Cardiovascular trials: 35 years and counting

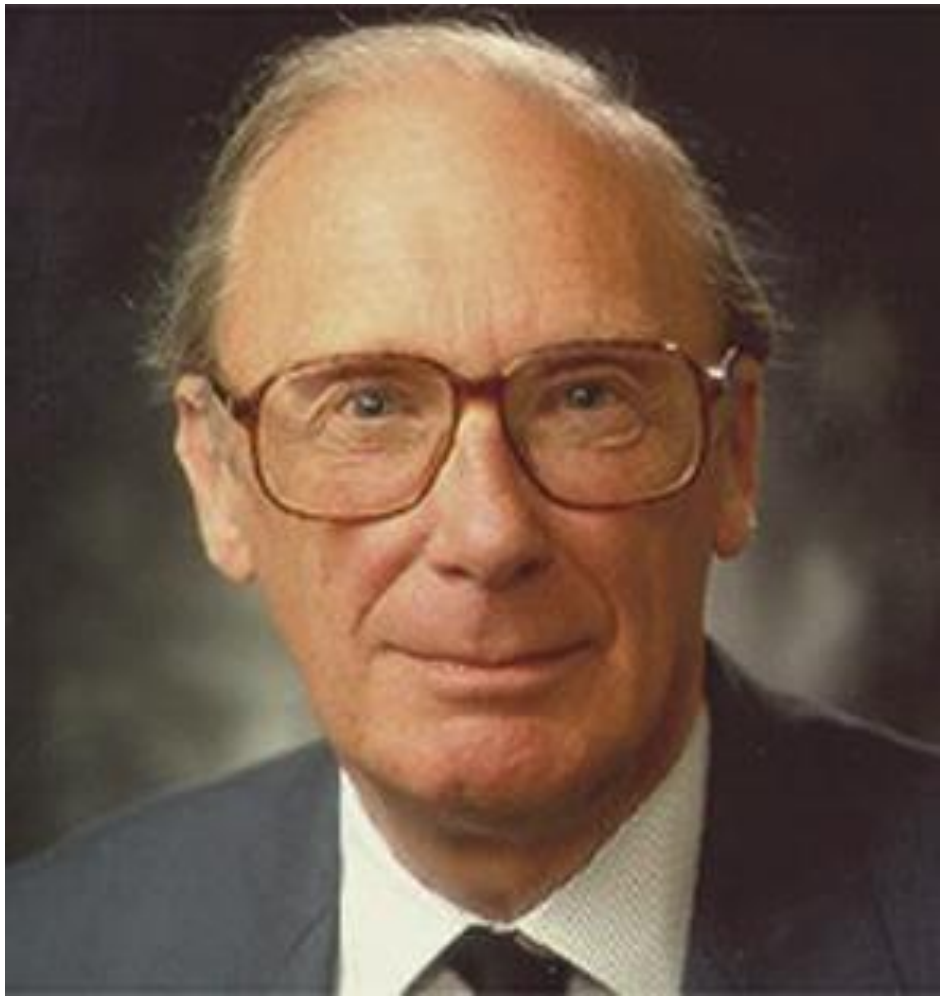
Richard Evans, Senior Manager, LSHTM Clinical Trials Unit

Desmond Julian

- Proposed Coronary Care Units (CCU) in 1961 (Lancet)
- Set up 1st CCU in Europe in 1964
- Organised world's 1st coronary care conference 1967
- First Medical Director of the British Heart Foundation (BHF) between 1987 and 1993

Widened scope of BHF to include randomized controlled trials

"Professor Julian's work has undoubtedly shaped modern cardiology and has saved many lives."
Nilesh Samani (current BHF Medical Director)



And also…

Late 1980’s - Desmond Julian encouraged Stuart Pocock to focus on statistics applied to clinical trials

1989

The Randomised Intervention Treatment of Angina (RITA) Trial protocol: a long term study of coronary angioplasty and coronary artery bypass surgery in patients with angina

Br Heart J 1989;**62**:411–4

1993

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Coronary angioplasty versus coronary artery bypass surgery: the Randomised Intervention Treatment of Angina (RITA) trial

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Lancet 1993; **341**: 573–80.

Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial

Lancet 1997; **350:** 461–68

2002

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Coronary angioplasty versus coronary artery bypass surgery: the Randomised Intervention Treatment of Angina (RITA) trial

Lancet 1993; **341**: 573–80.

Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial

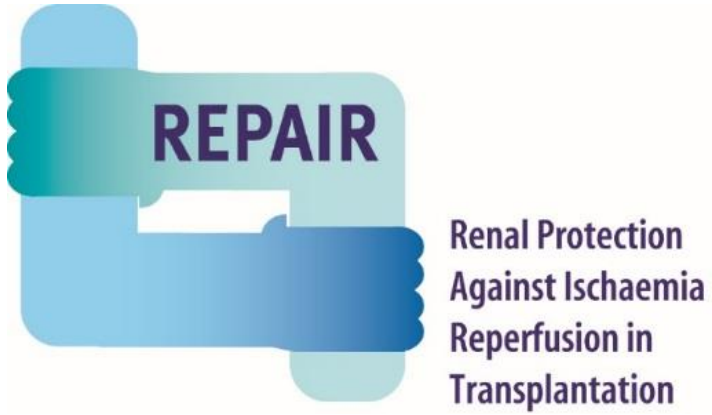
Lancet 1997; **350:** 461–68

Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial

Lancet 2002; **360:** 743–51.

A slight detour…

2008



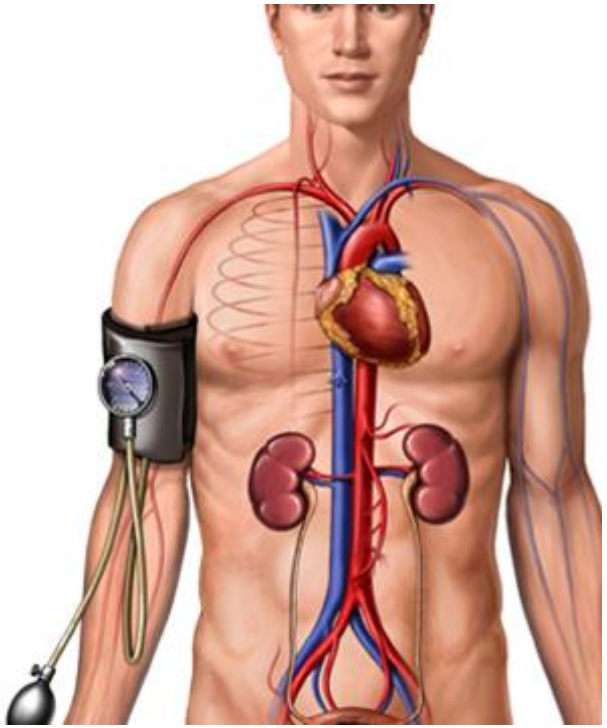
- REPAIR trial funded in 2008
- Remote Ischaemic Conditioning in Kidney transplantation

- Beginnings of the current cardiovascular trials team

ERICCA Trial

- 1610 patients undergoing heart bypass surgery
- Remote Ischaemic Conditioning
- NIHR and BHF joint funding

2010



Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery

Derek J. Hausenloy, M.B., Ch.B., Ph.D., Luciano Candilio, M.D.(Res.), Richard Evans, B.A., Cono Ariti, M.Sc., David P. Jenkins, M.B., B.S., Shyam Kolvekar, M.B., B.S., M.Ch., Rosemary Knight, Dip.N., Gudrun Kunst, M.D., Ph.D., Christopher Laing, M.B., Ch.B., M.D.(Res.), Jennifer Nicholas, Ph.D., John Pepper, M.Chir., Steven Robertson, B.A., et al., for the ERICCA Trial Investigators*

