Registry based randomized clinical trials (R-RCT) - from SWEDEHEART to EuroHeart

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What is a National Quality registry?

- Contains individual standardized structured data on patients, treatments, and outcomes
- Integrated into the clinical workflow – including all patients
- Capacity to generate feed-back in real time
- Supported by an organization of health care professionals, researchers, patient reps
- Used for continuous learning, quality improvement, research and trials
- Might preferably be integrated in EHR

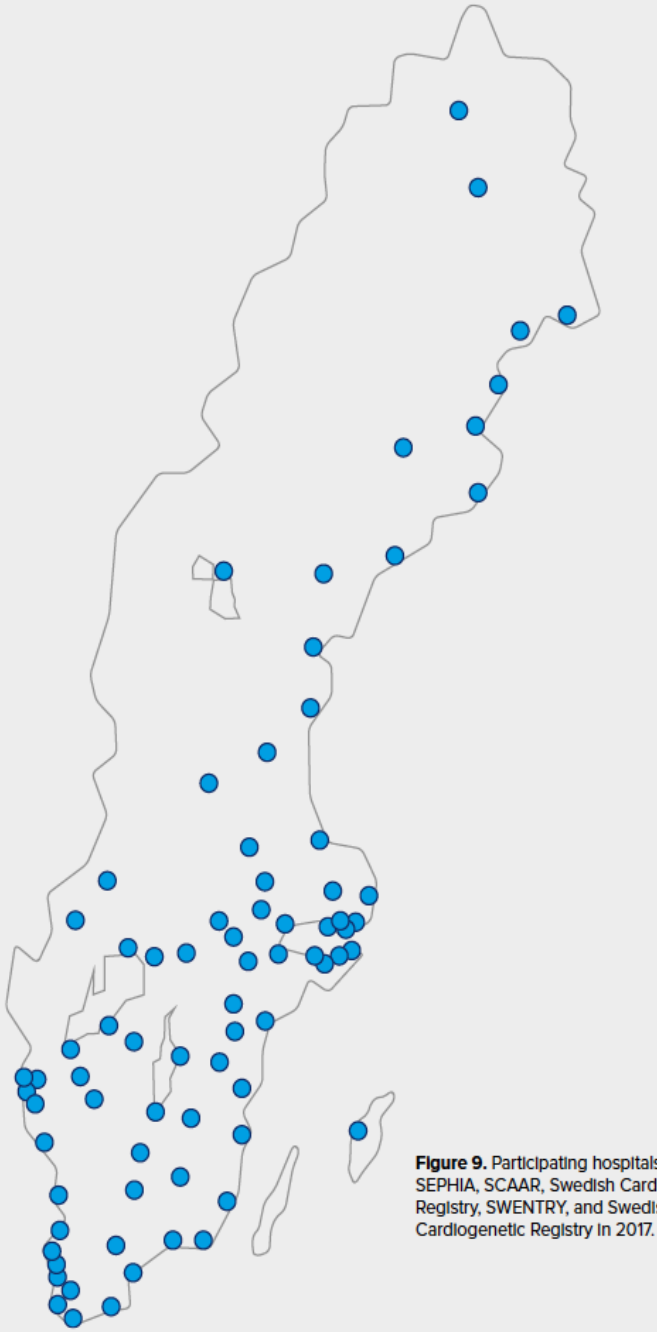
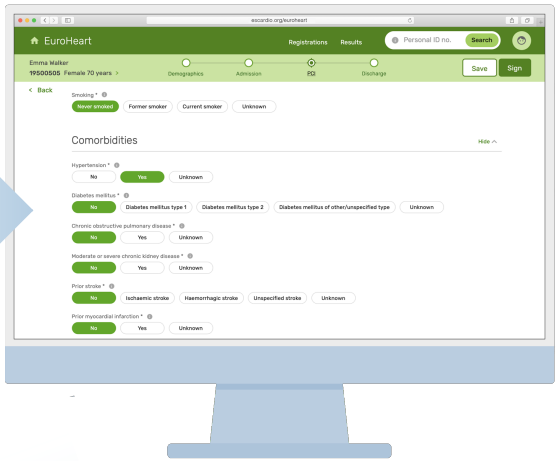


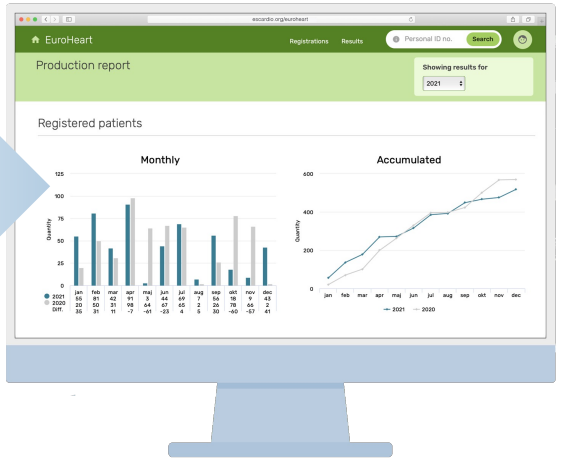
Figure 9. Participating hospitals in RIKS-HIA, SEPHIA, SCAAR, Swedish Cardiac Surgery Registry, SWENTRY, and Swedish National Cardiogenetic Registry in 2017.

How do Quality registries work?

Data recorded by healthcare provides



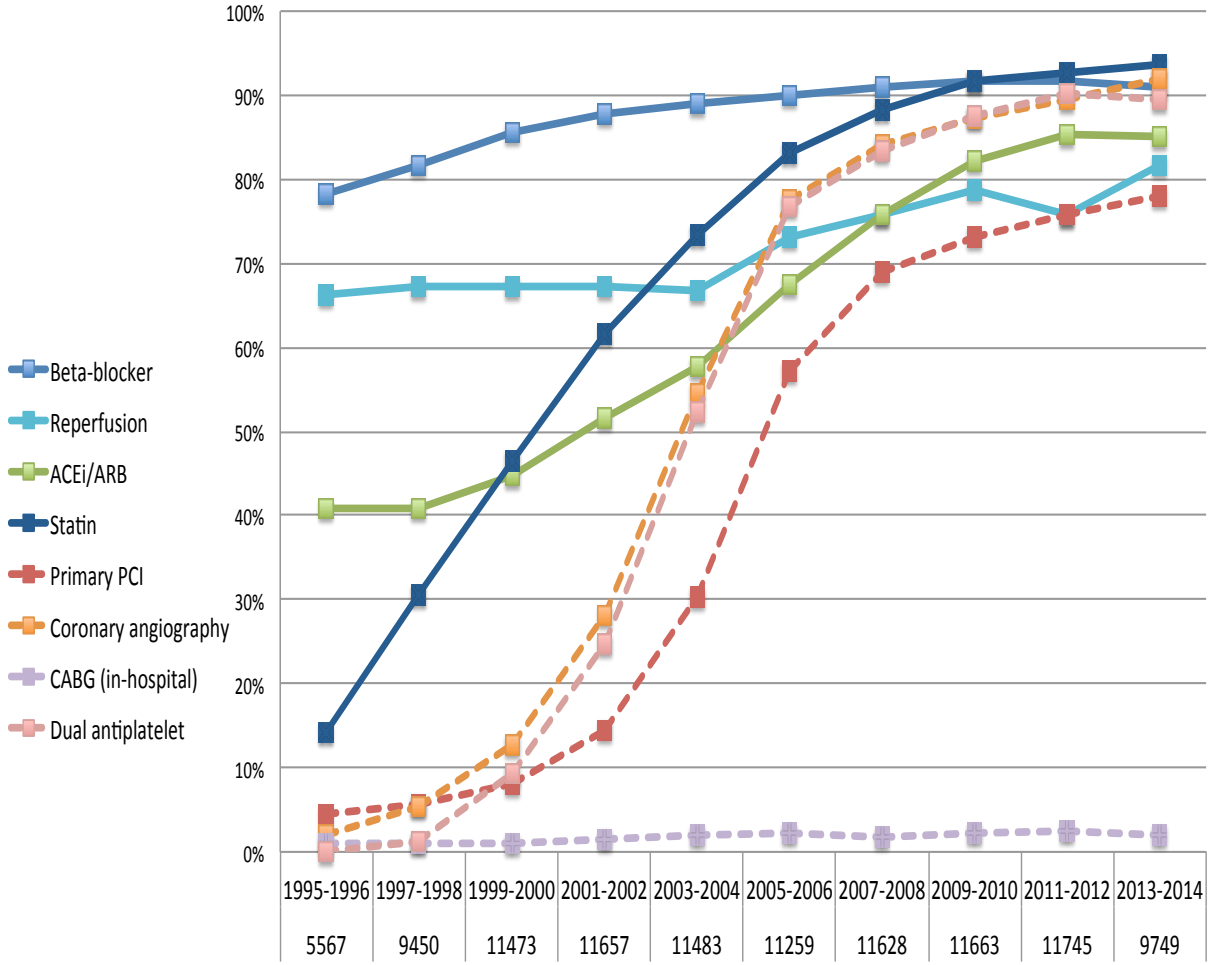
Data presented in real time and as regular reports



