The future of randomized trials Use of country-wide registries in pragmatic clinical trials

Lars Wallentin

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Uppsala Clinical Research Centre
Uppsala University Uppsala, Sweden

UCR

SWEDEHEART

Number of cases annually: > 80 000

RIKS-HIA	73 CCU hospitals, 100%
SCAAR	30 PCI hospitals, 100%
Percutaneous valves	7 hospitals, 100%
Heart surgery	7 hospitals, 100%
Secondary prevention	67 hospitals, 85%
Cardio genetics	5 university hospitals
Cardiac CT	10 large hospitals
Continuous bio banking	3 university hospitals

>300 variables - baseline, procedural, outcomes

At monitoring: 95-96% agreement.

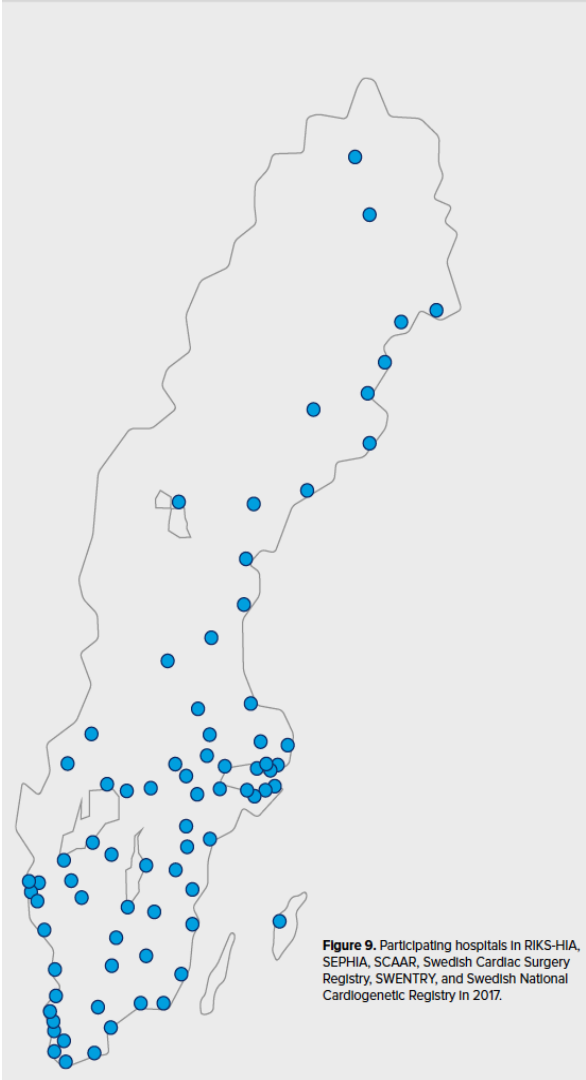
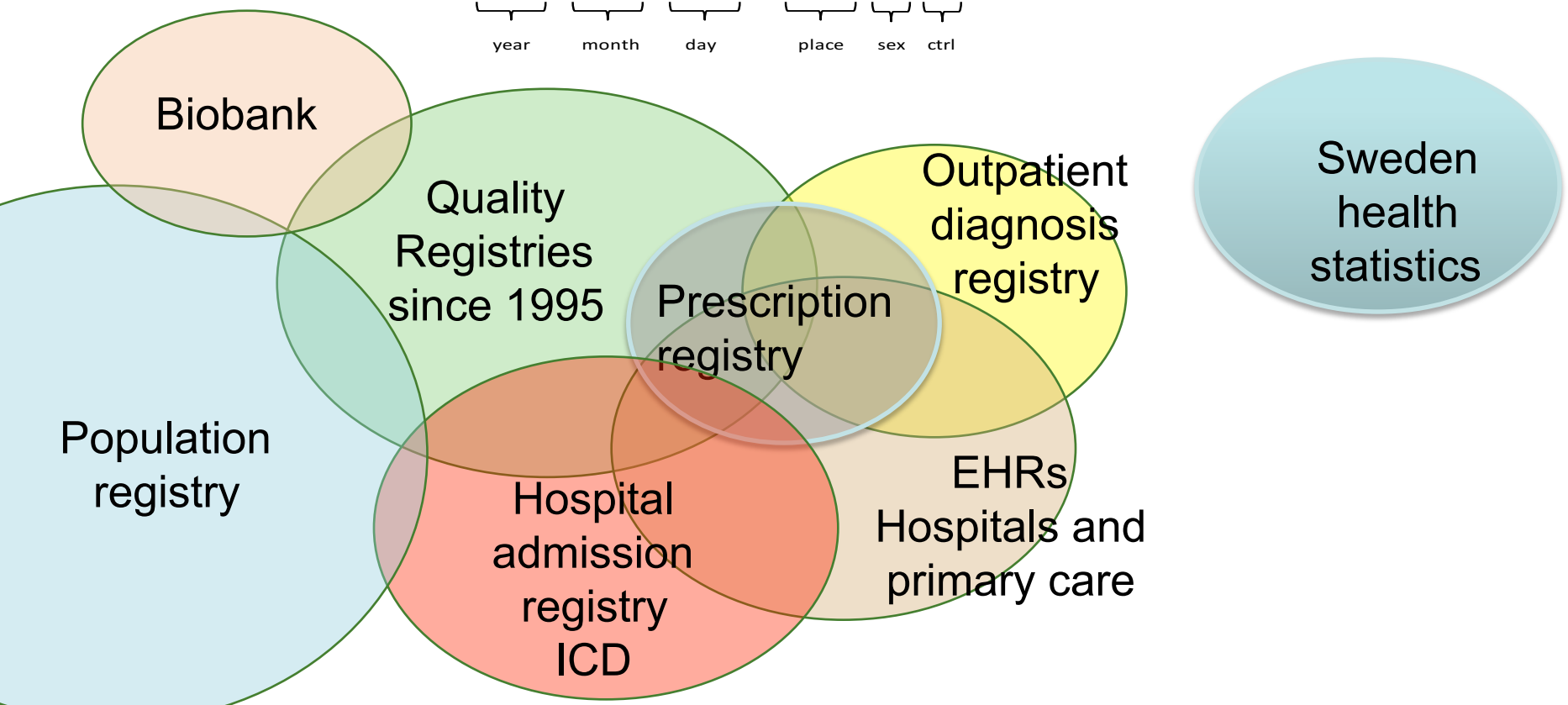


Figure 9. Participating hospitals in RIKS-HIA, SEPHIA, SCAAR, Swedish Cardiac Surgery Registry, SWENTRY, and Swedish National Cardiogenetic Registry in 2017.

