospital, DK
- Rigshospitalet, Copenhagen, DK
- National Emergency Service, DK
- University Hospital Asturias, S
- Regional Emergency Service, Asturias, S
- University Hospital Belgrade, SRB

- Department of Clinical Epidemiology and Clinical Trial Unit, Department of Cardiology, Aarhus University Hospital



## • ERIC-PPCI

- The Hatter Cardiovascular Institute, University College London, London, UK
- St Bartholomew's Hospital, London,
- Royal Bournemouth Hospital
- Leeds General Infirmary
- Lister Hospital, Stevenage
- Norfolk and Norwich University Hospital, Norwich
- William Harvey Hospital, Ashford
- University Hospitals Coventry & Warwickshire, Coventry
- Royal Sussex County Hospital, Brighton
- Northern General Hospital, Sheffield
- Kettering General Hospital, Kettering
- King's College Hospital, London
- New Cross Hospital, Wolverhampton
- Royal Stoke University Hospital, Stoke-on-Trent
- Bristol Royal Infirmary, Bristol
- Royal Papworth Hospital, Cambridge
- Basildon University Hospital, Basildon
- Hammersmith Hospital, London
- Birmingham Heartlands Hospital, Birmingham
- John Radcliffe Hospital, Oxford
- Queen Alexandra Hospital, Portsmouth
- Cumberland Infirmary, Carlisle
- Lincoln County Hospital, Lincoln
- Blackpool Victoria Hospital, Blackpool
- Royal Free Hospital, London
- St Thomas' Hospital, London
- Manchester Royal Infirmary, Manchester

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# Recruitment and randomisation ERIC-PPCI

- Patients randomly assigned in a 1:1, in ERIC-PPCI sham but not in CONDI-2
- Data management study team was blinded to the treatment allocation

## • Denmark and Spain



## • UK and Serbia



|           |           |           |           |           |           |           |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| 5 min.    | 5 min.    | 5 min.    | 5 min.    | 5 min.    | 5 min.    | 5 min.    |
| Inflation | Deflation | Inflation | Deflation | Inflation | Deflation | Inflation |



# Key Inclusion / Exclusion Criteria ERIC-PPCI

- **Inclusion**

- Eligible for PPCI
- Symptoms
- ST-elevation
- > 18 years

- **Exclusion**

- LBBB
- CABG
- Therapeutic hypothermia
- Conditions precluding RIC
- Life expectancy < 1 year



# CONSORT

**Enrollment**

5401

**Allocation**

Control  
2701

RIC  
2700

Excluded on  
arrival to  
hospital

**Follow-up**

2662

2671

Lost to follow-  
up

**Analysis**

-intention-to-treat

2569

2546



# Baseline characteristics

| Demographics               | Control<br>(n=2569) | RIC<br>(n=2546) |
|----------------------------|---------------------|-----------------|
| Age (yrs) mean $\pm$ SD    | 63.1 $\pm$ 12.2     | 63.9 $\pm$ 12.1 |
| Female (%)                 | 22.4                | 24.0            |
| <b>Comorbidity (%)</b>     |                     |                 |
| Hypertension               | 40.1                | 43.7            |
| Previous MI                | 9.9                 | 10.5            |
| Hypercholesterolaemia      | 27.2                | 28.0            |
| Diabetes mellitus          | 10.4                | 11.9            |
| <b>BP and Killip class</b> |                     |                 |
| Sys BP (mm Hg)             | 131 $\pm$ 24        | 131 $\pm$ 24    |
| Dia BP (mm Hg)             | 77 $\pm$ 15         | 76 $\pm$ 15     |
| Killip class I             | 95.9                | 95.6            |
| <b>RIC procedure</b>       |                     |                 |
| > 3 completed cycles (%)   | -                   | 96.5            |

|                             | Control<br>(n=2569) | RIC<br>(n=2546) |
|-----------------------------|---------------------|-----------------|
| <b>Medication (% users)</b> |                     |                 |
| Sulphonylurea               | 2.5                 | 2.4             |
| Metformin                   | 7.8                 | 8.8             |
| Insulin                     | 2.9                 | 3.2             |
| Clopidogrel                 | 3.3                 | 3.9             |
| Ticagrelor                  | 2.0                 | 2.5             |
| Prasugrel                   | 0.2                 | 0.1             |
| Statins                     | 25.6                | 26.3            |
| Aspirin                     | 17.9                | 19.2            |
| Betablocker                 | 15.1                | 16.1            |
| ACE-inhibitor               | 17.9                | 18.5            |