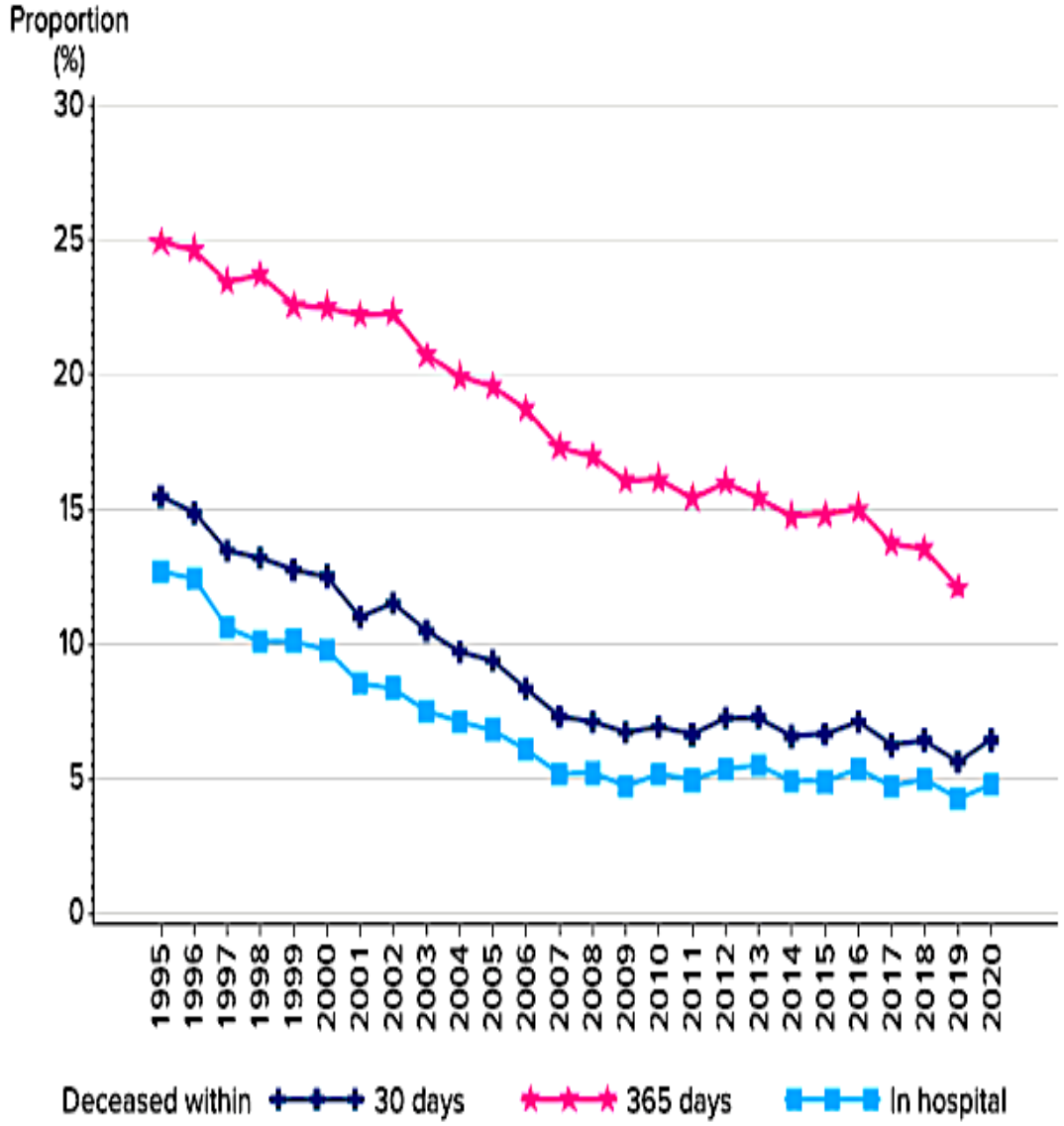
Data warehouse

Research database

SWEDEHEART
implementation of treatments in STEMI



SWEDEHEART
mortality in MI over 25 years



Szummer et al. Eur Heart J. 2017

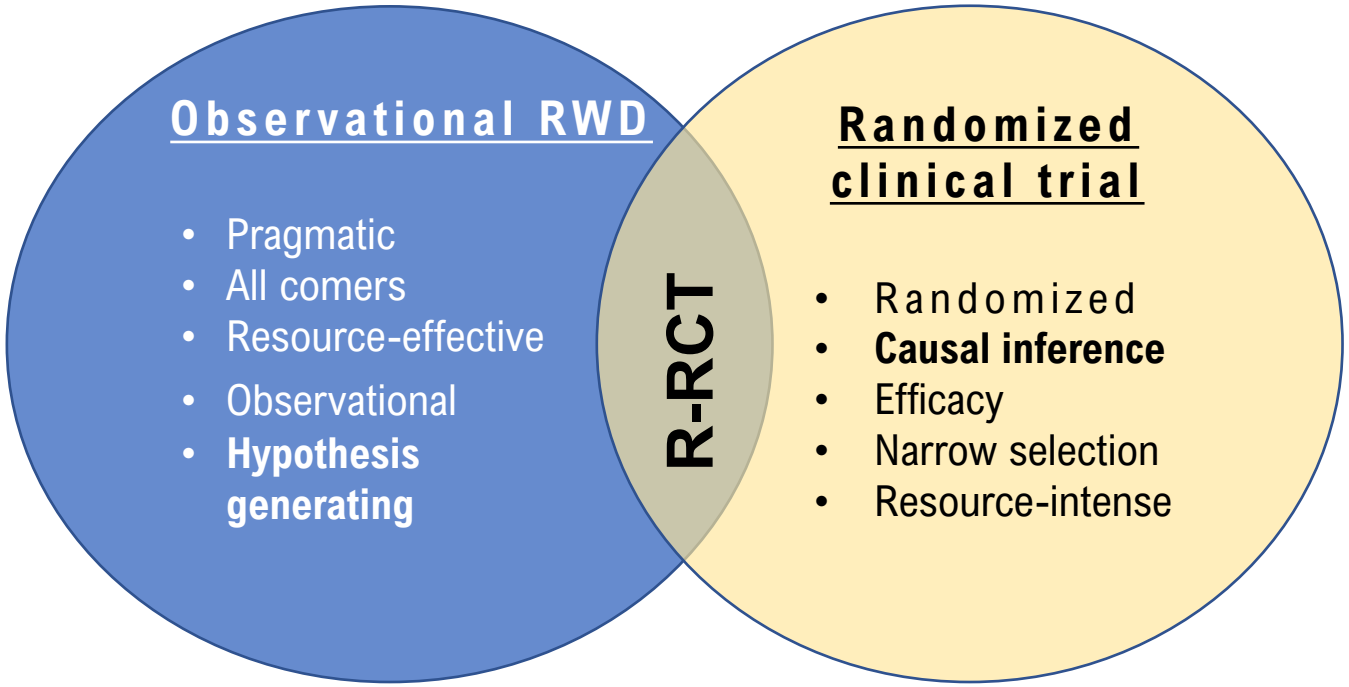
Registry-based randomized clinical trials—a new clinical trial paradigm

Stefan James, Sunil V. Rao and Christopher B. Granger