Data bases in Sweden based on personal number with patient characteristics, treatments and outcomes

Since 1947 **540219-9750**

year month day place sex ctrl



Aims of SWEDEHEART

To support development and implementation of evidence-based therapy in coronary artery disease and catheter-based or surgical valve intervention:

- To monitor patient mix, care needs, investigations, treatments, adherence to guide-lines and outcomes
- To support continuous quality improvement
- To form the basis for research
- To form an infrastructure for RRCT

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Aims of SWEDEHEART

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R-RCT vs. classical RCT

- Combines the advantages of a clinical registry and randomized study
- Complement to classical RCT – No substitute
- No formal definition

RRCT

Evaluation of therapeutic options available/used in routine clinical care

RCT

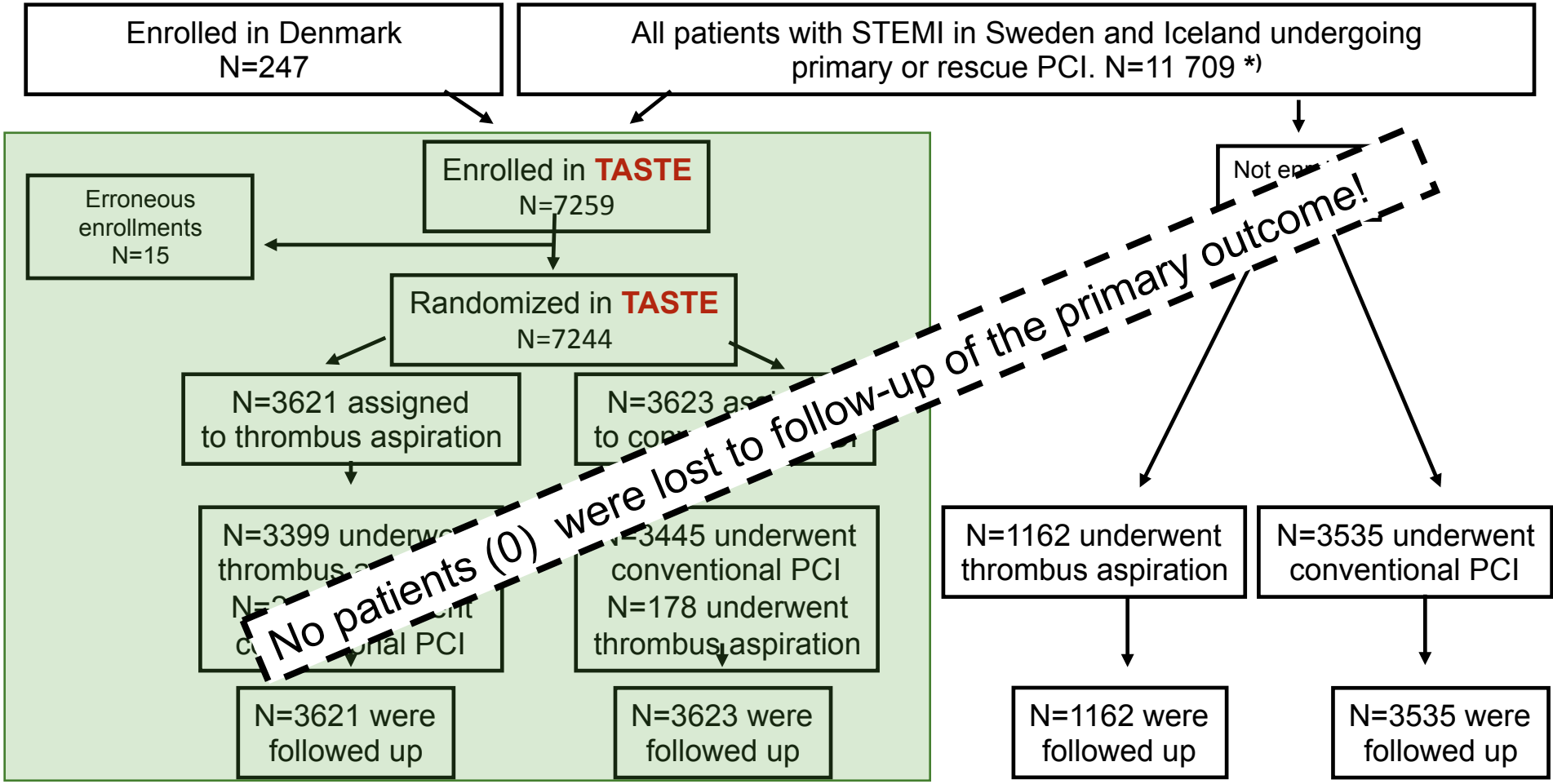
Approval of new pharmaceutical agents and medical devices

