Changing the paradigm: registry-based randomized trials

Stefan James

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Scientific director Uppsala Clinical research center, Uppsala University

Senior Interventional Cardiologist Uppsala University Hospital

President Swedish Cardiac society, Sweden

ORIGINAL CONTRIBUTION

Which Treatment is Best for Whom? High-Quality Evidence is Scarce
< 15% of guideline recommendations supported by high quality evidence

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

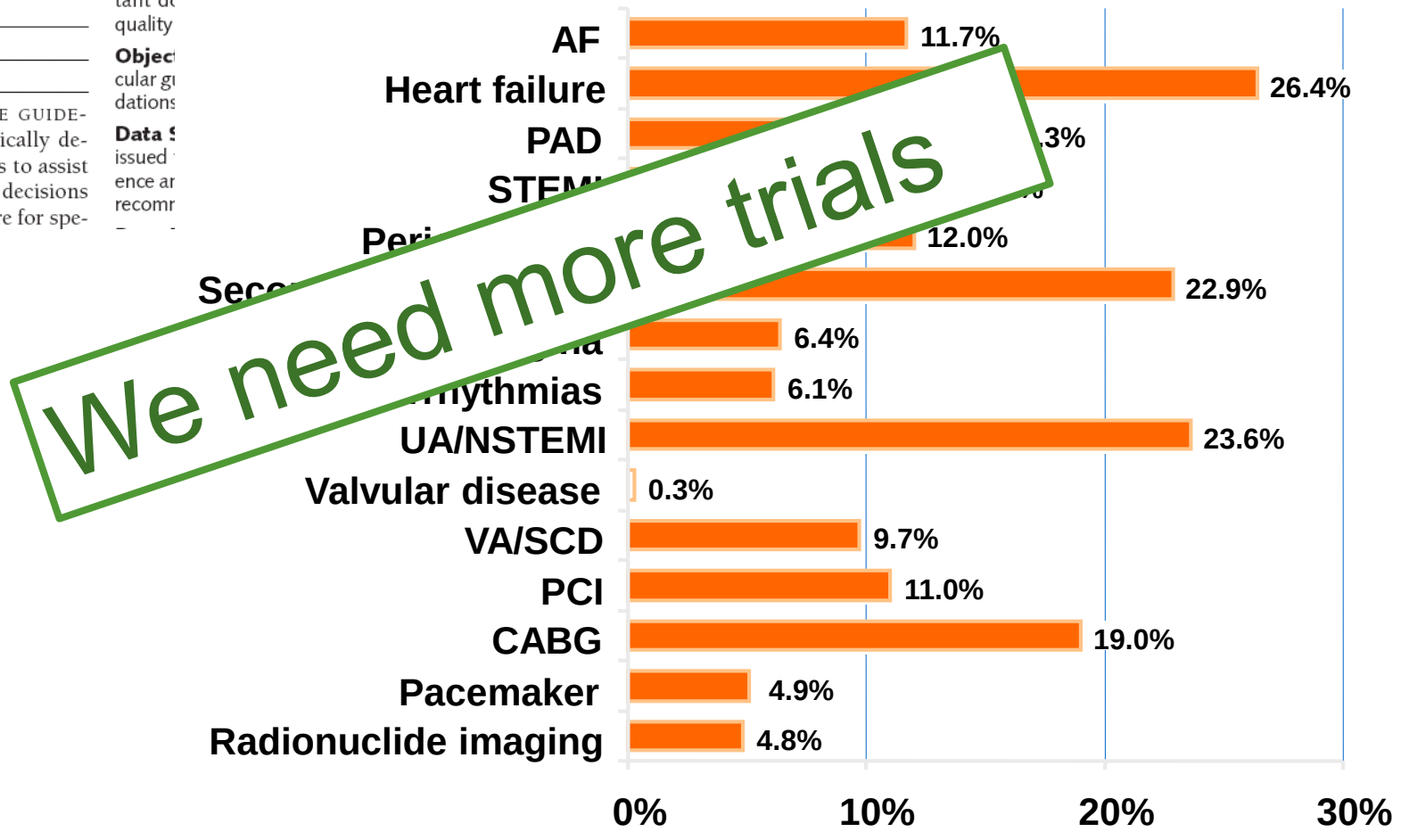
Pierluigi Tricoci, MD, MHS, PhD
Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality

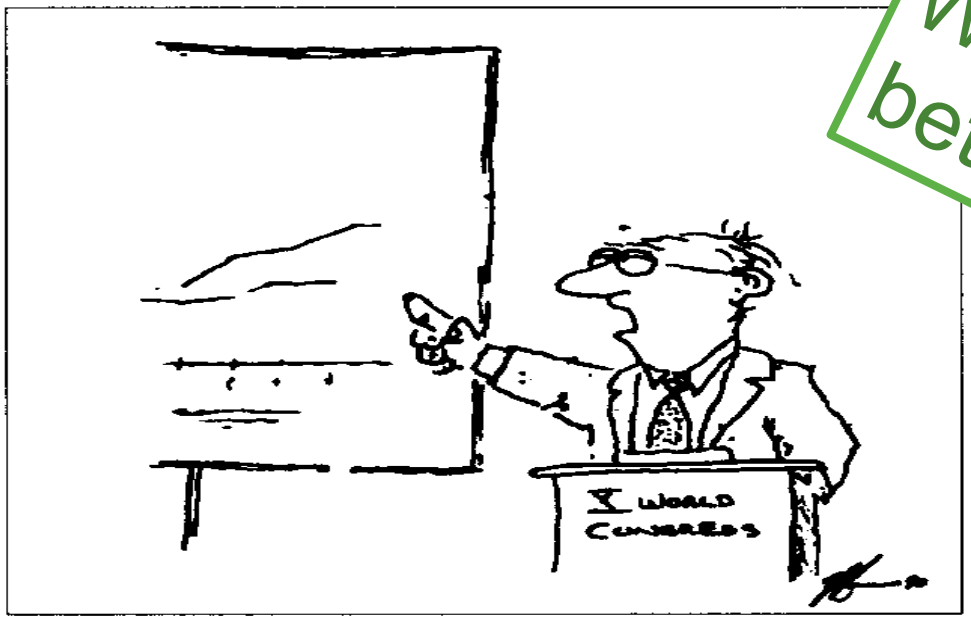
Objec cular gu dations

Data S issued ence ar recomm

CLINICAL PRACTICE GUIDELINES are systematically developed statements to assist practitioners with decisions about appropriate health care for spe-



We need faster and better designed trials



"This randomized, double-blind trial involving over 20,000 patients was conducted over a 10 year period. Unfortunately we've forgotten why."