Nature Rev Cardiol. 2015 May;12(5):312-6

Registry-based Randomized Clinical Trial - R-RCT

Prosective randomized trial that uses a clinical registry
for one or several major functions for trial conduct and outcomes reporting.



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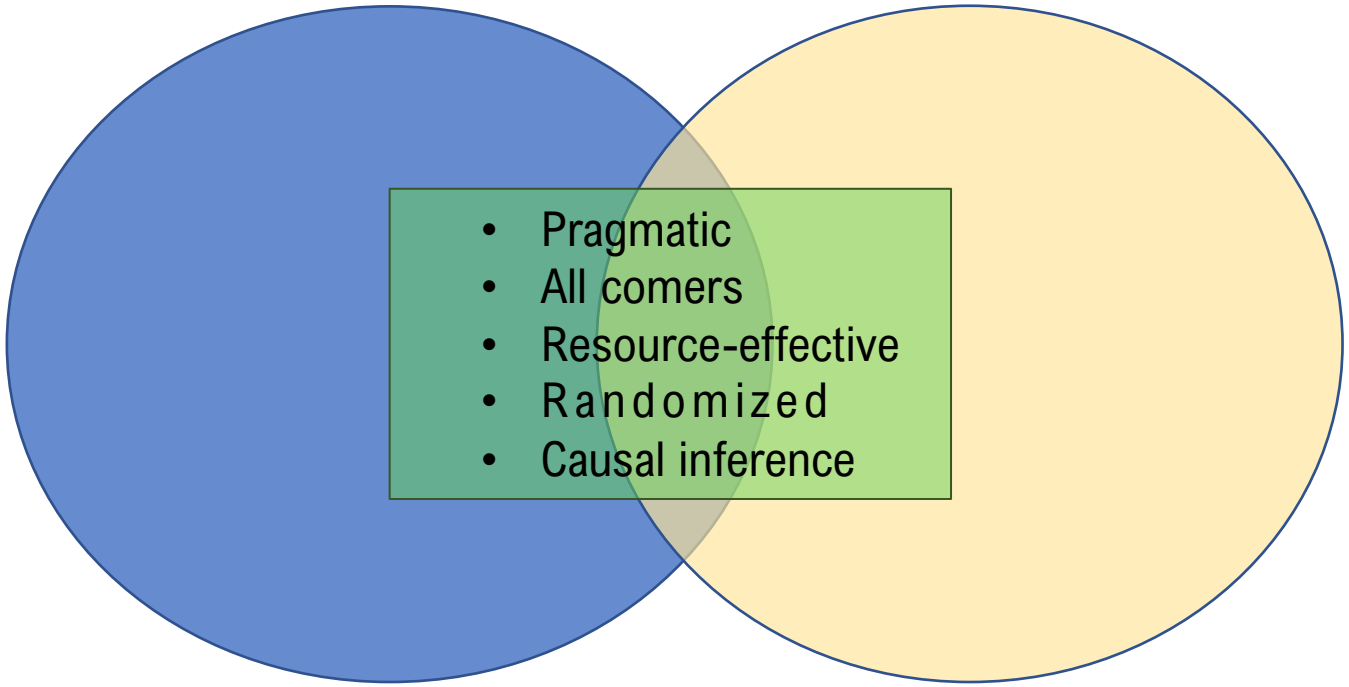
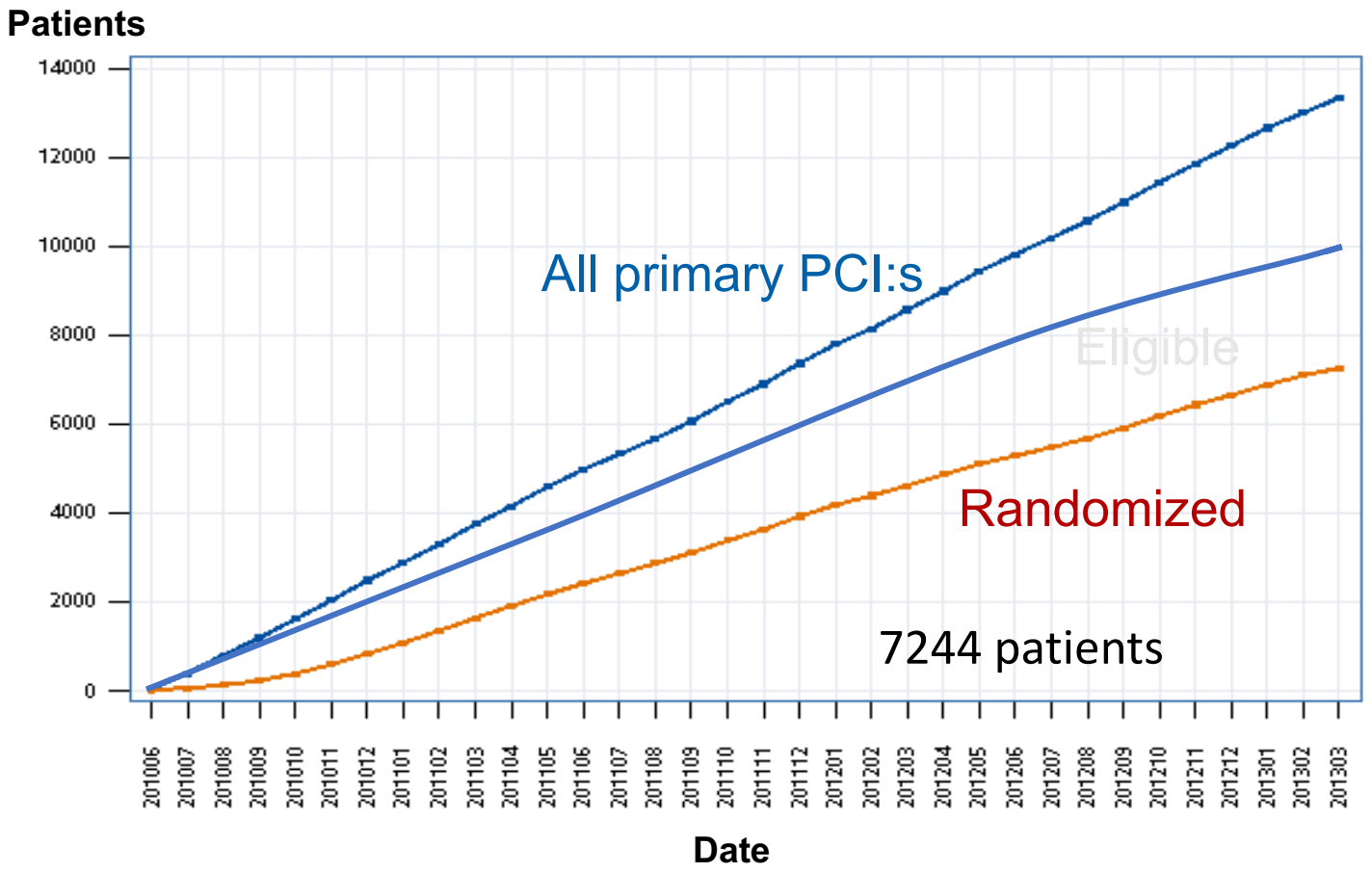