Thrombus aspiration

SCAAR
SWEDE HEART

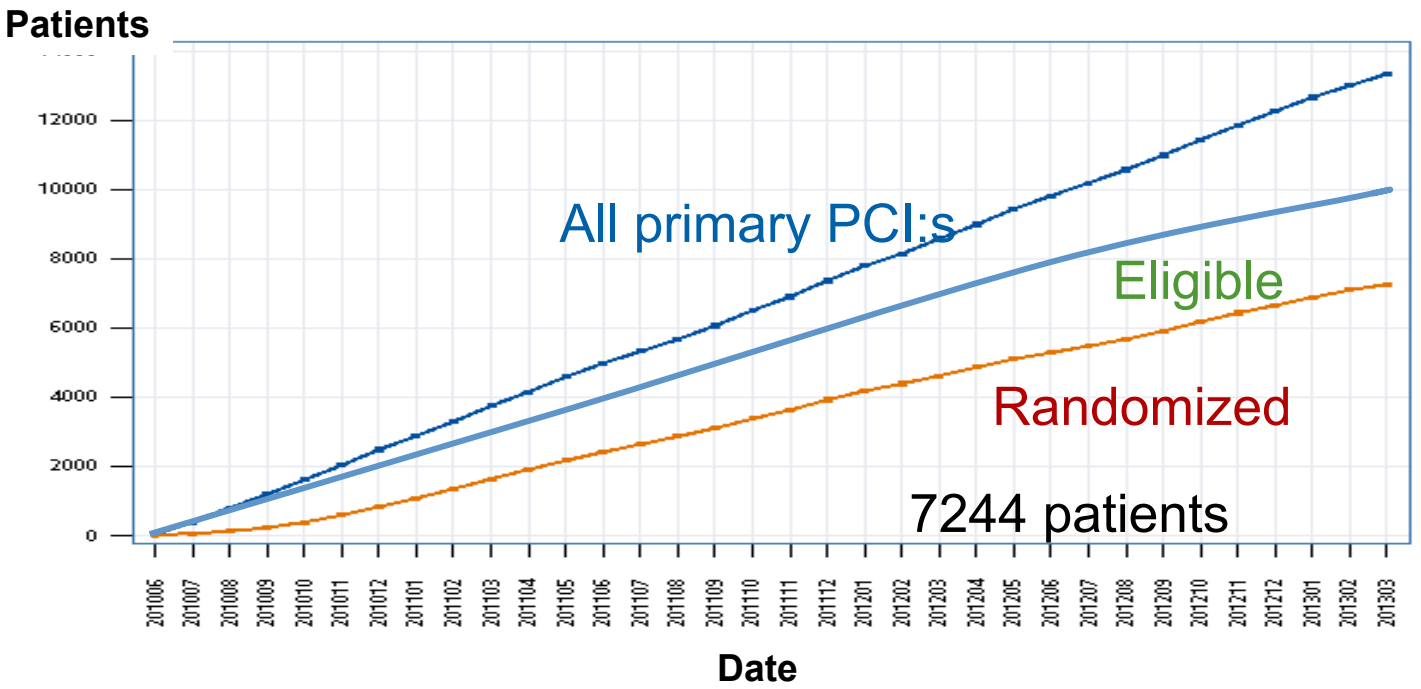
TASTE

TASTE trial enrollment flow chart



TASTE

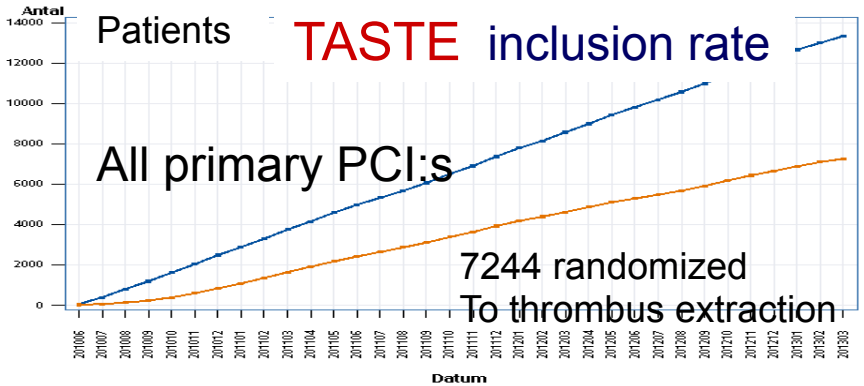
TASTE inclusion rate

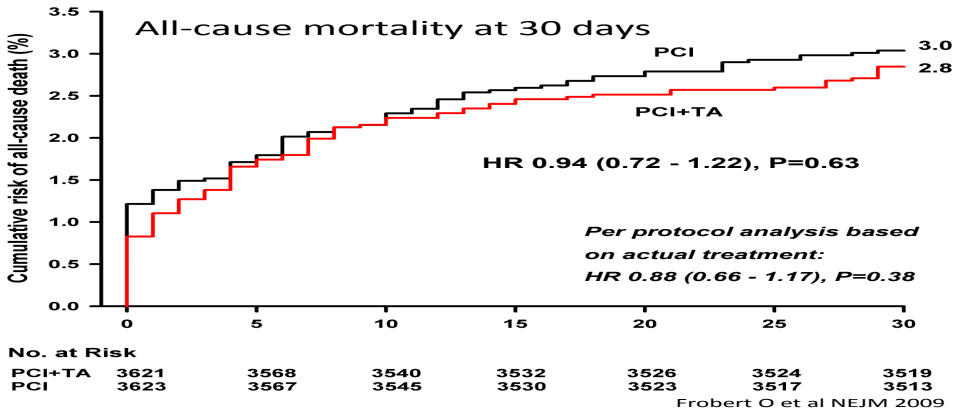


The NEW ENGLAND JOURNAL of MEDICINE

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

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





Registry Randomized Clinical Trial - RRCT

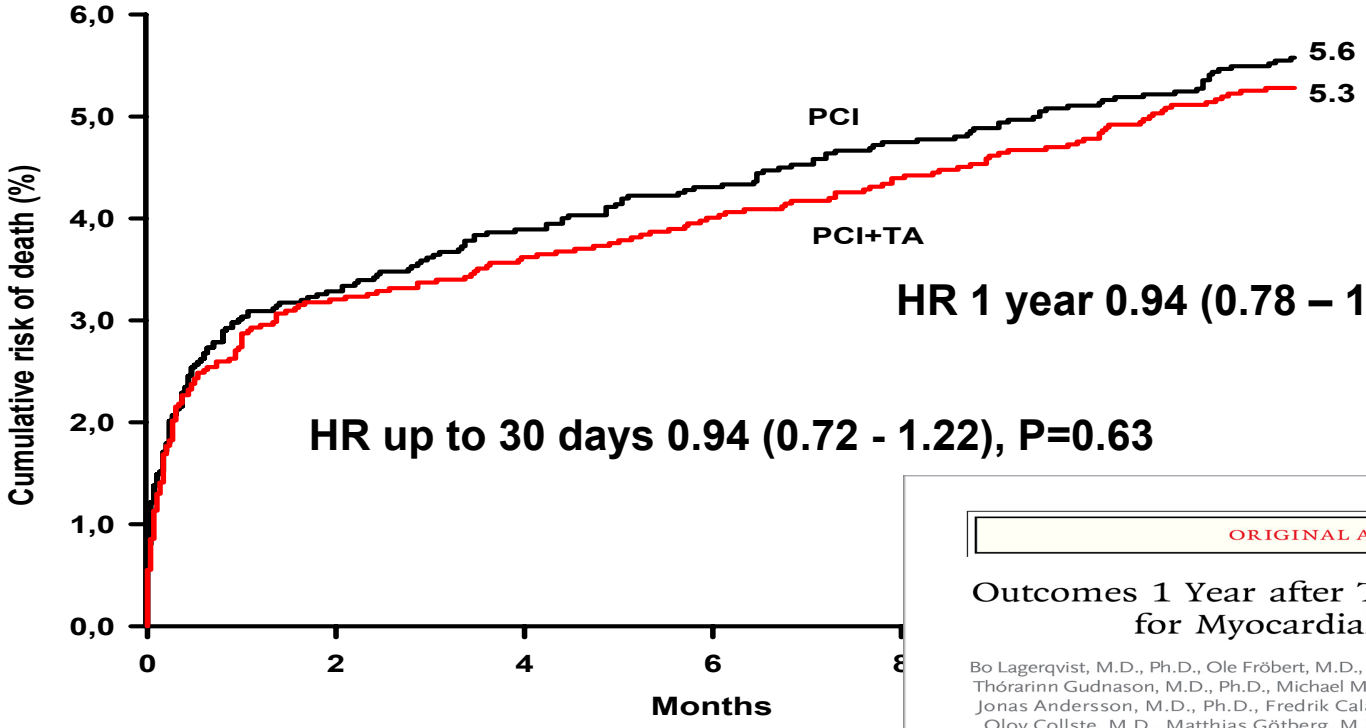
- New concept for clinical research
- Integrates a randomized study with a clinical registry
- Complement to classical RCT