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# Procedural characteristics

| PPCI procedure                          | Control<br>(n=2569) | RIC<br>(n=2546) |
|-----------------------------------------|---------------------|-----------------|
| <b>TIMI flow grade at admission (%)</b> |                     |                 |
| 0-I                                     | 74.8                | 73.7            |
| II-III                                  | 25.2                | 26.3            |
| <b>Symptom to balloon time (min)</b>    | 177 [128-279]       | 178 [130-278]   |
| <b>Infarct related artery (%)</b>       | 9.9                 | 10.5            |
| LAD                                     | 43.1                | 40.9            |
| CX                                      | 13.2                | 13.4            |
| RCA                                     | 43.6                | 45.6            |
| Other                                   | 0.1                 | 0.1             |
| <b>Stenting of culprit lesion (%)</b>   | 93.2                | 93.4            |
| <b>TIMI III flow after PPCI</b>         | 92.8                | 94.5            |
| <b>Supplementary staged revasc (%)</b>  | 15.2                | 14.5            |

|                                 | Control<br>(n=2569) | RIC<br>(n=2546) |
|---------------------------------|---------------------|-----------------|
| <b>Medication</b>               |                     |                 |
| Opioids*                        | 52.1                | 50.2            |
| Aspirin                         | 95.2                | 95.9            |
| Clopidogrel                     | 27.0                | 25.7            |
| Ticagrelor                      | 68.7                | 69.8            |
| Prasugrel                       | 4.6                 | 4.4             |
| Nitrates                        | 79.1                | 77.5            |
| Glycoprotein IIb/IIIa inhibitor | 20.0                | 18.2            |
| Bivalirudin                     | 22.4                | 22.0            |
| Cangrelor*                      | 12.3                | 11.7            |

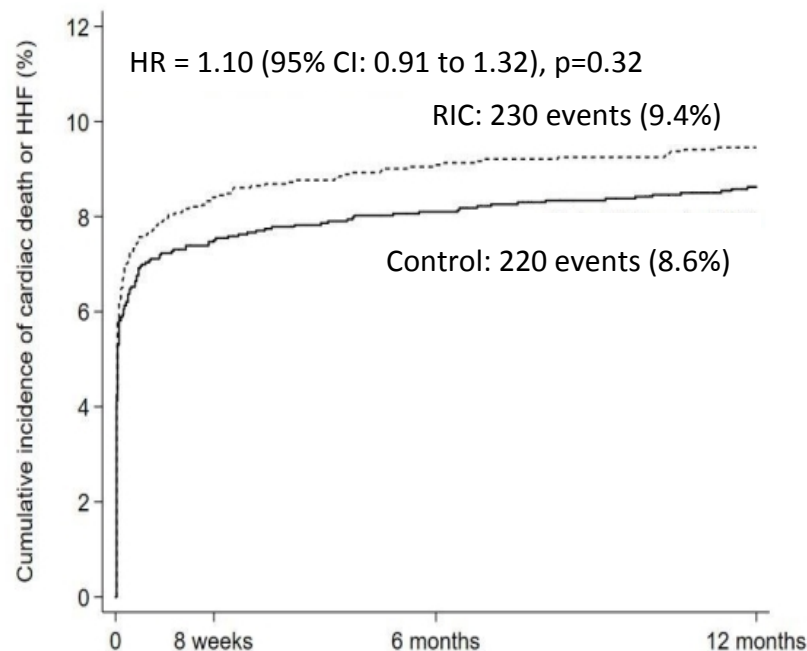
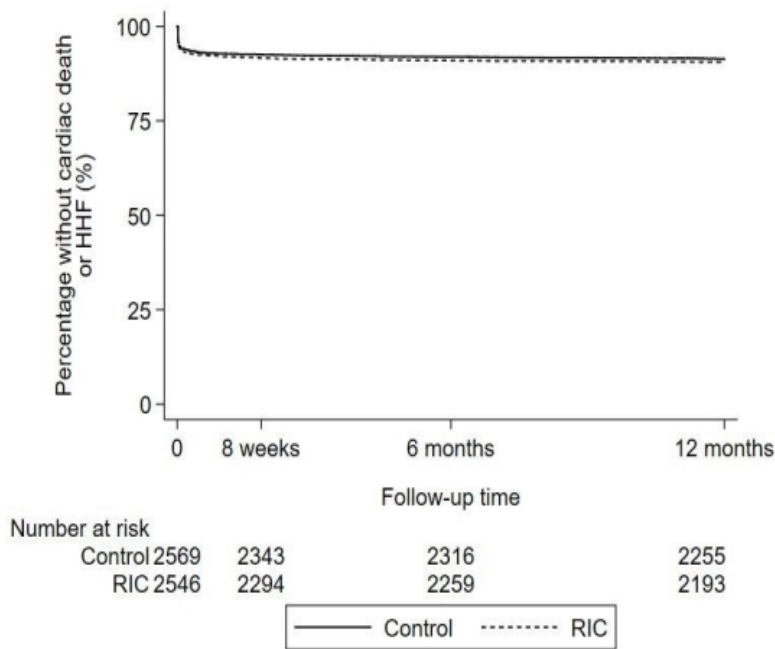
\* Only registered in CONDI-2 trial