TASTE

TASTE trial on Thrombectomy in ST-elevation myocarial infarction

SWEDE HEART

TASTE inclusion rate



Perspective

The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

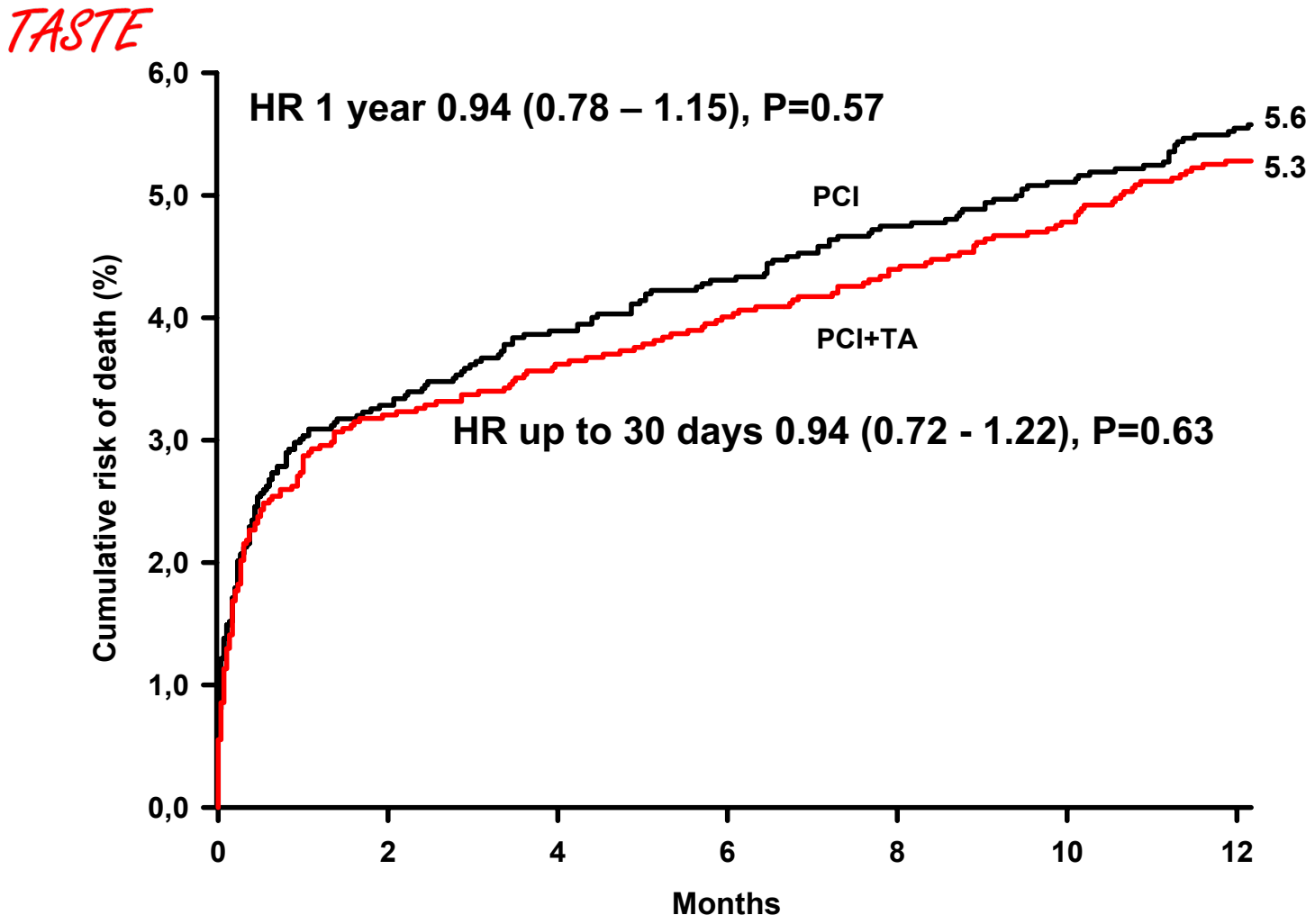
The randomized trial is one of the most powerful tools clinical researchers possess, a tool that enables them to evaluate the effectiveness of new (or established) therapies while accounting for

United States and abroad have collected vast amounts of data from patients with acute coronary syndromes, stable coronary disease, and heart failure, as well as

NEJM 2013

TASTE trial

simple single intervention, simple endpoint and pragmatic design



ORIGINAL ARTICLE

Outcomes 1 Year after Thrombus Aspiration for Myocardial Infarction

Bo Lagerqvist, M.D., Ph.D., Ole Fröbert, M.D., Ph.D., Göran K. Olivecrona, M.D., Ph.D., Thórarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Patrik Alström, M.D., Jonas Andersson, M.D., Ph.D., Fredrik Calais, M.D., Jörg Carlsson, M.D., Ph.D., Olov Collste, M.D., Matthias Götberg, M.D., Ph.D., Peter Hårdhammar, M.D., Dan Ioanes, M.D., Anders Kallryd, M.D., Rickard Linder, M.D., Ph.D., Anders Lundin, M.D., Jacob Odenstedt, M.D., Elmir Omerovic, M.D., Ph.D., Verner Puskar, M.D., Tim Tödt, M.D., Ph.D., Eva Zelleroth, M.D., Ollie Östlund, Ph.D., and Stefan K. James, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction

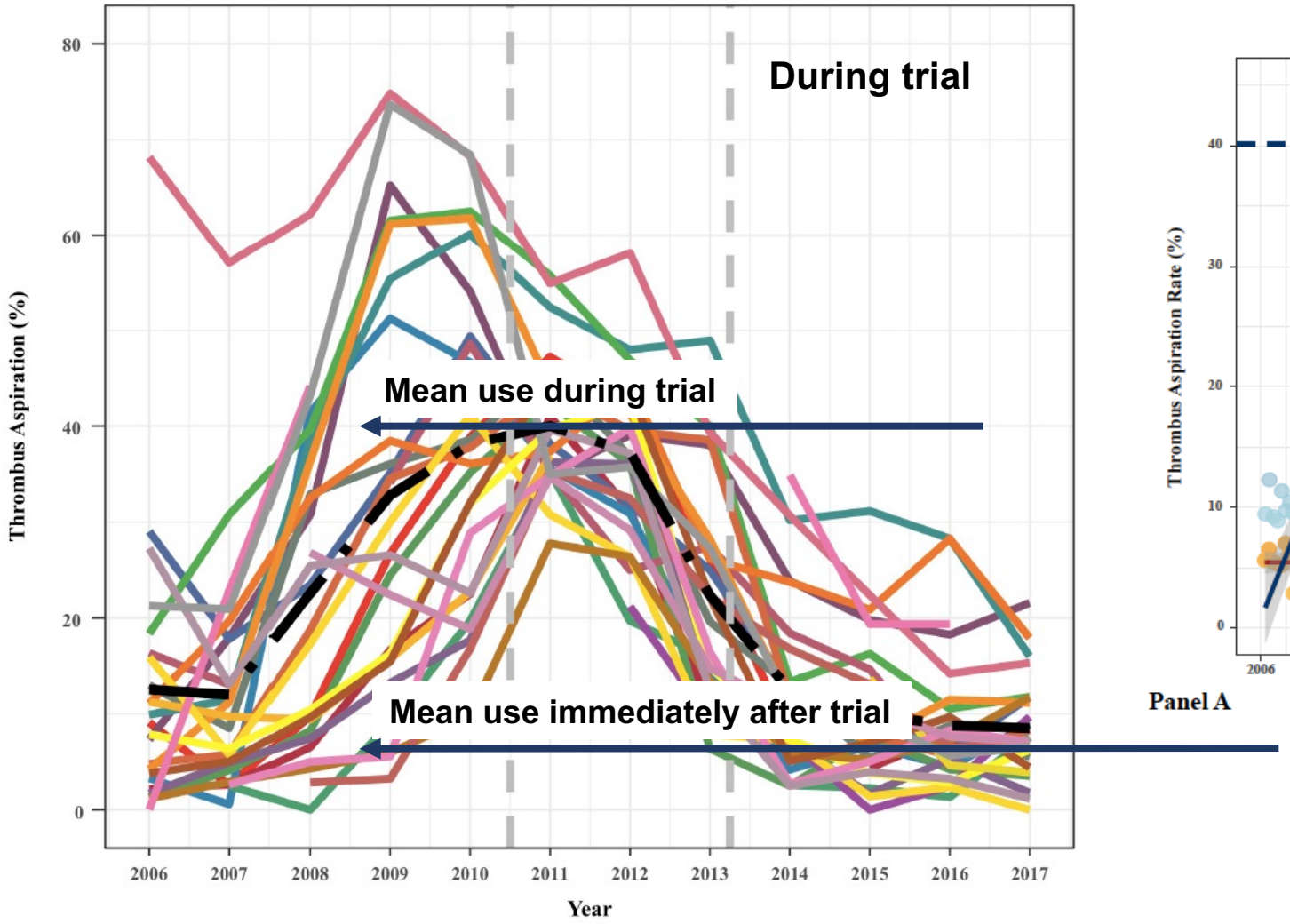
Ole Fröbert, M.D., Ph.D., Bo Lagerqvist, M.D., Ph.D., Göran K. Olivecrona, M.D., Ph.D., Elmir Omerovic, M.D., Ph.D., Thorarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Mikael Aasa, M.D., Ph.D., Oskar Angerås, M.D., Fredrik Calais, M.D., Mikael Danielewicz, M.D., David Erlinge, M.D., Ph.D., Lars Hellsten, M.D., Ulf Jensen, M.D., Ph.D., Agneta C. Johansson, M.D., Amra Kåregren, M.D., Johan Nilsson, M.D., Ph.D., Lotta Robertson, M.D., Lennart Sandhall, M.D., Iwar Sjögren, M.D., Ollie Östlund, Ph.D., Jan Harnek, M.D., Ph.D., and Stefan K. James, M.D., Ph.D.

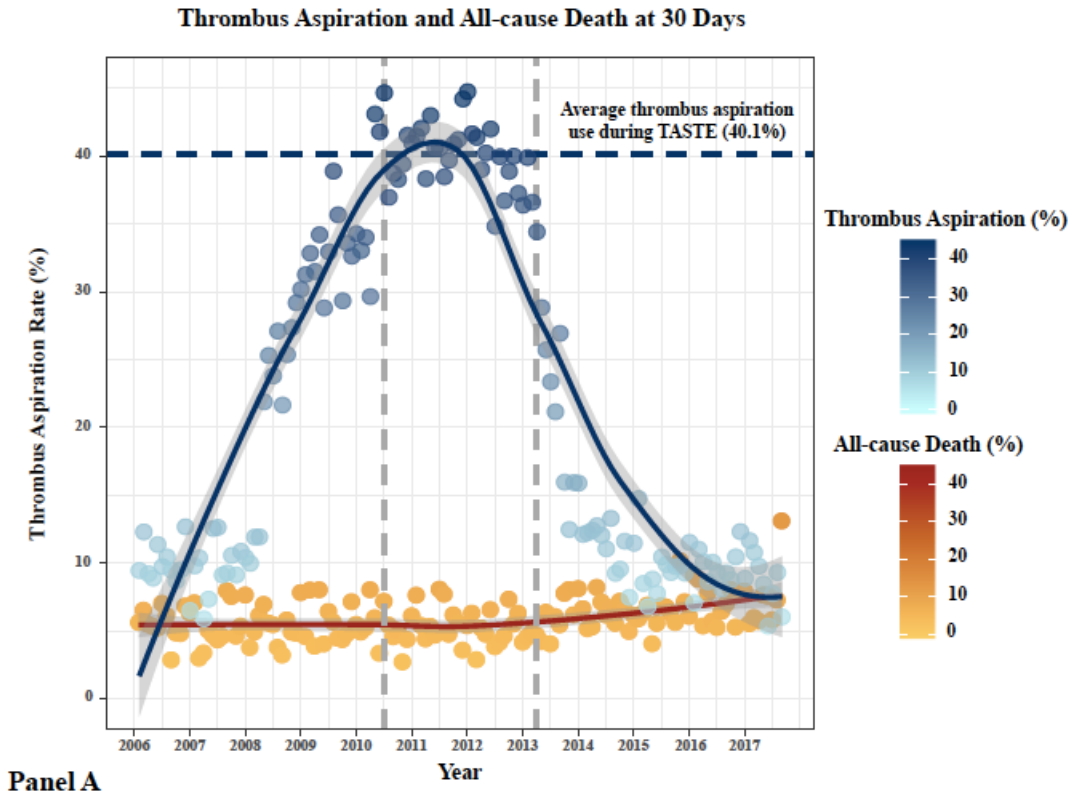
NEJM 2013 & 2014

ORIGINAL ARTICLE

Assessing the Nationwide Impact of a Registry-Based Randomized Clinical Trial on Cardiovascular Practice