Fröbert O, Lagerqvist B, James S NEJM 2013, 2014

TASTE

SWEDE HEART

1-year complete follow-up



HR 1 year 0.94 (0.78 – 1.15), P=0.57

HR up to 30 days 0.94 (0.72 - 1.22), P=0.63

ORIGINAL ARTICLE

Outcomes 1 Year after Thrombus Aspiration for Myocardial Infarction

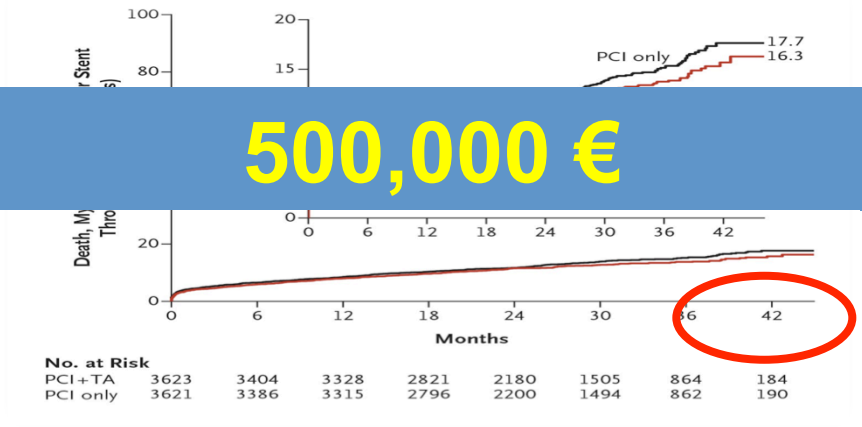
Bo Lagerqvist, M.D., Ph.D., Ole Fröbert, M.D., Ph.D., Göran K. Olivecrona, M.D., Ph.D., Thórarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Patrik Alström, M.D., Jonas Andersson, M.D., Ph.D., Fredrik Calais, M.D., Jörg Carlsson, M.D., Ph.D., Olov Collste, M.D., Matthias Götberg, M.D., Ph.D., 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.

Registry based vs. Patient Follow-up

STEMI Thrombectomy Story

TASTE

Registry-based Follow-up



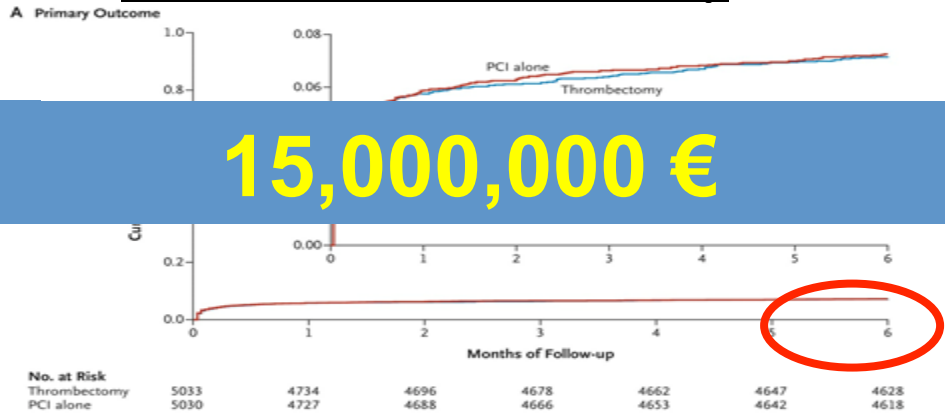
500,000 €

1st patient: June 2010
30 centers
33 months to full enrollment

Fröbert et al. N Engl J Med 2013 Oct 24;369(17):1587-97
Lagerqvist B et al. N Engl J Med 2014;371:1111-1120