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Cost of doing trials

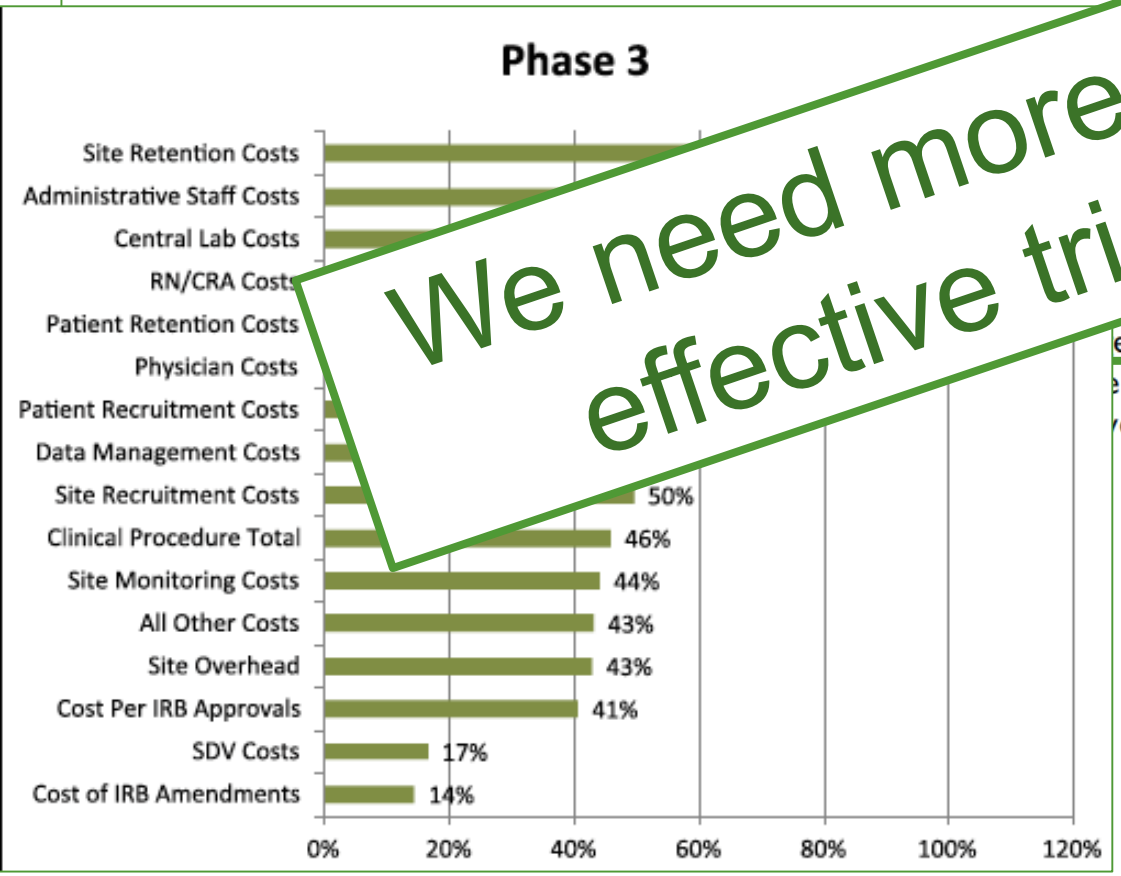
Regulation and Policy

CLINICAL TRIALS

Clinical Trials
2016, Vol. 13(2) 117–126

10.1177/1740774515625964

Key cost drivers of pharmaceutical clinical trials in the United States



We need more cost effective trials

cost of a Phase I
(immunomodulation),
. A Phase 2 study cost from
a Phase 3 study cost ranged from
e. Across all study phases and excluding esti-
top three cost drivers of clinical trial expen-
e staff costs (11%–29% of total), and site

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Pragmatic Clinical Tri

We need clinically relevant trials

	Traditional Clinical trial	Pragmatic Clinical trial
Research question	Is the treatment effective under ideal circumstances	Is the treatment effective in clinical reality
Aim	Biological or mechanistic	What matters to patients and decision makers
Patient selection	Narrow	Broad, representative
Endpoints	Surrogate, mechanistic	Clinically important
Goal	Deeper scientific understanding	Treatment choice

"Some degree of pragmatism should be included in every clinical trial"

Bob Harrington, Stanford

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Beautiful but expensive and cumbersome