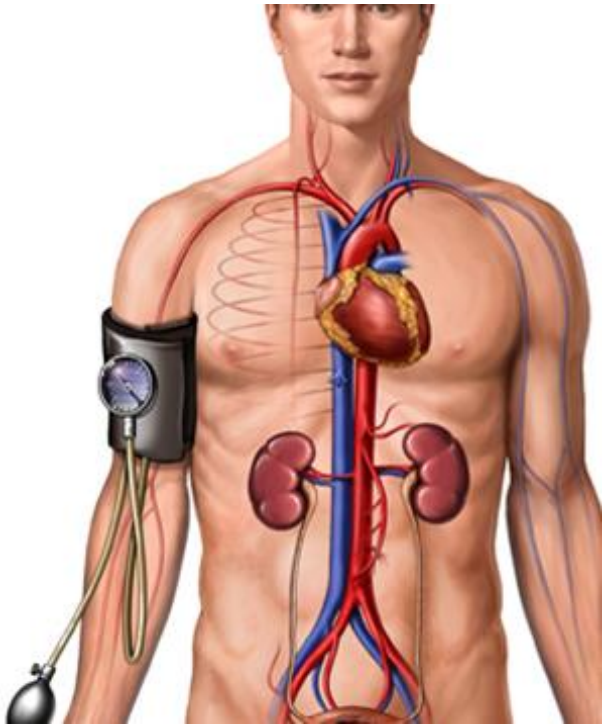
NEJM 2015

ERIC-PPCI Trial

2015

- 2800 patients in UK with ST-elevation MI
- BHF Funded
- Collaboration with CONDI-2 trial (Denmark, Spain, Serbia)
- 5401 patients in total

ERIC-PPCI



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

Prof Derek J Hausenloy, PhD * • Rajesh K Kharbanda, PhD * • Ulla Kristine Møller, PhD • Manish Ramlall, MBChB • Jens Aarøe, MD • Robert Butler, MD • Heerajnarain Bulluck, PhD • Prof Tim Clayton, MSc • Ali Dana, PhD • Matthew Dodd, MSc • Prof Thomas Engstrom, DMSci • Richard Evans, BA •

Lancet 2019

AIMS Trial

Aortic Irbesartan Marfan Study

- BHF funded – Royal Brompton CTU
- Under-recruited and was terminated early (192/490 participants)

2015

- LSHTM CTU carried out modified follow-up and analysis
- Showed irbesartan (an angiotensin receptor blocker) is associated with lower rates of aortic dilation in children and young adults with Marfan syndrome

Lancet 2019

REVIVED Trial (PI Divaka Perera)

- REVIVED investigated whether stenting (percutaneous coronary intervention / PCI) could improve mortality and hospitalisation for heart failure in patients with;
  - Stable heart failure (no exertional angina, recent heart attack)
  - Significant coronary artery disease
  - Heart muscle that showed potential to respond to blood flow being improved