TOTAL

Standard site-based Follow-up

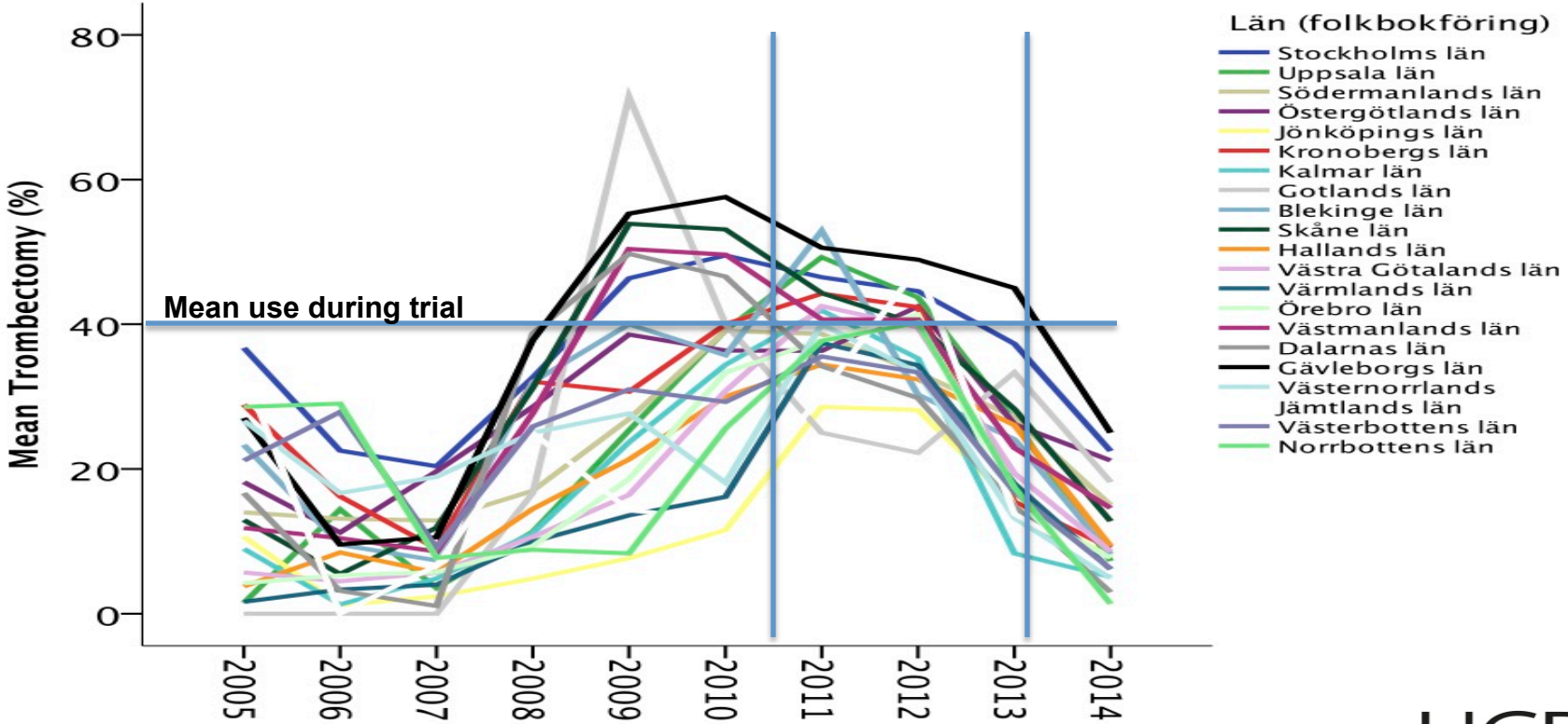


15,000,000 €

1st patient: August 2010
87 centers
48 months to full enrollment

Jolly SS et al. N Engl J Med 2015;372:1389-1398

Thrombus aspiration post Taste



Randomisation Module

Primärt beslut	9 PCI ad hoc *
Avböjd från operation	
	Spara

Randomisation results

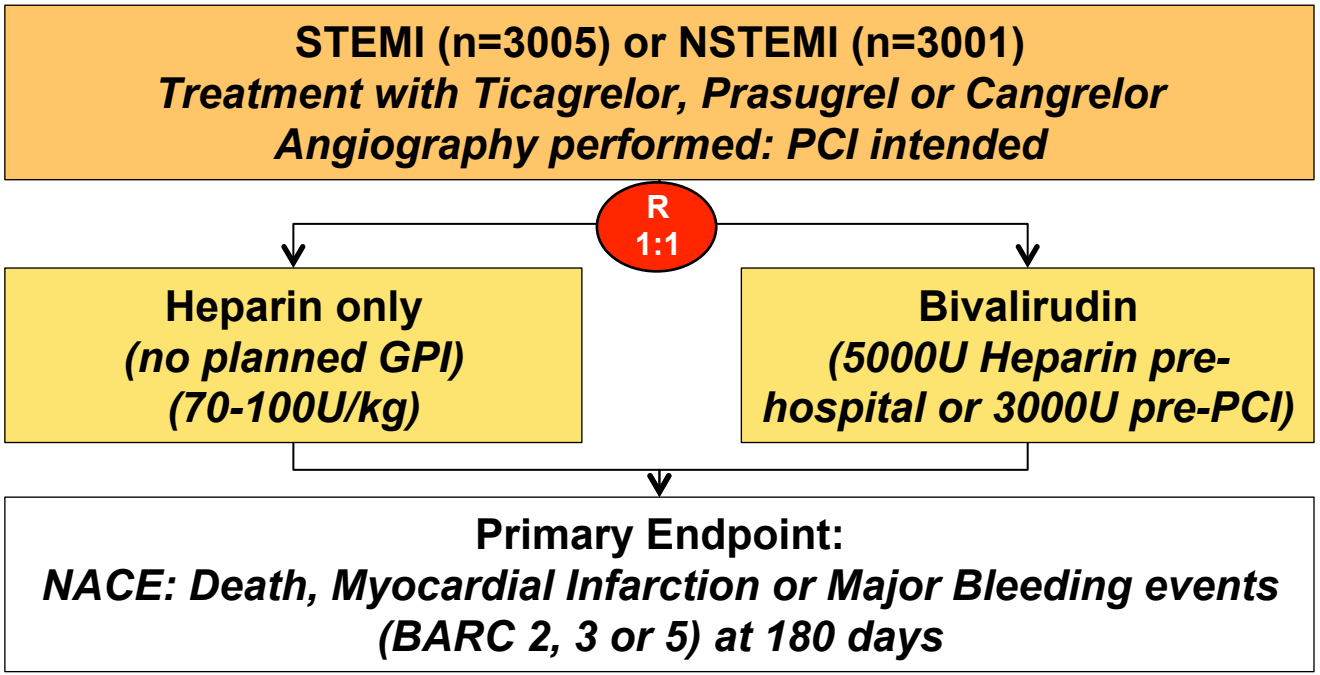
Validate

Studienummer	100001
Randomiseras till	Heparin
TIMI-flöde före	1 Partiell fyllnad *
Synlig tromb i kärlet?	2 Liten (största diameter < ½ kärldiameter KD) *
Avvek du från radomiserad behandling?	0 Nej *
Hade du någon trombotisk komplikation under proceduren?	2 Ja, ledare, guide el dylikt trombotiserade *
TIMI-flöde efter	3 Normalt *
Kommentar (studierelaterat, skrivs ej ut på utlåtandet)	
Totalmängd heparin givet under procedur:	8000 *
Mättes ACT?	1 Ja *
Vad var max ACT?	325 *
Hur lång tid innan PCI fick patienten ticagrelor/prasugrel?	3 3–6 timmar *

PCI

- Register identifies eligible patients
- Asks the operator if patient agrees to participate
- If yes, immediate randomisation result
- Performed in a few seconds
- A few study related question, eg intraprocedural thrombosis

Study design



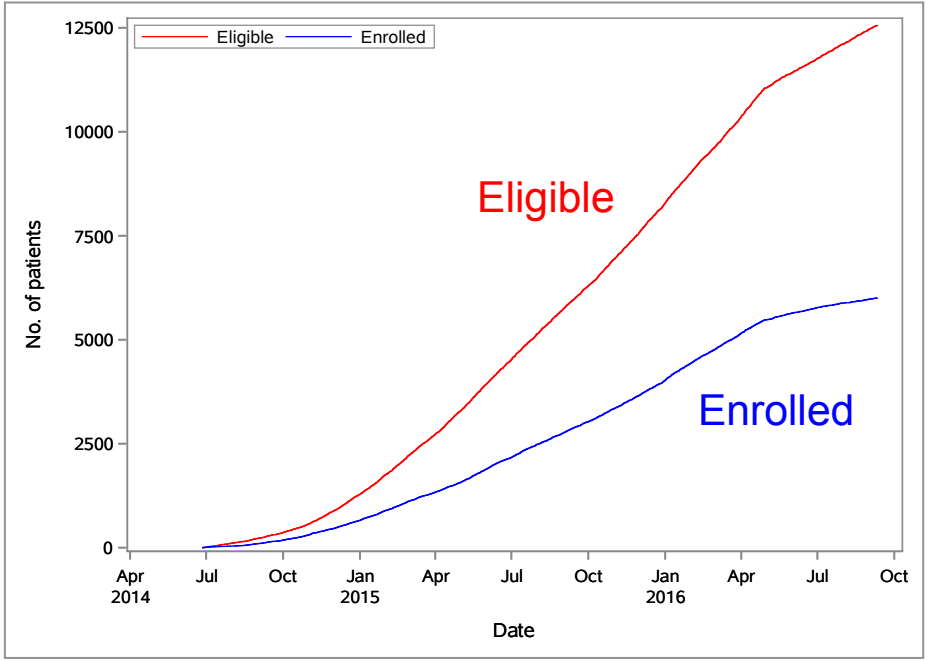
Coordinating PI: *David Erlinge, Lund University, Sweden*