The TASTE Trial in Perspective





Bucceri Circ CV Int 2019

SWEDEPAD

Patients planned for infrainguinal endovascular procedure

Critical ischemia
SWEDEPAD 1

Intermittent claudication
SWEDEPAD 2

Randomization
in registry

Randomization
in registry

DE

No-DE

DE

No-DE

Register follow-up (one month, one year)

Additional follow-up (letter/phone call, healthcare registries)
(Three and five years)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Document Mail Center – WO66-0609
Silver Spring, MD 20993-0002

Mårten Falkenberg MD, Ph D
SWEDEPAD Steering Committee
Department of Radiology
Bruna Stråket 11
Sahlgrenska University Hospital
413 45 Gothenburg
Sweden
marten.falkenberg@vgregion.se

3 September 2019

Dear Dr. Falkenberg:

The US Food and Drug Administration (FDA) has been evaluating a late mortality signal associated with the use of paclitaxel-coated devices in the treatment of femoropopliteal peripheral arterial disease.

As discussed at a public meeting of FDA's Circulatory System Devices Panel of the Medical Devices Advisory Committee on 19-20 June 2019 and summarized in FDA's updated Letter to Health Care Providers on 7 August 2019, based on available data, a late mortality signal has been identified in patients treated with paclitaxel-coated devices. Specifically, FDA's meta-analysis of randomized trials of devices approved in the US showed a 1.57 relative risk (95% confidence interval 1.16 – 2.13) for increased mortality at 5 years in patient treated with paclitaxel-coated devices vs. those treated with uncoated devices.

FDA acknowledges there is uncertainty regarding the late mortality signal associated with paclitaxel-coated devices because of multiple limitations in the available data including wide confidence intervals due to a small sample size, pooling of studies of different paclitaxel-coated devices that were not intended to be combined, substantial amounts of missing study data, no clear evidence of a paclitaxel dose effect on mortality, and no identified pathophysiologic mechanism for the late deaths.

Based on currently available information, paclitaxel-coated balloon and stents remain available in the US.

To address the limitations of the currently available information regarding the late mortality risk, and in recognition of the benefit of paclitaxel-coated devices to improve blood flow and lower the likelihood of repeat procedures to reopen blocked blood vessels, FDA strongly supports the completion of well-monitored clinical investigations of paclitaxel-coated devices. Considering the benefit-risk profile of paclitaxel-coated device use in appropriate patients, FDA believes that sufficient clinical equipoise exists to justify the continuation of high-quality clinical trials. These studies will promote public health by providing substantially more information that will enhance the interpretability of the data and confirm or refute the late mortality

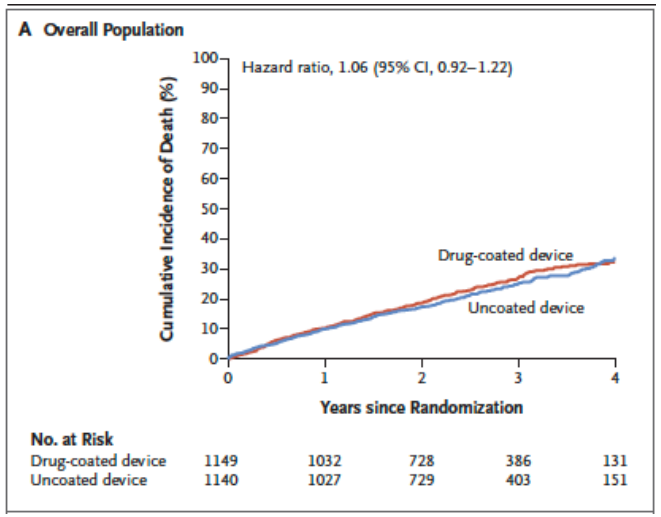
1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mortality with Paclitaxel-Coated Devices in Peripheral Artery Disease

J. Nordanstig, S. James, Manne Andersson, Mattias Andersson, P. Danielsson, P. Gillgren, M. Delle, J. Engström, T. Fransson, M. Hamoud, A. Hilbertson, P. Johansson, L. Karlsson, B. Kragsterman, H. Lindgren, K. Ludwigs, S. Mellander, N. Nyman, H. Renlund, B. Sigvant, P. Skoog, J. Starck, G. Tegler, A. Toivola, M. Truedson, C.-M. Wahlgren, J. Wallinder, A. Öjersjö, and M. Falkenberg



NEJM 2020

Device trial with complex endpoints performed for regulatory approval

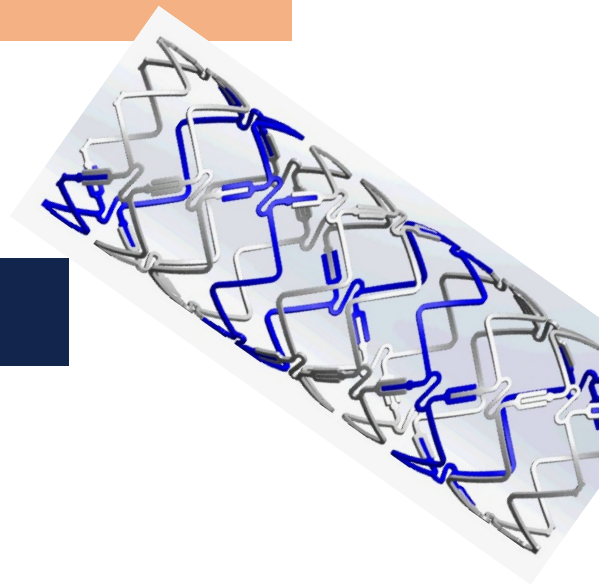
Infinity-Swedeheart

Prospective, Multi-Center, Single-Blind, Registry-Based Randomized Clinical Trial
Up to 20 Sites in Sweden

1:1 Randomization
DynamX Bioadaptor : Resolute Onyx
N = 2,400

DynamX Bioadaptor
N = 1,200

Resolute Onyx
N = 1,200



Clinical Follow-Up

Enrollment / Randomization → **Index PCI**

30 Day Phone FU → **Primary Analysis Period**

1 Year Phone FU → **Long-Term Registry Follow Up (2-5 years)**

Registry Follow-Up

6 Month Registry Query → **Primary Analysis Period**

Registry Queries Years 2-5 → **Long-Term Registry Follow Up (2-5 years)**

Sponsor: Elixir

Pharma (parentral) trial with complex endpoints

VALIDATE (R-RCT)

STEMI (n=3000) or NSTEMI (n=3000)
Pre-treatment with Ticagrelor, Prasugrel or Cangrelor
Angiography: PCI intended