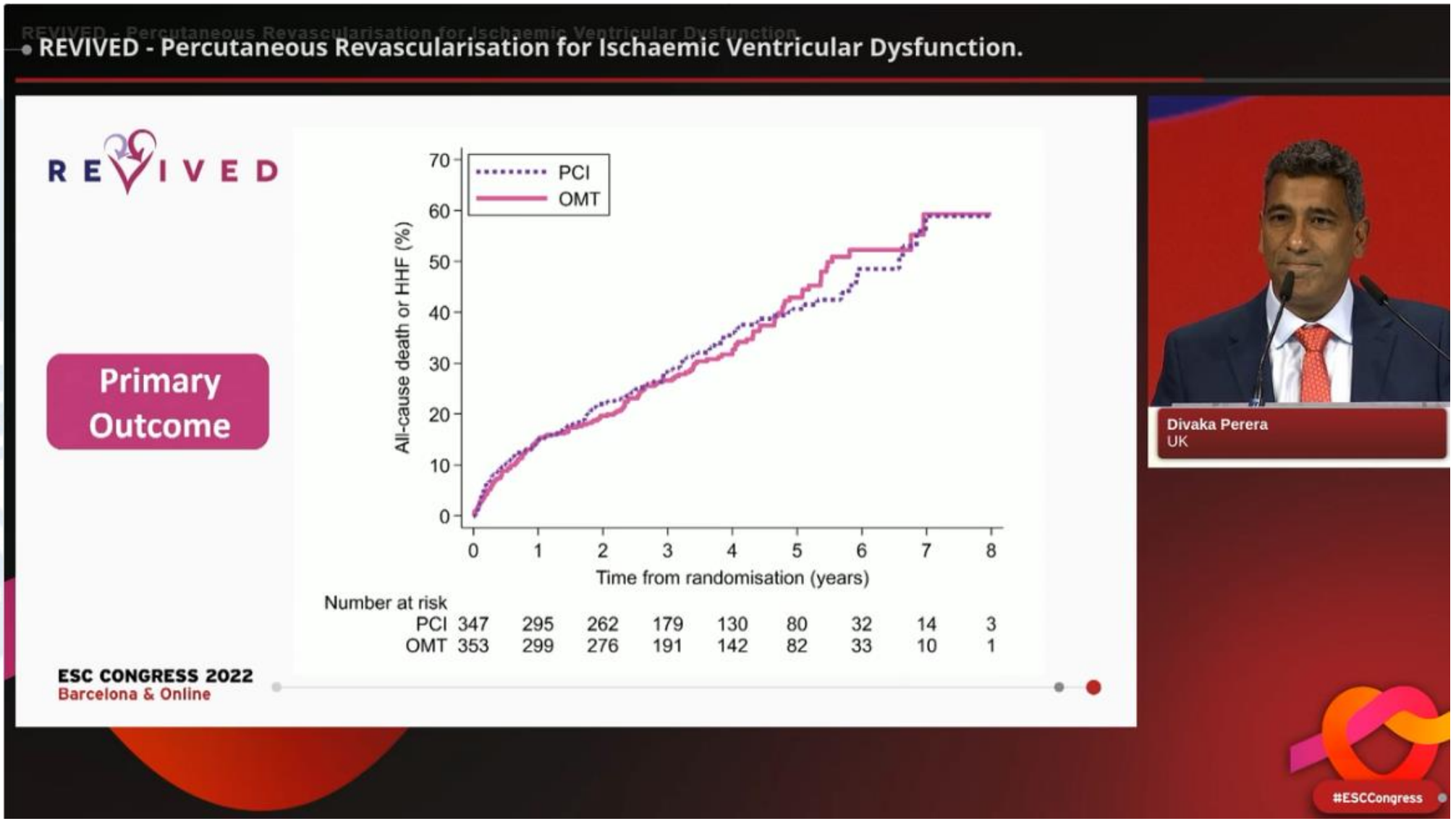
Aim To evaluate the efficacy and safety of percutaneous coronary intervention compared to optimal medical therapy alone for ischaemic cardiomyopathy (**PCI+OMT** vs **OMT**)

Sample size 700 participants over 3.5 years at (initially) 20 sites

REVIVED Trial

- Funded June 2013 by NIHR
- Particularly challenging trial to recruit to;
  - Complex eligibility
  - Long screening process (3-4 months)
  - Strong existing views on whether PCI was effective - *“The patients I've identified.....I’ve felt quite strongly that I wanted to revascularise - so although they would have fulfilled criteria I felt unhappy to randomise.”*
- NIHR supported a 3 year extension
- Final participant recruited in March 2020 (6 ½ year recruitment period)
- Completed follow-up in April 2022

REVIVED Trial



REVIVED Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction

Divaka Perera, M.D., Tim Clayton, M.Sc., Peter D. O'Kane, M.D., John P. Greenwood, Ph.D., Roshan Weerackody, Ph.D., Matthew Ryan, Ph.D., Holly P. Morgan, M.B., B.Ch., Matthew Dodd, M.Sc., Richard Evans, B.A., Ruth Canter, M.Sc., Sophie Arnold, M.Sc., Lana J. Dixon, Ph.D., Richard J. Edwards, Ph.D., Kalpa De Silva, Ph.D., James C. Spratt, M.D., Dwayne Conway, M.D., James Cotton, M.D., Margaret McEntegart, Ph.D., Amedeo Chiribiri, Ph.D., Pedro Saramago, Ph.D., Anthony Gershlick, M.D., Ajay Shah, M.D., Andrew L. Clark, M.D., and Mark C. Petrie, M.D., for the REVIVED-BCIS2 Investigators*

Circulation
Volume 148, Issue 11, 12 September 2023; Pages 862-871
https://doi.org/10.1161/CIRCULATIONAHA.123.065300