Chairman: *Stefan James, Uppsala University, Sweden*

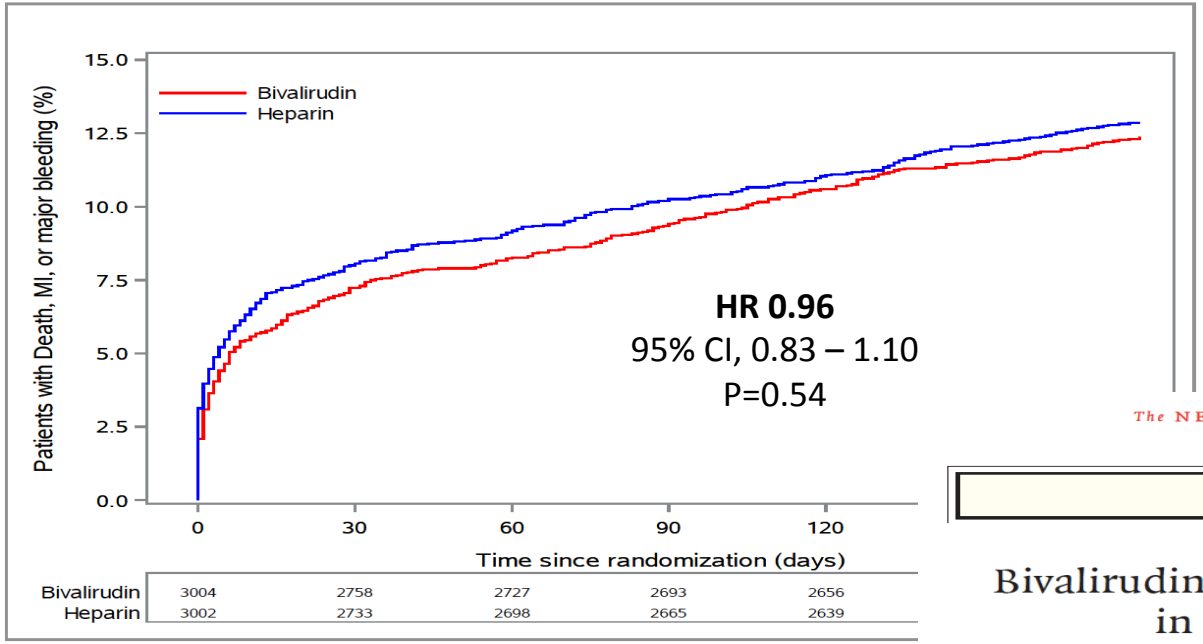
Trial design: *Erlinge et al., Am Heart J 2014*

Results

- 25 PCI centers out of 29 in Sweden participated in the trial
- 47.8% (6006 of 12,561) of all patients in Sweden presenting at enrolling hospitals with an initial diagnosis of STEMI or NSTEMI planned for PCI were randomized.
- Of all patients potentially eligible for enrollment, 70.0% (6006 of 8585) were randomized within 27 months



Primary Endpoint at 180 days



The NEW ENGLAND JOURNAL of MEDICINE

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

Study Flow Chart

DETO2X | SWEDEHEART

Patient contact with EMS, ED, CCU or cath lab

Eligible patient

Initial oral informed consent (written confirmation within 24h)