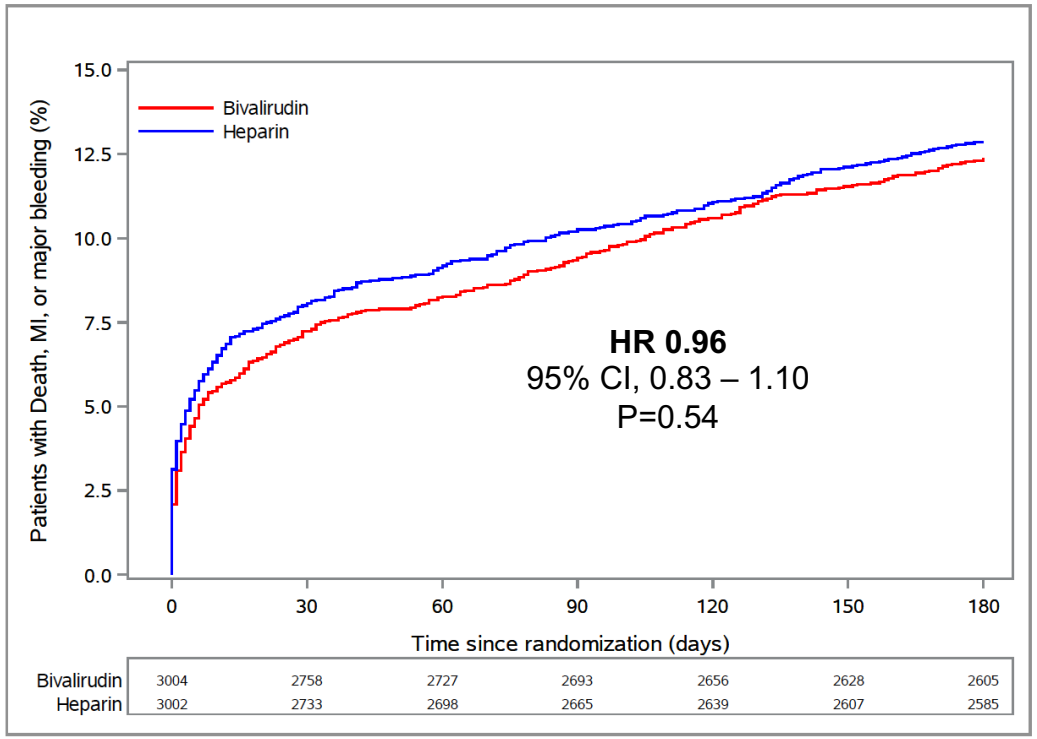
R 1:1

- Heparin only (70-100U/kg)
- Bivalirudin (5000U Heparin pre-hospital or 3000U pre-PCI)

Primary Endpoint:
NACE: Death, Myocardial Infarction or Bleeding complication (BARC 2, 3 or 5)
at 6 months

- FU: Register data, combined with phone call endpoint follow up and CEC
- Funding: Heart-lung foundation. Swedish research council, Astra Zeneca, The Medicines company.

Primary Endpoint at 180 days



ORIGINAL ARTICLE

Bivalirudin versus Heparin Monotherapy in Myocardial Infarction

D. Erlinge, E. Omerovic, O. Fröbert, R. Linder, M. Danielewicz, M. Hamid, E. Swahn, L. Henareh, H. Wagner, P. Hårdhammar, I. Sjögren, J. Stewart, P. Grimfjärd, J. Jensen, M. Aasa, L. Robertsson, P. Lindroos, J. Haupt, H. Wikström, A. Ulvenstam, P. Bhiladvala, B. Lindvall, A. Lundin, T. Tödt, D. Ioanes, T. Råmunddal, T. Kellerth, L. Zagozdzon, M. Götberg, J. Andersson, O. Angerås, O. Östlund, B. Lagerqvist, C. Held, L. Wallentin, F. Scherstén, P. Eriksson, S. Koul, and S. James

NEJM 2017

Double blind placebo-controlled pharma (oral) trial in 2 countries for regulatory approval

~50 clinical centres in Sweden connected to

SWEDEHEART

DAPAMI

6400* patients with

- MI (STEMI & NSTEMI) within 7 d
- Reduced LVEF or Q wave MI
- No T1DM or T2DM
- WRITTEN INFORMED CONSENT

R

Dapagliflozin 10 mg once daily on top of SoC

Placebo once daily on top of SoC

~50 clinical centres in UK connected to

MINAP

Visits @ 6-10 weeks post-randomisation (on-site) and at 1 y; thereafter every 10th month until EoT

Primary composite endpoint: Time to first event of hospitalisation for heart failure or CV death

Key assumptions

- Primary annual event rate: 7.5%
- RRR: 20%
- Power: 85%
- P: <0.05

Event-driven trial (722 events)
Recruitment time: 18 months
Total trial duration: 30 months

UCR Uppsala Clinical Research Center

NICOR

R-RCT in Sweden 2022

	Active	Published
Cardiology	9	6
Bariatric surgery	1	1
Vascular surgery	1	1
Stroke		1*
Obstetrics	1	
Gynecology	2	
Pulmonary medicine	1	
GI cancer	1	
Orthopedic surgery	4	
Diabetes	1	
Renal faulure	1**	

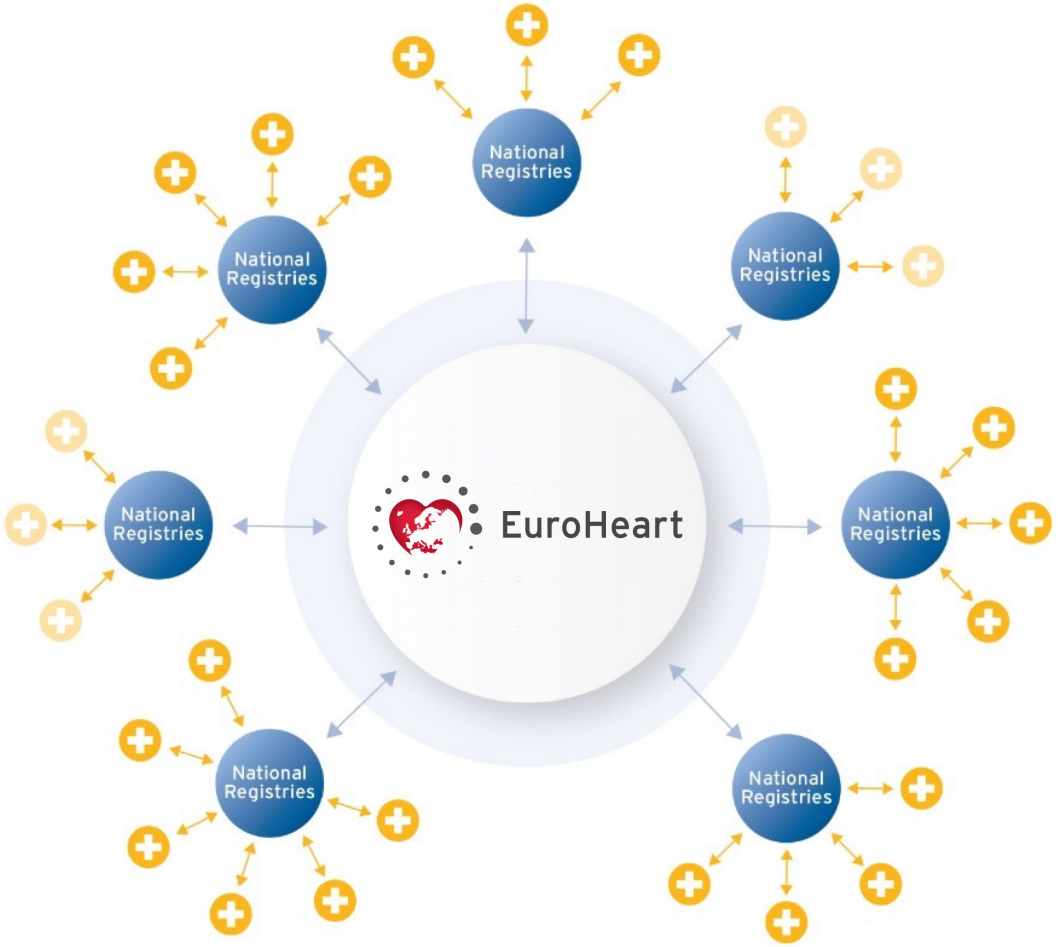
UCRO
Uppsala Clinical Research Center

EuroHeart
European Unified Registries for Heart Care Evaluation and Randomised Trials