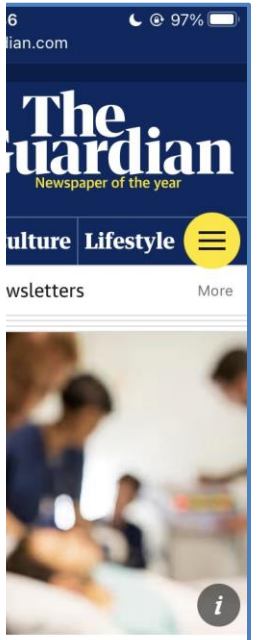
ORIGINAL RESEARCH ARTICLE

Arrhythmia and Death Following Percutaneous Revascularization in Ischemic Left Ventricular Dysfunction: Prespecified Analyses From the REVIVED-BCIS2 Trial

Divaka Perera, MD, Holly P. Morgan, MBBCh, Matthew Ryan, PhD, Matthew Dodd, MSc, Tim Clayton, MSc, Peter D. O'Kane, MD, John P. Greenwood, PhD, Simon J. Walsh, MD, Roshan Weerackody, PhD, Adam McDiarmid, PhD, George Amin-Youssef, MD, Julian Strange, MD, Bhavik Modi, PhD, Timothy Lockie, PhD, Kai Hogrefe, MD, Fozia Z. Ahmed, MD, Miles Behan, MD, Nicholas Jenkins, MD, Eltigani Abdelaal, MD, Michelle Anderson, BA, Stuart Watkins, MD, Richard Evans, BA, Christopher A. Rinaldi, MD, and Mark C. Petrie, MD

Background: Ventricular arrhythmia is an important cause of mortality in patients with ischemic left ventricular dysfunction. Revascularization with coronary artery bypass graft or percutaneous coronary intervention is often recommended for these patients before implantation of a cardiac defibrillator because it is assumed that this may reduce the incidence of fatal and potentially fatal ventricular arrhythmias, although this premise has not been evaluated in a randomized trial to date.

Methods: Patients with severe left ventricular dysfunction, extensive coronary disease, and viable myocardium were randomly assigned to receive either percutaneous coronary intervention (PCI) plus optimal medical and device therapy (OMT) or OMT alone. The composite primary outcome was all-cause death or aborted sudden death (defined as an appropriate implantable cardioverter defibrillator therapy or a resuscitated cardiac arrest) at a minimum of 24 months, analyzed as time to first event on an intention-to-treat basis. Secondary outcomes included cardiovascular death or aborted sudden death, appropriate implantable cardioverter defibrillator (ICD) therapy or sustained ventricular arrhythmia, and number of appropriate ICD therapies.



patients 'are at risk of life-threatenin
complications from stent operations
that DON'T benefit them'

- Thousands of NHS heart failure patients given unnecessary heart stent surg
- This could put them at risk of life-threatening complications with no benefit
- It was thought artery unblocker tubes could help 1m heart failure sufferers
- 100,000 stents are fitted in the UK each year with 1 in 10 to treat heart failure

By MARTYN HALLE FOR THE MAIL ON SUNDAY
PUBLISHED: 22:01, 1 October 2022 | UPDATED: 22:13, 1 October 2022

ARREST Trial (PI Simon Redwood / clinical lead Tiffany Patterson)

A clinical trial to determine the best post-resuscitation care pathway for cardiac arrest patients without ST elevation

ARREST
A randomised trial of expedited transfer to a cardiac arrest centre for non-ST elevation out-of-hospital cardiac arrest

- OHCA, with return of spontaneous circulation
- Without a presumed non-cardiac cause (for example; significant trauma, drowning, suicide, drug overdose)
- Patients unable to consent so were enrolled under consent waiver
- Awarded grant in 2016 by the British Heart Foundation

Control arm - Transfer to nearest Emergency Department (28 across London)

Intervention arm - Direct to nearest “Cardiac Arrest Centres” (7 across London)

ARREST Trial (PI Simon Redwood / clinical lead Tiffany Patterson)

- In adult patients without ST elevation, transfer direct to a cardiac arrest centre following resuscitated out-of-hospital cardiac arrest in the community did not reduce deaths at 30 days.
- There was no difference in deaths at 3 months
- There was no difference in neurological outcome