Good enough

Simple, inexpensive but inapproprate

Usual Clinical Trial after Regulatory/FDA/Academic Interactions

Well planned and conducted pragmatic trial

Poorly planned pragmatic trial

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

Since 1947

540219-9750

Year/month/day-control

Used for all interaction with the society

Population registry

By the taxation authority

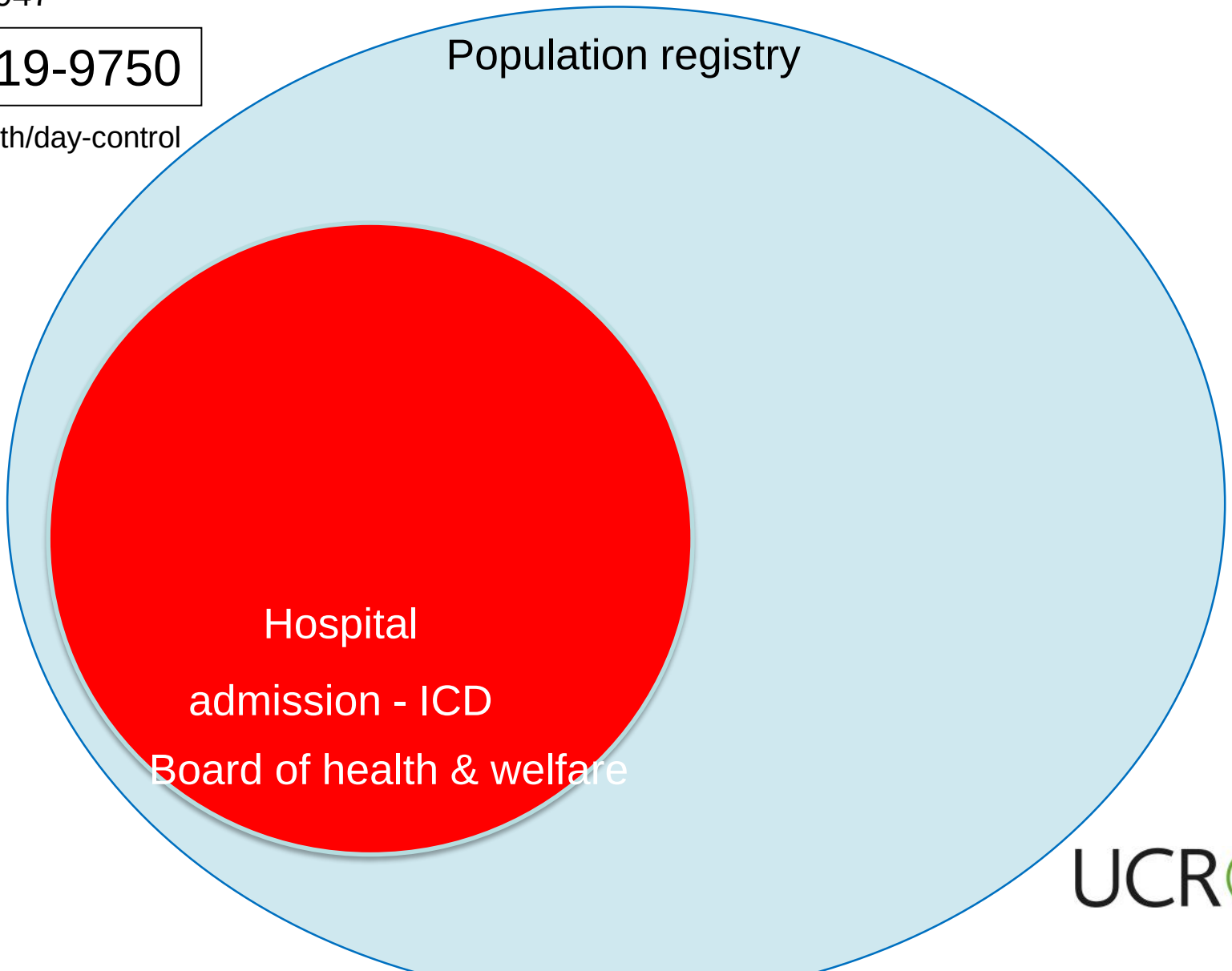
For all inhabitants

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

Since 1947

540219-9750

Year/month/day-control



A selection of mandatory Swedish national registries by The National Board of Health and Welfare

Health data registers:

Registry	Contents
Swedish Population Registry	Place of residency; country of own and parents' birth; marital status
Swedish Censuses	Socioeconomic group; education; income; sick leave
Swedish National Insurance Agency	Sick leave, pensions
Swedish Education Registry	Highest education
Swedish 9th Grade Registry	Junior high school grades
Swedish Multi-Generation Registry	Number of children and siblings; identity of parents if born after 1932
Swedish Medical Birth Registry (since 1973)	Numbers of pregnancies and births; pregnancy outcomes
Swedish Prescription Registry (since 2005)	Pharmacy-expedited drug prescriptions
Swedish In-Patient Registry (since 1987)	All diagnoses of all hospitalisations; surgical and other procedures
Swedish Cancer Registry (since the 50's)	All cancer diagnoses
Swedish Cause-of Death Registry (since 1749)	Causes of death, including conributing factors
Swedish Out-Patient Registries (since 2005)	Hospital-based -> mandatory; primary care -> voluntary