# Result: Primary end point

ERIC-PPCI

## Combined EP: cumulative Incidence of Cardiac Death or HHF at 12 Months





# Secondary outcomes

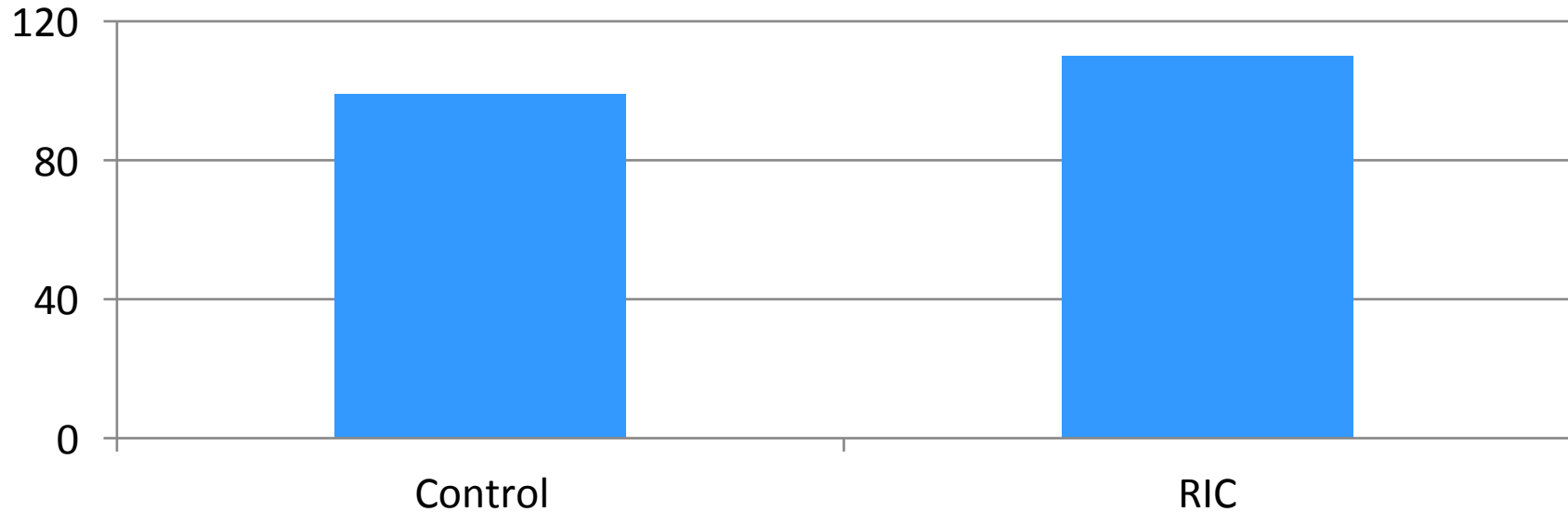
| Secondary outcome, %                                            | Control<br>(n=2569) | RIC<br>(n=2546)    | Treatment effect<br>(95% CI) | P-value     |
|-----------------------------------------------------------------|---------------------|--------------------|------------------------------|-------------|
| <b>MACCE within 12 mo</b>                                       | <b>7.8</b>          | <b>8.4</b>         | <b>1.09 (0.90-1.32)</b>      | <b>0.38</b> |
| - All-cause death                                               | 3.9                 | 4.8                | 1.24 (0.95-1.61)             | 0.11        |
| - Re-infarction                                                 | 1.7                 | 1.5                | 0.89 (0.58-1.38)             | 0.61        |
| - Unplanned revascularization                                   | 2.4                 | 2.5                | 1.02 (0.71-1.45)             | 0.93        |
| -Stroke                                                         | 0.8                 | 0.9                | 1.11 (0.61-2.00)             | 0.73        |
| <b>Combined HHF and cardiac death within 30 days</b>            | <b>7.2</b>          | <b>8.0</b>         | <b>1.11 (0.91-1.36)</b>      | <b>0.29</b> |
| -Cardiac death                                                  | 1.8                 | 2.3                | 1.27 (0.87-1.86)             | 0.22        |
| -HHF                                                            | 6.3                 | 6.8                | 1.06 (0.86-1.32)             | 0.57        |
| <b>ICD implantation within 12 months</b>                        | <b>1.1</b>          | <b>1.5</b>         | <b>1.34 (0.82-2.18)</b>      | <b>0.24</b> |
| <b>Repeat episodes of HHF within 12 months, mean count (SD)</b> | <b>0.09 (0.36)</b>  | <b>0.09 (0.36)</b> | <b>1.0 (0.81-1.24)</b>       | <b>1.00</b> |