Unrestricted online randomization using SWEDEHEART

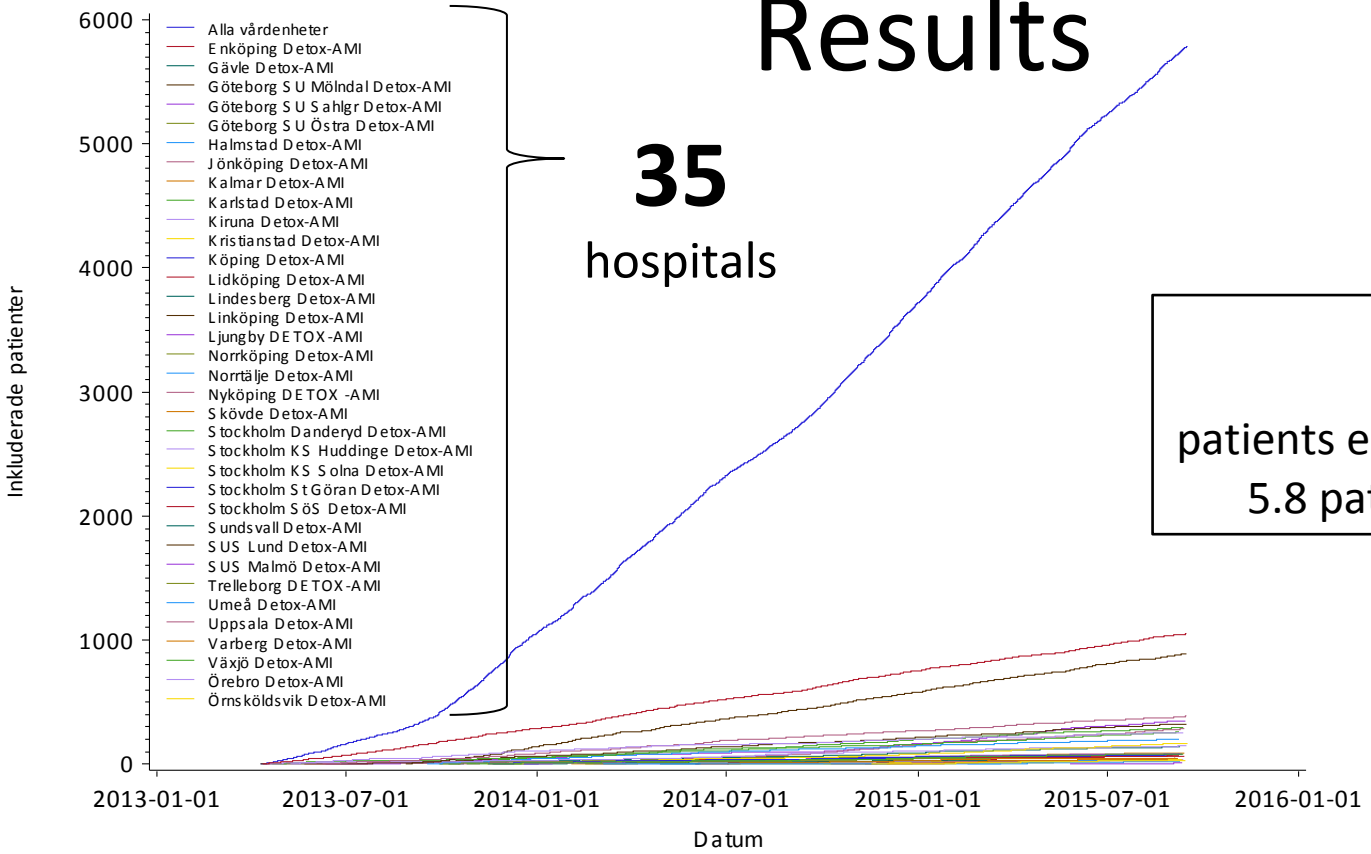
Oxygen

Delivered by open face mask at 6L/min for 6-12 hours

Ambient Air

Data analysis through the **Swedish Population Registry** and **SWEDEHEART**

Results



35

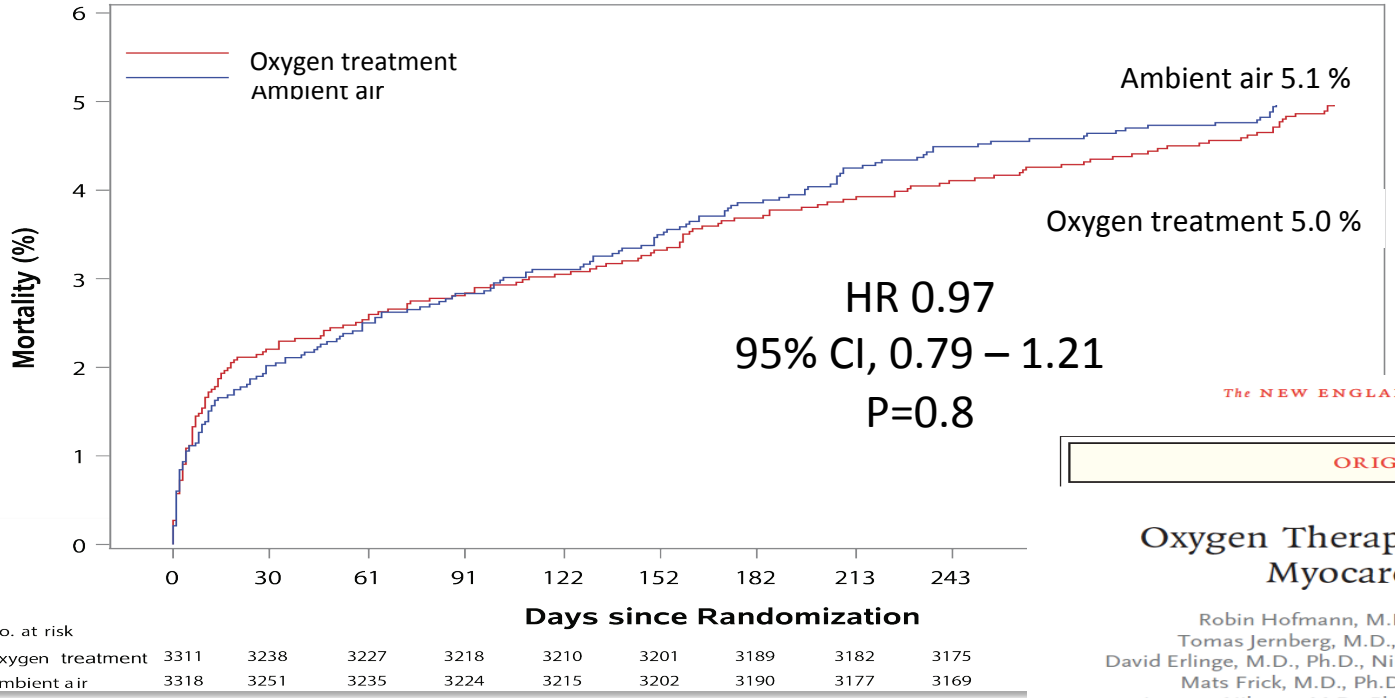
hospitals

6629

patients enrolled within 2.5 years

5.8 patients / site / month

Primary Endpoint up to 365 days



HR 0.97
95% CI, 0.79 – 1.21
P=0.8

No. at risk

Oxygen treatment	3311	3238	3227	3218	3210	3201	3189	3182	3175
Ambient air	3318	3251	3235	3224	3215	3202	3190	3177	3169

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oxygen Therapy in Suspected Acute Myocardial Infarction

Robin Hofmann, M.D., Stefan K. James, M.D., Ph.D., Tomas Jernberg, M.D., Ph.D., Bertil Lindahl, M.D., Ph.D., David Erlinge, M.D., Ph.D., Nils Witt, M.D., Ph.D., Gabriel Arefalk, M.D., Mats Frick, M.D., Ph.D., Joakim Alfredsson, M.D., Ph.D., Lennart Nilsson, M.D., Ph.D., Annica Ravn-Fischer, M.D., Ph.D., Elmir Omerovic, M.D., Ph.D., Thomas Kellerth, M.D., David Sparv, B.Sc., Ulf Ekelund, M.D., Ph.D., Rickard Linder, M.D., Ph.D., Mattias Ekström, M.D., Ph.D., Jörg Lauermann, M.D., Urban Haaga, B.Sc., John Pernow, M.D., Ph.D., Ollie Östlund, Ph.D., Johan Herlitz, M.D., Ph.D., and Leif Svensson, M.D., Ph.D., for the DETO2X–SWEDEHEART Investigators*

R-RCTs in Sweden (in AMI)

TASTE (n=7200) **Thrombus aspiration in primary PCI** — ***Completed***
Clinical registry: Swedeheart
Funding: Swedish Heart-Lung foundation, Sw Research council, Medtronic, Vascular Solutions, Terumo.
Study sponsor and ARO:

iFR Swedeheart (n=2018) **iFR vs FFR in stable angina or ACS** — ***Completed***
Clinical registry: Swedehear
Funding: Volcano. Study sponsor and ARO: UCR.

VALIDATE (n=6006) **Bivalirudin vs UFH for PCI in ACS** — ***Completed***
Clinical registry: Swedeheart
Funding: Swedish Heart-Lung foundation, Sw Research council, The MedCo, AZ
Study sponsor and ARO: UCR

DETO2X (n=6629) **Oxygen therapy in suspected myocardial infarction** — ***Completed***
Clinical registry: Swedeheart
Funding: Swedish Heart-Lung foundation, Sw Research council.
Study sponsor: Karolinska Institute. ARO: UCR

PROSPECT-2 (n=1200, hybrid trial) near infrared spectroscopy — ***Ongoing***
Clinical registry: Swedeheart
Funding: The Medicines Company/ Abbot vascular. Study sponsor: UCR

FULL-REVASC (n=4000) **FFR-guidance for ST elevation myocardial infarction revascularization** — ***Ongoing***
Clinical registry: Swedeheart
Funding: Swedish Research council (VR), Study sponsor: Karolinska Institute. ARO: UCR

IAMI (n=4400) **Influenza vaccination After Myocardial Infarction** — ***Ongoing***
Clinical registry: Swedeheart
Funding: Sanofi, Study sponsor: Örebro University hospital. ARO: KTC

REDUCE (n=6600) **Betablocker post MI in patients with normal left ventricular function.** — ***Ongoing***
Funding: Swedish Research council (VR),
Study sponsor: Karolinska Institute. ARO: UCR

MINOCA BAT (n=2048) **ACE/ARBi after MI with non-obstructive coronary arteries** — ***Soon to start***
Clinical registry: Swedeheart
Funding: Swedish Research council (VR).
Study sponsor: UCR. ARO: UCR

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R-RCTs in Sweden (other areas)

SPIRRIT HFpEF (n=3200) Spironolactone for HFpEF — *Ongoing*
Clinical registry: SwedeHF
Funding: Swedish Heart and lung foundation. NIH, Erling Persson, Swedish Research council (VR),
Study sponsor: UCR. ARO: UCR

TIMING (n=3000) Time point for NOAC treatment after ischemic stroke in atrial fibrillation — *Ongoing*
Clinical registry: Swedish Stroke Registry
Funding: Swedish Research council (VR), Study sponsor: UCR. ARO: UCR

ABC AF (n=6500) ABC-risk score based treatment strategies in patients with AF — *Planned*
Clinical registry: AURICULA
Funding: Swedish Foundation for Strategic Research, Sw Heart-Lung Foundation, Roche Diagnostics.
Study sponsor: UCR

SWEDEPAD (N=2400) Drug Elution trial in Peripheral Arterial Disease, — *Ongoing*
Clinical registry: SwedVasc - Swedish vascular surgery registry
Funding: Sw Research council. Study sponsor: Göteborg University. ARO: UCR

Swedegraft (n=800) Patency of vein grafts for CABG surgery evaluated by coronary CT — *Soon to start*
Clinical registry: Swedeheart
Funding: Swedish Heart and lung foundation, Swedish Research council (VR),
Study sponsor: UCR. ARO: UCR