Social Services registers

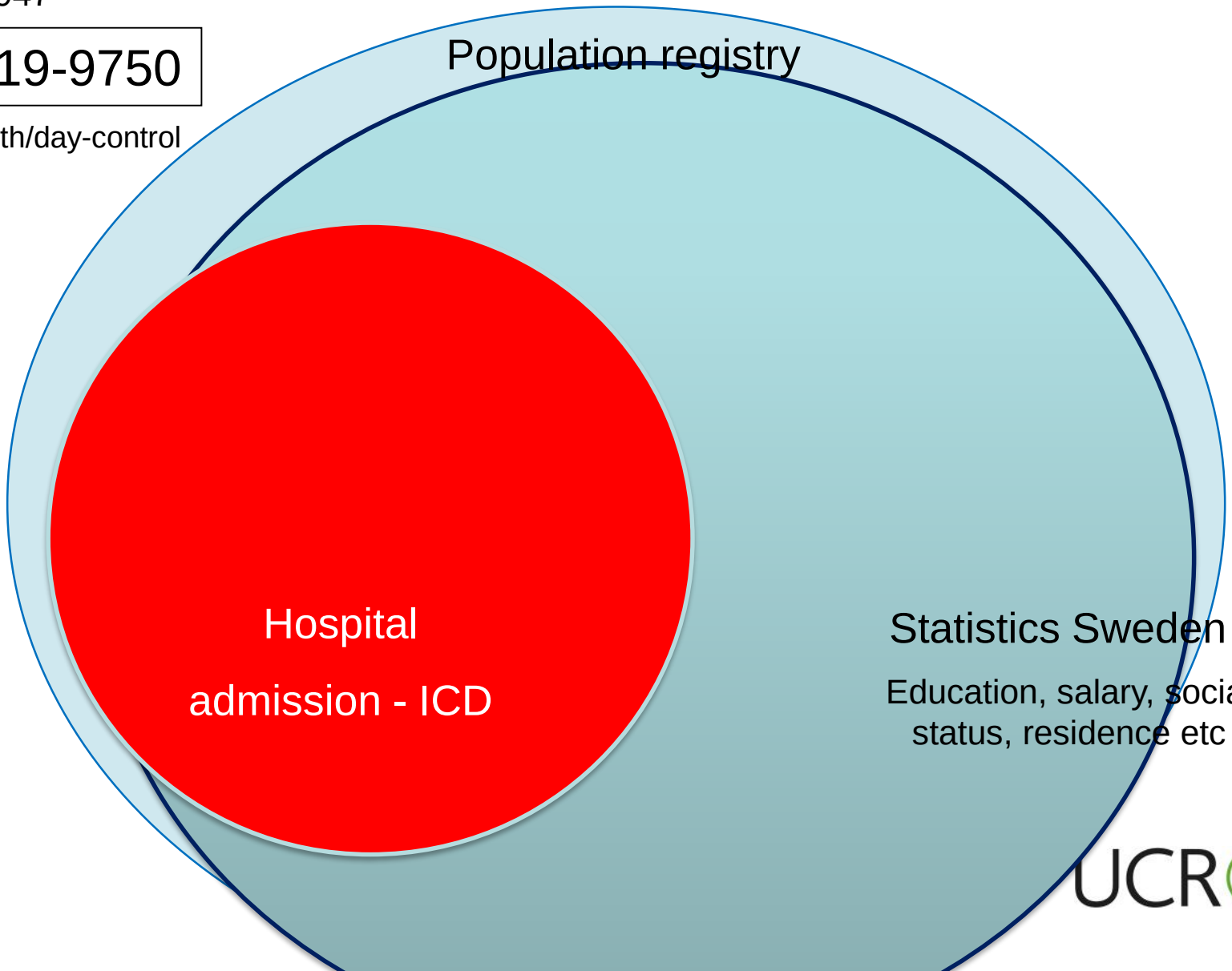
Social services to the elderly and functionally impaired (2007)
Persons with impairments – activities according to LSS (2004)
Social (financial) assistance (2012)