# Secondary outcomes

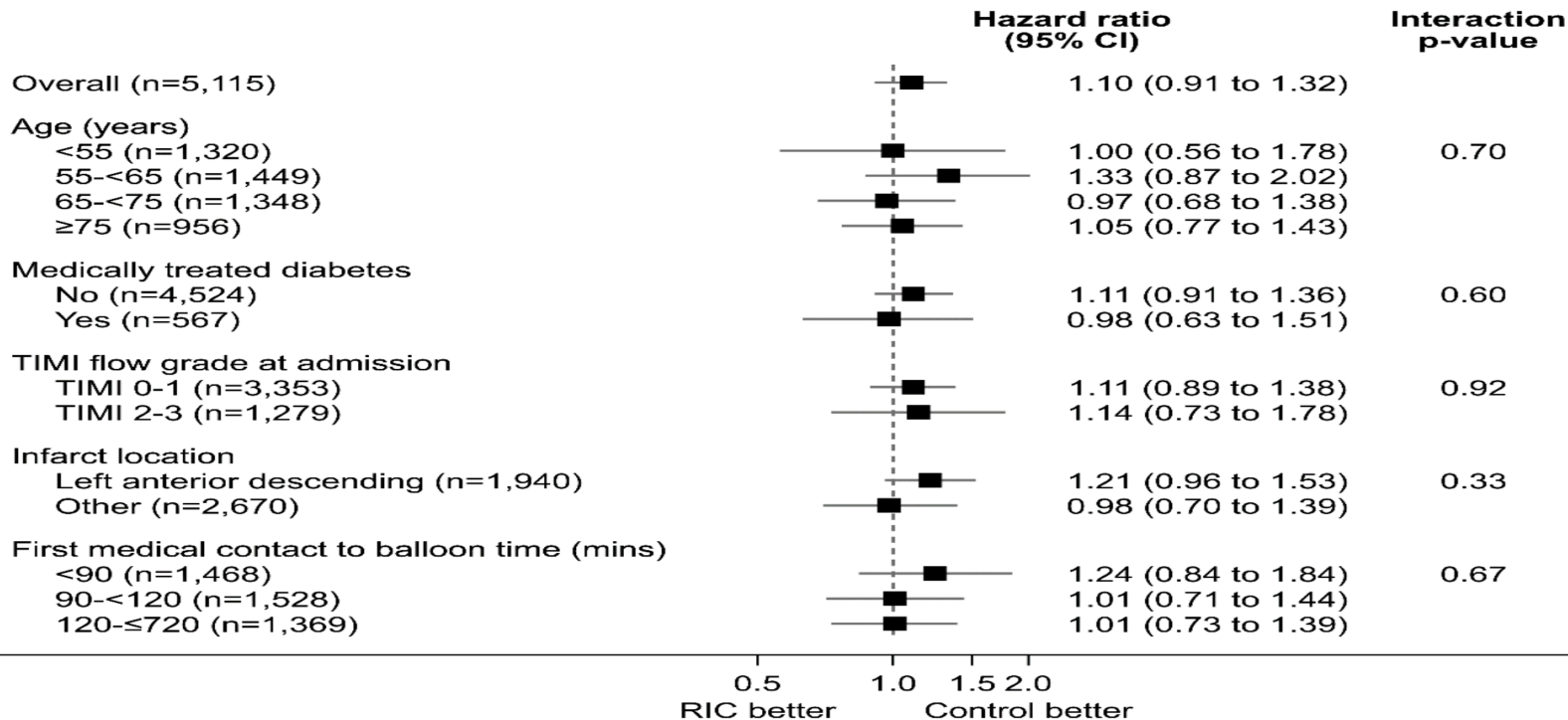
ERIC-PPCI

0 – 48 h AUC for high-sensitivity troponin T (ng x h/L)





# Prespecified subgroup analysis



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# Why no benefit?

- Ischaemia-reperfusion injury as target?
- Improved treatment and outcome
  - Target for cardioprotection diminished
- Follow-up period





# Conclusion



- Remote ischaemic conditioning did not improve clinical outcomes (cardiac death or HHF) at 12 months in STEMI patients undergoing PPCI

# Lancet Online 2019, September 5

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## Effect of remote ischaemic conditioning on clinical outcomes in patients with acute myocardial infarction (CONDI-2/ERIC-PPCI): a single-blind randomised controlled trial

*Derek J Hausenloy\*, Rajesh K Kharbanda\*, Ulla Kristine Møller, Manish Ramlall, Jens Aarøe, Robert Butler, Heerajnarain Bulluck, Timothy Clayton, Ali Dana, Matthew Dodd, Thomas Engstrom, Richard Evans, Jens Flensted Lassen, Erika Frischknecht Christensen, José Manuel Garcia-Ruiz, Diana A Gorog, Jakob Hjort, Richard F Houghton, Borja Ibanez, Rosemary Knight, Freddy K Lippert, Jacob T Lønborg, Michael Maeng, Dejan Milasinovic, Ranjit More, Jennifer M Nicholas, Lisette Okkels Jensen, Alexander Perkins, Nebojsa Radovanovic, Roby D Rakhit, Jan Ravkilde, Alisdair D Ryding, Michael R Schmidt, Ingunn Skogstad Riddervold, Henrik Toft Sørensen, Goran Stankovic, Madhusudhan Varma, Ian Webb, Christian Juhl Terkelsen, John P Greenwood, Derek M Yellon†, Hans Erik Bøtker†, on behalf of the CONDI-2/ERIC-PPCI Investigators‡*

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ESC Congress  
Paris 2019

World Congress  
of Cardiology





# Thank you

ERIC-PPCI

- Ulla Kristine Møller PhD
- Jens Aarøe MD
- Thomas Engstrom PhD, Dmsci
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- Erika Frischknecht Christensen MD
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- Jakob Hjort MPH
- Richard F. Houghton MD
- Borja Ibanez MD PhD
- Freddy K. Lippert MD
- Jacob T. Lønborg MD, PhD, DMSc
- Michael Maeng PhD
- Dejan Milasinovic MD
- Lisette Okkels Jensen DMSci, MD, PhD
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- Michael R Schmidt PhD, DMSc
- Ingunn Skogstad Riddervold PhD
- Henrik Toft Sørensen DMSc
- Goran Stankovic MD, PhD
- Christian Juhl Terkelsen MD, DMSc, PhD