EuroHeart – The mission

International collaboration with general availability to systems with **continuous online registration** of **high quality and harmonised patient data** with real-time information supporting continuous improvement of care and outcomes in patients with common cardiovascular diseases.

International infrastructure for cost-effective safety surveillance of new drugs and devices and registry based randomised clinical trials in a general patient population across multiple geographies.

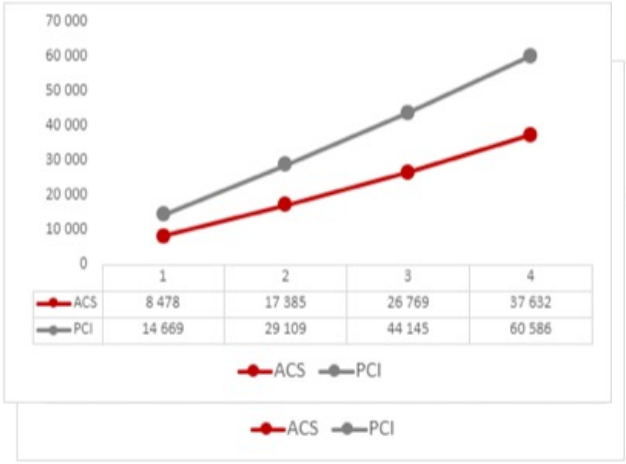


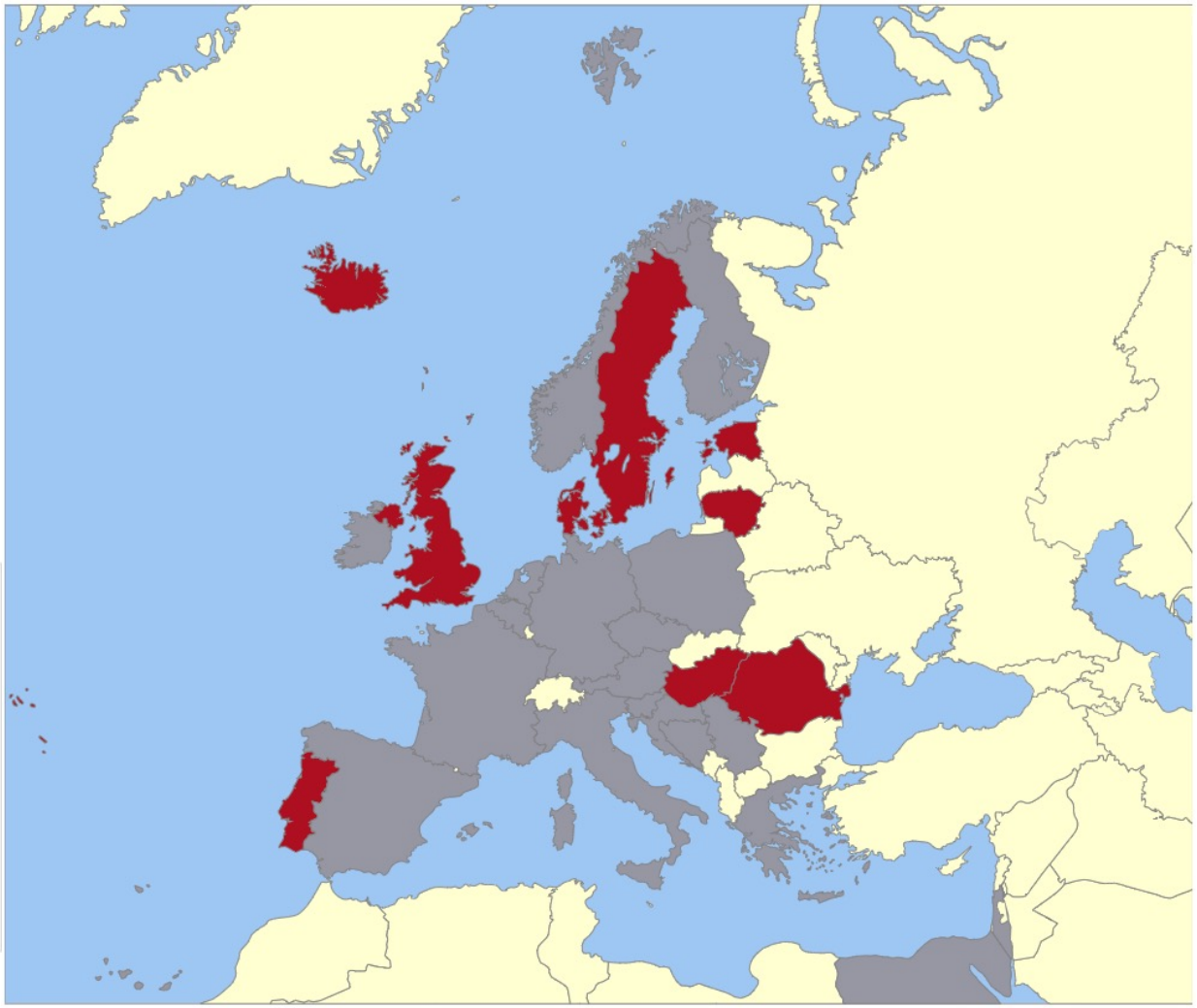
EuroHeart
European Unified Registries for Heart Care Evaluation and Randomised Trials

EuroHeart countries

Member countries 2022

- **Estonia**
- **Hungary**
- **Portugal**
- **Romania**
- **Sweden**
- **Lithuania**
- **Denmark**
- **Iceland**
- **Singapore**





In/planned communication

- Austria
- Belgium
- Bosnia and Herzegovina
- Croatia
- Czech Republic
- Egypt
- Finland
- France
- Germany
- Greece
- **Ireland**
- Israel
- Italy
- Netherlands
- Norway
- Poland
- Serbia
- Scotland and Wales
- Slovenia
- Spain
- England
- Pakistan

EuroHeart

Visit the EuroHeart website and the EuroHeart demos and movies at:
https://www.escardio.org/Research/euroheart

For more information contact us:
euroheart@escardio.org

EuroHeart
European Unified Registries for Heart Care Evaluation and Randomised Trials

www.escardio.org/euroheart

ESC
European Society of Cardiology