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

Since 1947

540219-9750

Year/month/day-control



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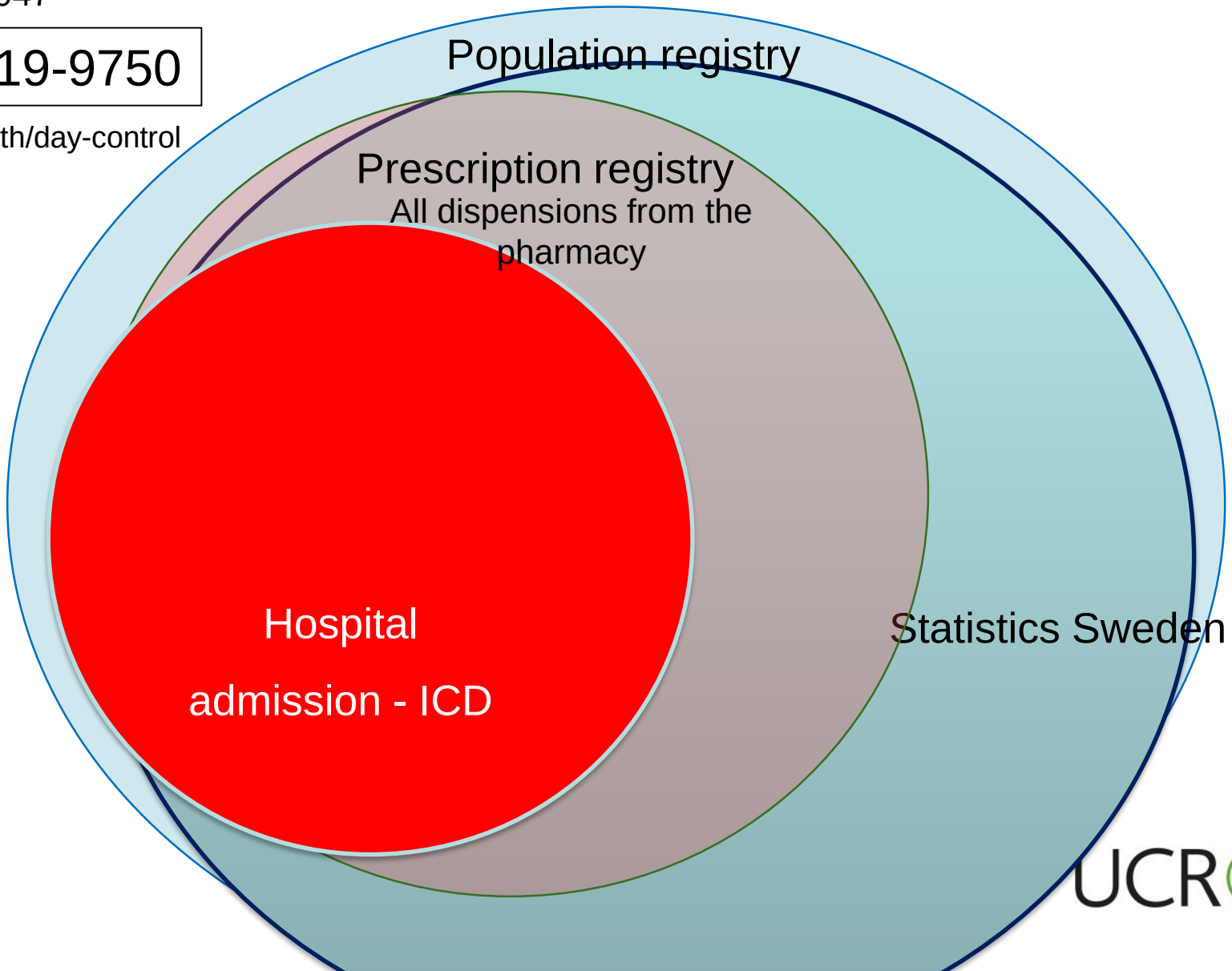