Innovationsfonden



Med støtte fra  
**TrygFonden**

- Rajesh K. Kharbanda, MD PhD
- Manish Ramlall MBChB
- Robert Butler MBChB, MD
- Heerajnarain Bulluck PhD
- Tim Clayton MSc
- Ali Dana PhD
- Matthew Dodd MSc
- Richard Evans BA
- Diana A. Gorog MD, PhD
- Rosemary Knight MSc
- Jennifer M. Nicholas PhD
- Ranjit More MBChB
- Alexander Perkins MSc
- Roby D. Rakhit MD
- Alisdair D. Ryding PhD
- Madhusudhan Varma MBBS, PhD
- Ian Webb MA, PhD
- John P. Greenwood MD, PhD
- Derek M Yellon PhD, DSc



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# Back-up slides



# Primary end point

ERIC-PPCI

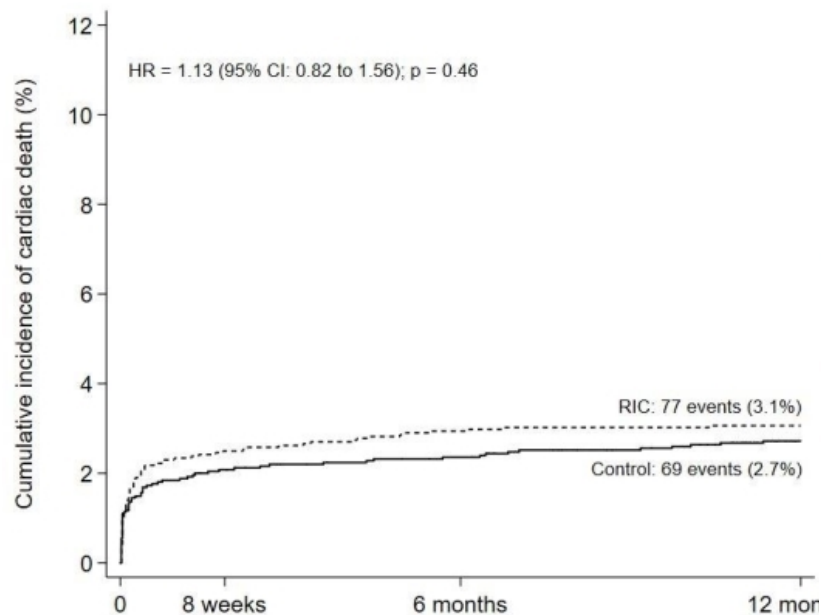
|                               | Control      | RIC          | Treatment effect (95% CI) | P-value |
|-------------------------------|--------------|--------------|---------------------------|---------|
| <b>Primary outcome, n (%)</b> |              |              |                           |         |
| Combined                      | 220<br>(8.6) | 239<br>(9.4) | 1.10 (0.91-1.32)          | 0.32    |
| - Cardiac death               | 69<br>(2.7)  | 77<br>(3.1)  | 1.13 (0.82-1.56)          | 0.46    |
| - HHF                         | 182<br>(7.1) | 192<br>(7.6) | 1.06<br>(0.87-1.30)       | 0.55    |