Expedited transfer to a cardiac arrest centre for non-ST-elevation out-of-hospital cardiac arrest (ARREST): a UK prospective, multicentre, parallel, randomised clinical trial

*Tiffany Patterson, Gavin D Perkins, Alexander Perkins, Tim Clayton, Richard Evans, Matthew Dodd, Steven Robertson, Karen Wilson, Adam Mellett-Smith, Rachael T Fothergill, Paul McCrone, Miles Dalby, Philip MacCarthy, Sam Firoozi, Iqbal Malik, Roby Rakhit, Ajay Jain, Jerry P Nolan, Simon R Redwood, for the ARREST trial collaborators**

- Published in the Lancet August 2023

BHF PROTECT-TAVI (PI Raj Kharbanda)

TAVI: Transcatheter aortic valve implantation
Inserts new valve inside existing diseased aortic valve

Stroke can be caused by debris released into the bloodstream by the procedure

Cerebral embolic protection (CEP) developed to capture this debris

Aim to assess impact on stroke in BHF PROTECT-TAVI
(BHF randomised clinical trial of cerebral embolic protection in transcatheter aortic valve implantation)

BHF PROTECT-TAVI

7730 patients planned: currently >5200 randomised

PROTECTED-TAVR randomised 3000 indicating a potential benefit:
2.3% vs. 2.9%; difference, −0.6%; 95% CI −1.7% to 0.5%; p=0.30

"Additional data on the effectiveness of CEP during TAVR are forthcoming from ongoing trials, in particular, the BHF PROTECT-TAVI" [NEJM Sept 2022]

A meta-analysis of the PROTECTED TAVR and BHF PROTECT TAVI data was prespecified and registered: nearly 11,000 patients will be included

CHIP-BCIS3 (PI Divaka Perera)

CHIP-BCIS3: Controlled trial of high-risk coronary intervention with percutaneous left ventricular unloading

Patients undergoing high risk, complex PCI, with extensive coronary artery disease and an already weakened heart

Use of small heart pump during PCI removed at the end of the procedure

Very expensive (~£13,000 per device)

136 of 250 patients randomised – challenging recruitment

TIGHT-K (PI Ben O'Brien)

Atrial fibrillation (irregular and often fast heart rate) is common after CABG and associated with increased mortality and morbidity

Many hospitals maintain serum potassium at the high-end of normal in the first few days after surgery, but is often unpleasant for patients, can be complex to administer and is expensive overall as given so widely

The TIGHT-K STUDY: Arrhythmias on the cardiac intensive care unit - does maintenance of high-normal serum potassium levels matter?

Aim to assess whether normal potassium levels are non-inferior to high-normal in new onset AF in the first 120 hours after CABG

1650 of 1690 randomised

TIGHT K

Arrhythmias on the cardiac intensive care unit – does maintenance of high-normal serum potassium levels matter?

The future

Commitment to keep delivering a very high standard of clinical trials

Directly addressing under-representation of women

Directly addressing under-representation of people from ethnic minority groups

Inclusion of PPI through all stages of a trial

Increased international collaboration, through the BHF and the Global Cardiovascular Research Funders Forum (GCRFF)

Investigation of electronic health records compared to prospective data capture

Administrative Support

Jo Astarci, Mari Tanaka, Rebecca Chu, Donna Davoren, Musa Faal, Lucy Collier, Dan Hetherington, Emma Fullerton-Frost, Thomas Duffy, Christina Sparks

Trial Managers

Addi Perkins, Zahra Jamal, Matt Kwok, Ruth Canter, Becky Swinson, Kim Potter, Megan Knight, Kiran Bal, Lauren Jerome, Rebecca Matthews, Jocelyn Wong

Data Managers

Steven Robertson, Laura Van Dyck, Alex Lyons, Faran Dhaliwal

Statisticians

Matt Dodd, Jenny Nicholas, Charles Opondo, Jo Sturgess, Tom Godec, Jo Dobson, Simon Newsome

Senior Managers

Rosey Knight, Richard Evans

LSHTM Leads / PIs

Tim Clayton, Diana Elbourne, Liz Allen, Tim Collier