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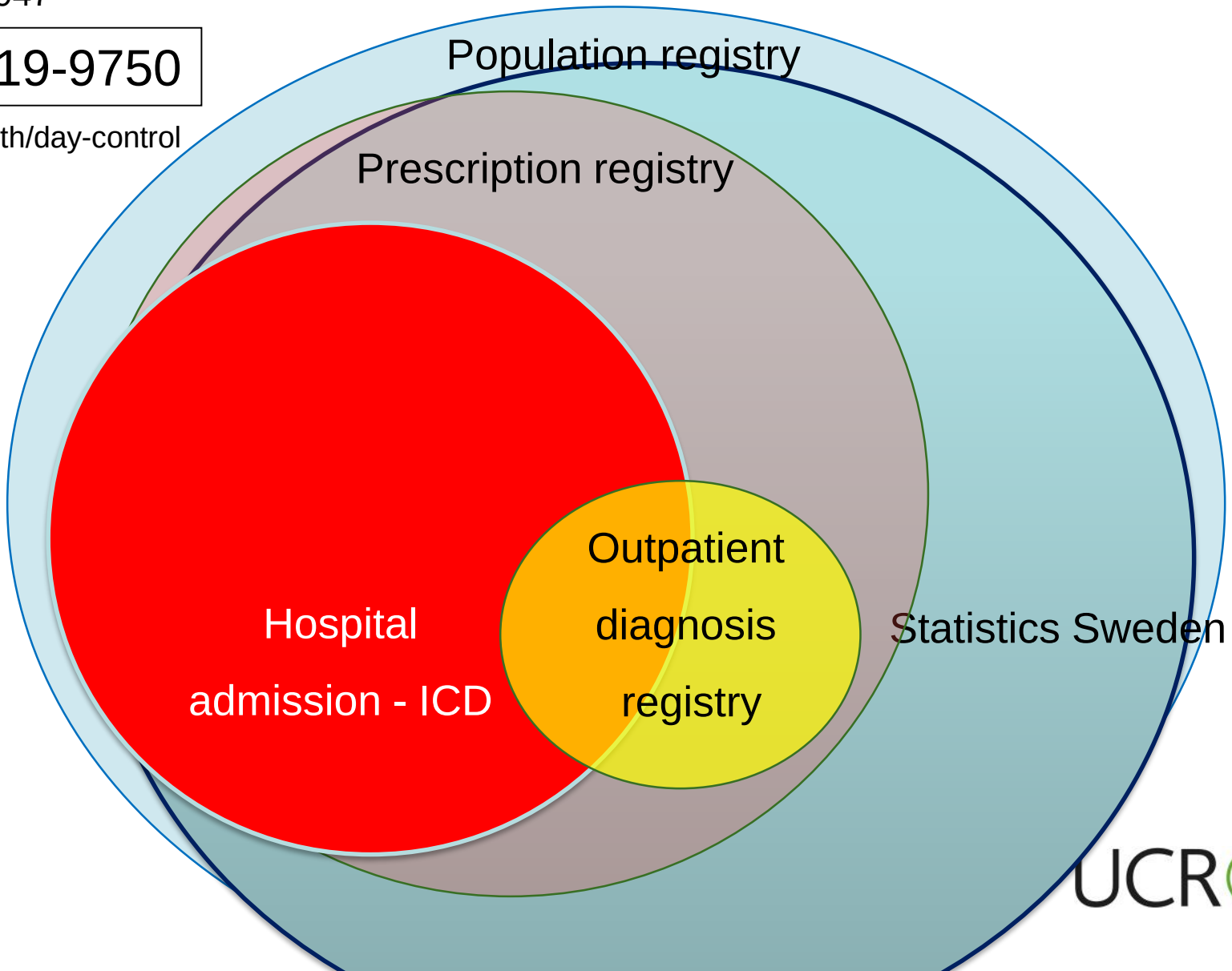