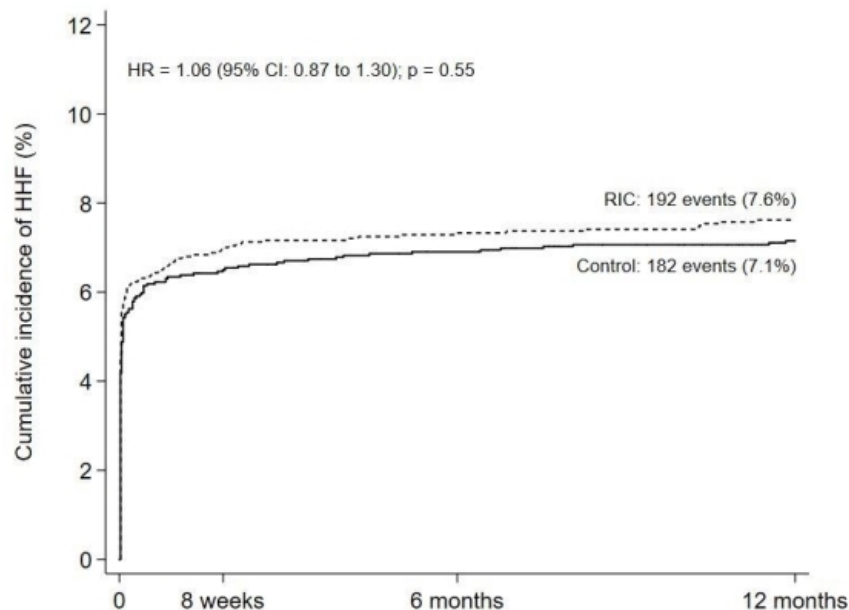
# Results: individual components

ERIC-PPCI

## Cardiac death



## Hospitalisation heart failure

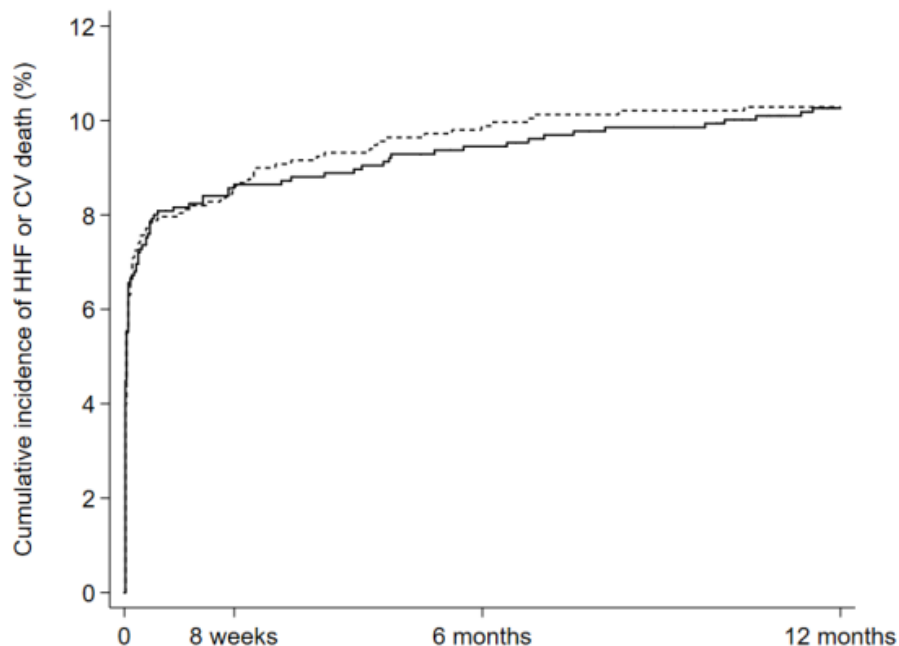
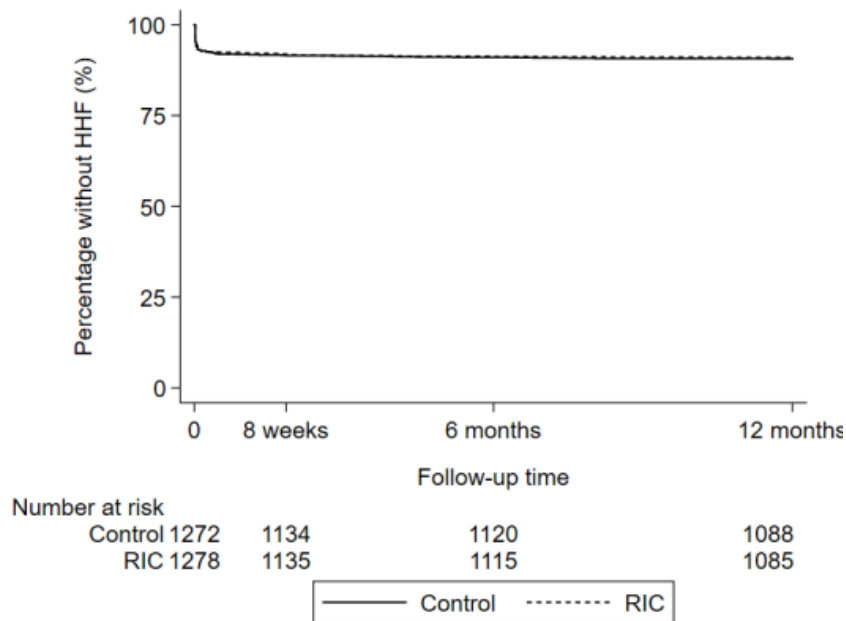


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# Results – CONDI-2

## Combined EP: cumulative Incidence of Cardiac Death or HHF at 12 Months – ITT



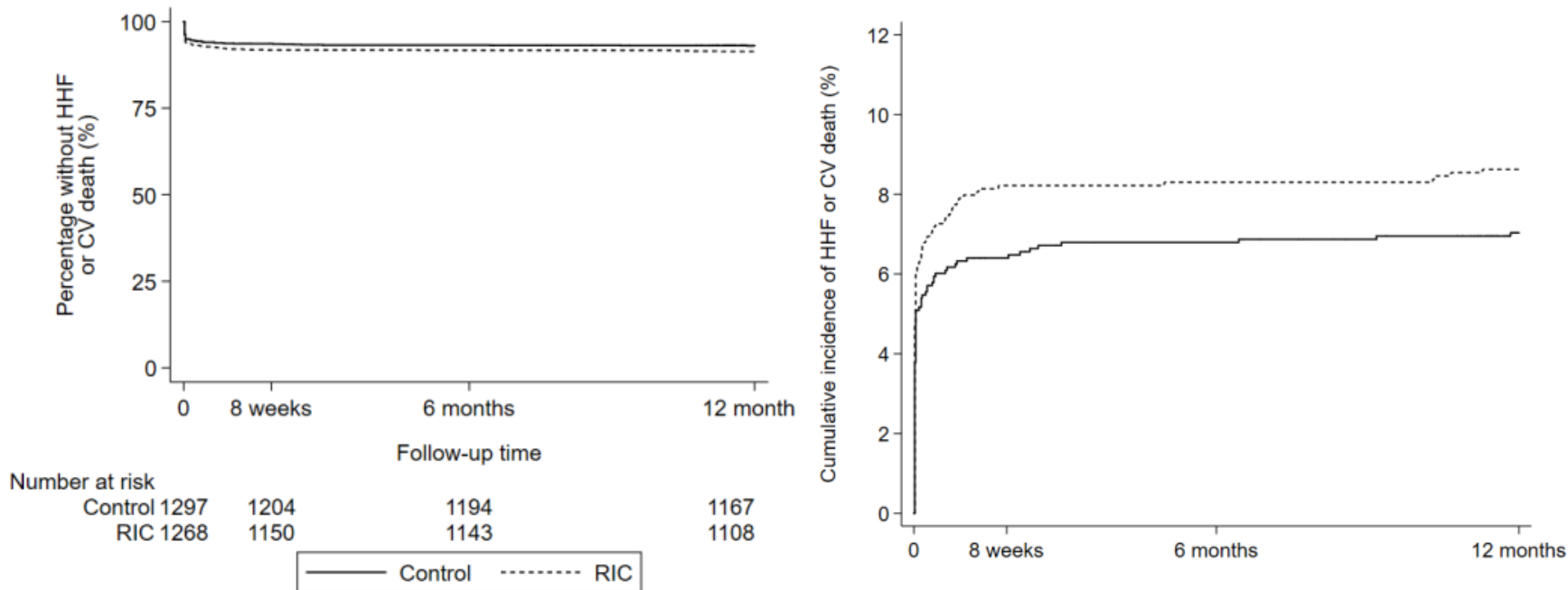
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# Results – ERIC-PPCI