SLITS (n=2507) Closure of the meso-defect at gastric by pass operation — *Completed*
Clinical registry: SOREG
Funding: Örebro County Council, Stockholm City Council, and the Erling-Persson Family Foundation
Sponsor: Örebro University

BEST (N=4000) Gastric by pass vs sleeve operation in obesity surgery — *Ongoing*
Clinical registry: SOREG
Study sponsor: Göteborg University

SWEPIS (n=10 000) Post-term Induction of labour — *Ongoing*
Clinical registry: Pregnancy Register and Swedish Neonatal Q registry
Study sponsor: Göteborg University

TACSI (n=2048) Ticagrelor and ASA vs. ASA alone after CABG in patients with ACS — *Planned*
Clinical registry: Heart surgery/ Swedeheart
Funding: Swedish Research council (VR).
Study sponsor: Göteborg University. ARO: UCR

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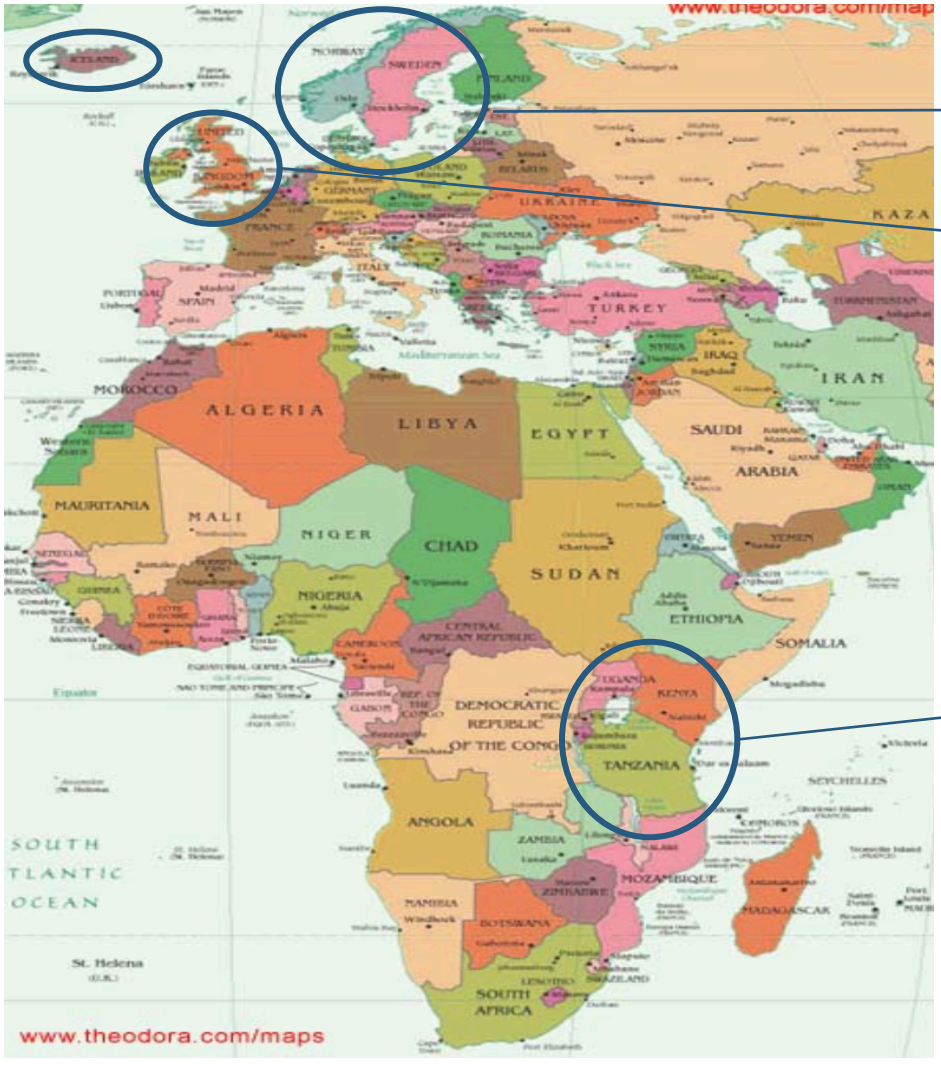
Next steps

- National RRCT technical framework established Q3 2018, developed with support from Clinical Studies Sweden/Swedish Research Council
- RRCTs in other health areas and quality registers
- Hybrid RRCTs utilizing registers, when available, but traditional eCRF/EDC systems in other settings/countries
- International RRCT using common platforms
- Decision support tools integrated in RRCT
- Collaboration with pharma industry using RRCT
- Improved automated follow-up with data public registers
- Electronic health records instead of clinical registers?



SWEDEHEART
(Tomas Jernberg)

UK-HEART
(NICOR)

AFRICAHEART
(Stefan Thelin)

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Califf: Leveraging Real World Evidence is 'Top Programmatic Priority' for FDA

Posted 11 May 2016

By Michael Mezher

The "top programmatic priority" for the US Food and Drug Administration (FDA), under Commissioner Robert Califf, is to leverage real world evidence from the healthcare system to inform FDA decision making, he told participants at the Food and Drug Law Institute's annual conference last week.

While Califf said his first priority as commissioner is to strengthen FDA's workforce, that stronger workforce will be critical to achieving FDA's goals in specific program areas such as real world evidence.

Specifically, Califf said he wants to see FDA develop a system for "[real world] evidence generation that can meet the demands of the next few decades."

Randomized trials conducted in the context of clinical practice, often called a pragmatic clinical trial, may be the most important source of knowledge in the future

Robert M Califf, Commissioner
U.S Food and Drug Administration
Honorary doctor of Medicine
Uppsala University 2017

PERSPECTIVES

OPINION

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

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

Abstract | Randomized clinical trials provide the foundation of clinical evidence to guide physicians in their selection of treatment options. Importantly, randomization is the only reliable method to control for confounding factors when comparing treatment groups. However, randomized trials have limitations, including the increasingly prohibitive costs of conducting adequately powered studies. Local and national regulatory requirements, delays in approval, and unnecessary trial processes have led to increased costs and decreased efficiency. Another limitation is that clinical trials involve selected patients who are treated according to protocols that might not represent real-world practice. A possible solution is registry-based randomized clinical trials. By including a randomization module in a large inclusive clinical registry with unselected consecutive enrolment, the advantages of a prospective randomized trial can be combined with the strengths of a large-scale all-comers clinical registry. We believe that prospective registry-based randomized clinical trials are a powerful tool for conducting studies efficiently and cost-effectively.

James, S. *et al. Nat. Rev. Cardiol.* **12**, 312–316 (2015); published online 17 March 2015;
doi:10.1038/nrcadio.2015.33

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Information and login

SWEDEHEART:
www.ucr.uu.se/swedeheart

RIKS-HIA:
www.ucr.uu.se/swedeheart/start-riks-hia

SEPHIA:
www.ucr.uu.se/swedeheart/start-sephia

SCAAR:
www.ucr.uu.se/swedeheart/start-scaar

Swedish Heart Surgery Registry:
www.ucr.uu.se/swedeheart/start-hjaertkirurgi

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