## Combined EP: cumulative Incidence of Cardiac Death or HHF at 12 Months – ITT



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# CONSORT

**Enrollment**

5401

**Allocation**

Control  
2701

RIC  
2700

Excluded on  
arrival to  
hospital

**Follow-up**

2662

2672

Lost to follow-  
up

**Analysis**

-intention-to-treat

2569

2546

-per protocol

2205

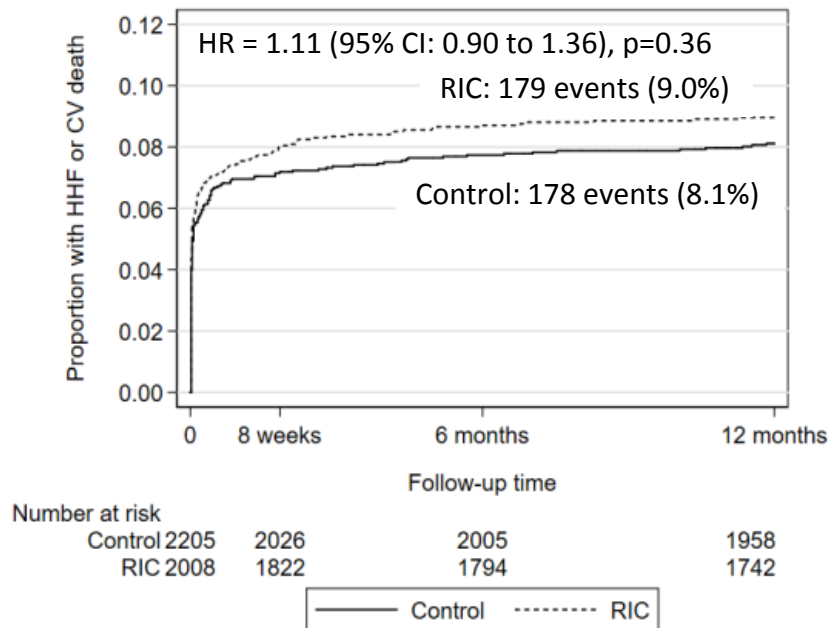
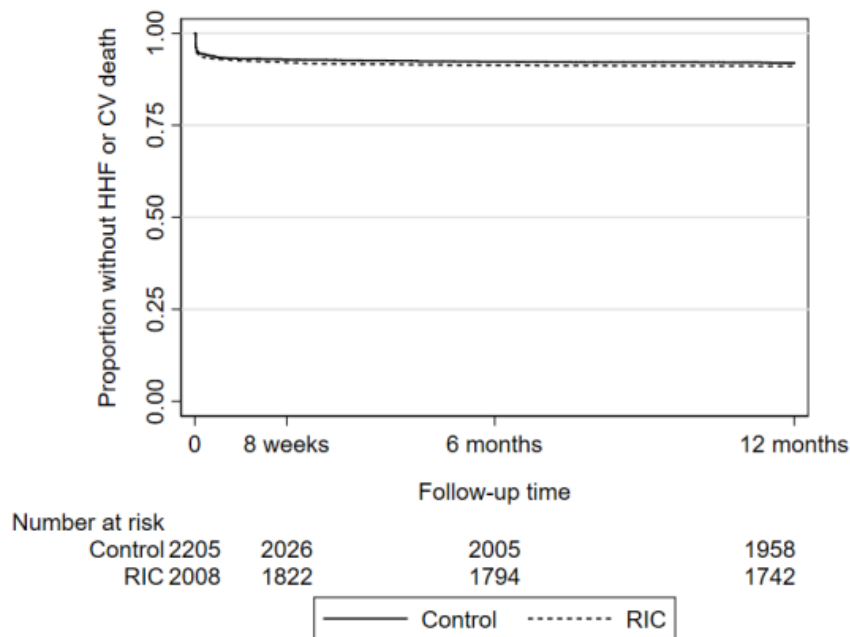
2008

No STEMI  
No PCI  
RIC not given



# Primary end point – per protocol

## Combined EP: cumulative Incidence of Cardiac Death or HHF at 12 Months



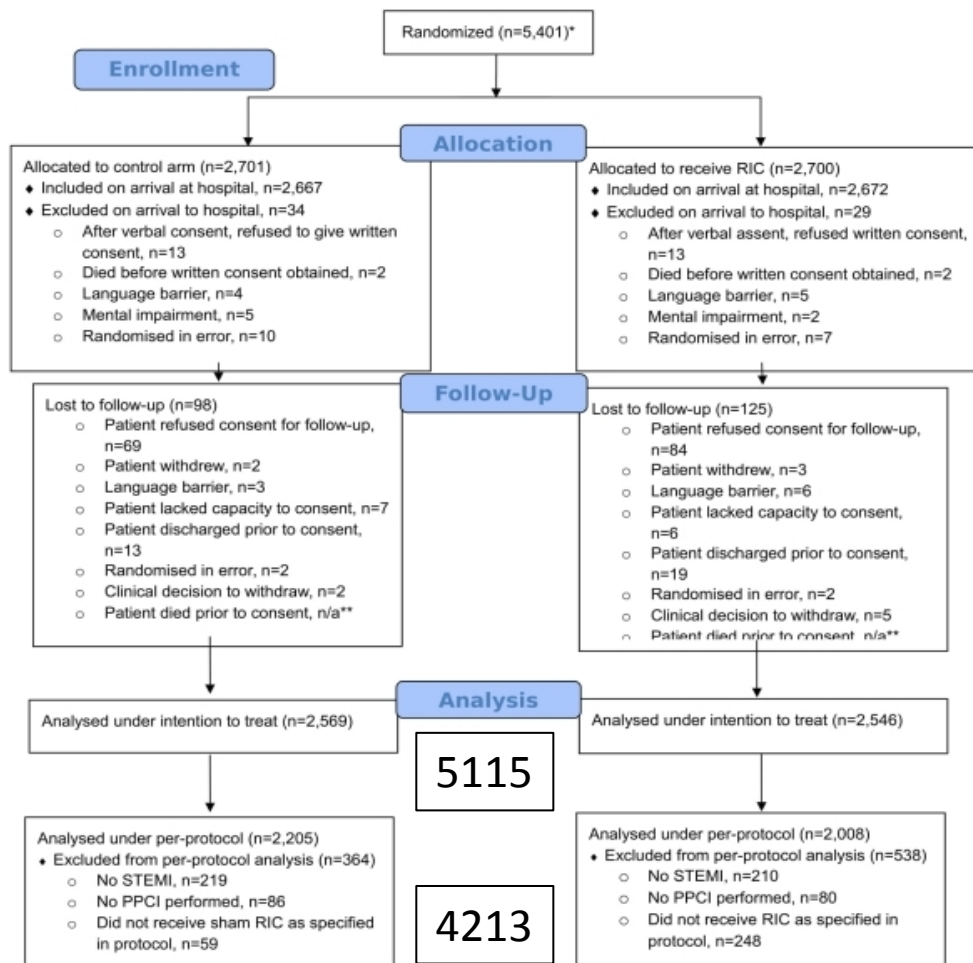
# CONSORT



ERIC-PPCI

\*Full screening log data were not available as not all sites were able to collect screening logs given the emergency context of patient enrolment and randomization.

\*\*ERIC-PPCI had approval from the UK Confidentiality Group (CAG) to collect data on patients who died before consent could be obtained.



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# Interference with ticagrelor

|                          | Control      | RIC          | Treatment effect (95% CI) | Interaction P-value |
|--------------------------|--------------|--------------|---------------------------|---------------------|
| <b>Ticagrelor, n (%)</b> |              |              |                           |                     |
| - No                     | 84<br>(10.4) | 91<br>(11.7) | 1.12 (0.84-1.51)          |                     |
| - Yes                    | 124<br>(7.6) | 131<br>(8.0) | 1.06 (0.83-1.35)          | 0.75                |

The Table presents Kaplan-Meier estimates of the n (%) experiencing hospitalization for heart failure or cardiovascular death within 12 months



# Power calculation



- Original primary outcome event rate 11.0% at 12 months
- A 25% relative reduction in the RIC group (from 11.0% to 8.25%) with 80% power, and 5% significance, would have required 4300 patients, allowing for 15% attrition
- Blinded review of accruing data revealed that the estimated event rate was 9%
- Sample size was increased to 5400 patients



# Spatial and temporal variants of conditioning

Ischaemia

Reperfusion



**Predictable:**



Ischaemia

Modified reperfusion

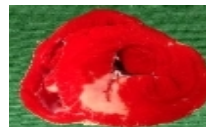


**Local and remote pre-C**

**Unpredictable:**

Ischaemia

Modified (gentle) reperfusion

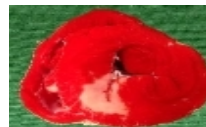


**Local post-C**



Ischaemia

Modified reperfusion



**Remote-C**



**Per-**

**Postconditioning**