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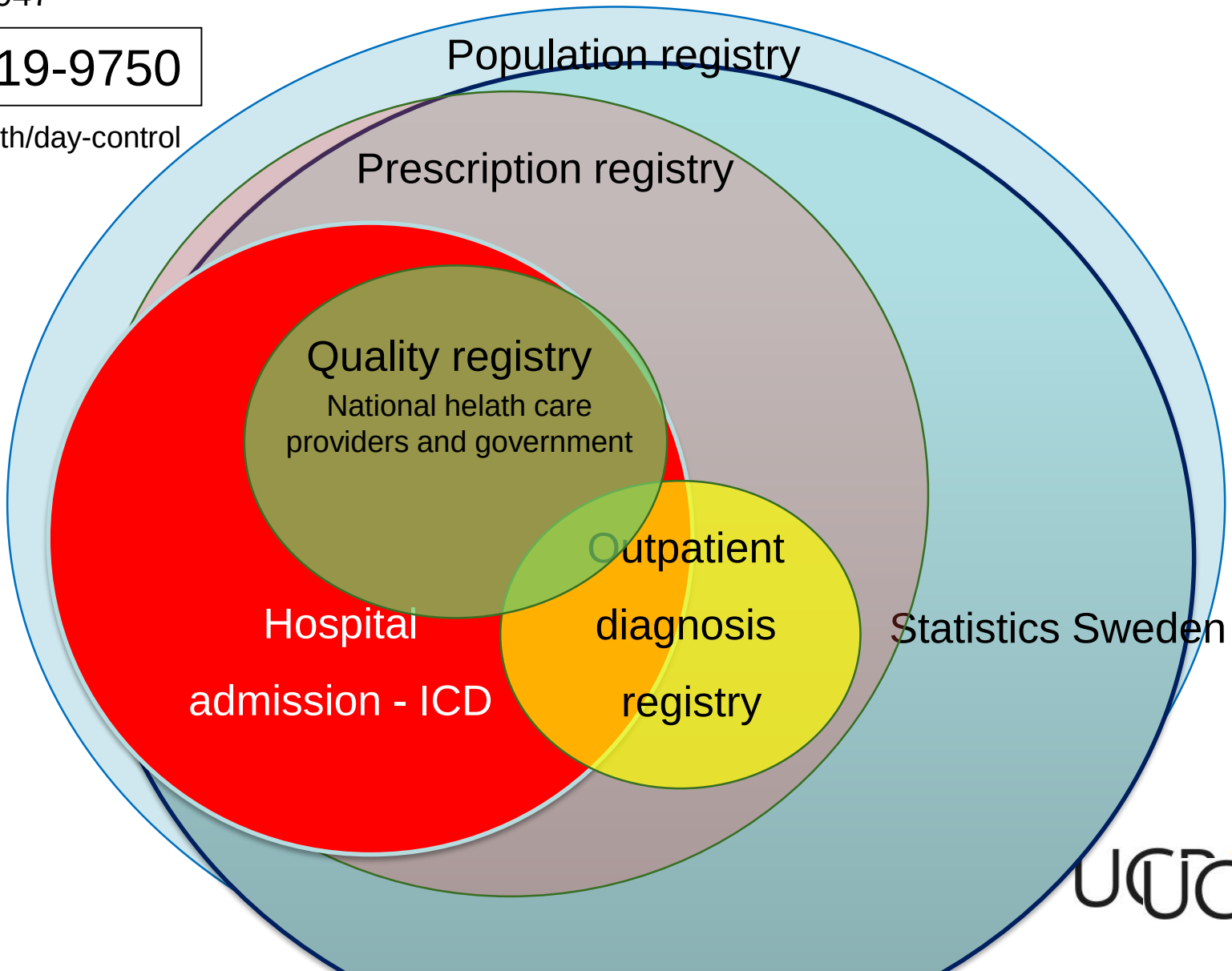

Sweden's > 100 quality registries

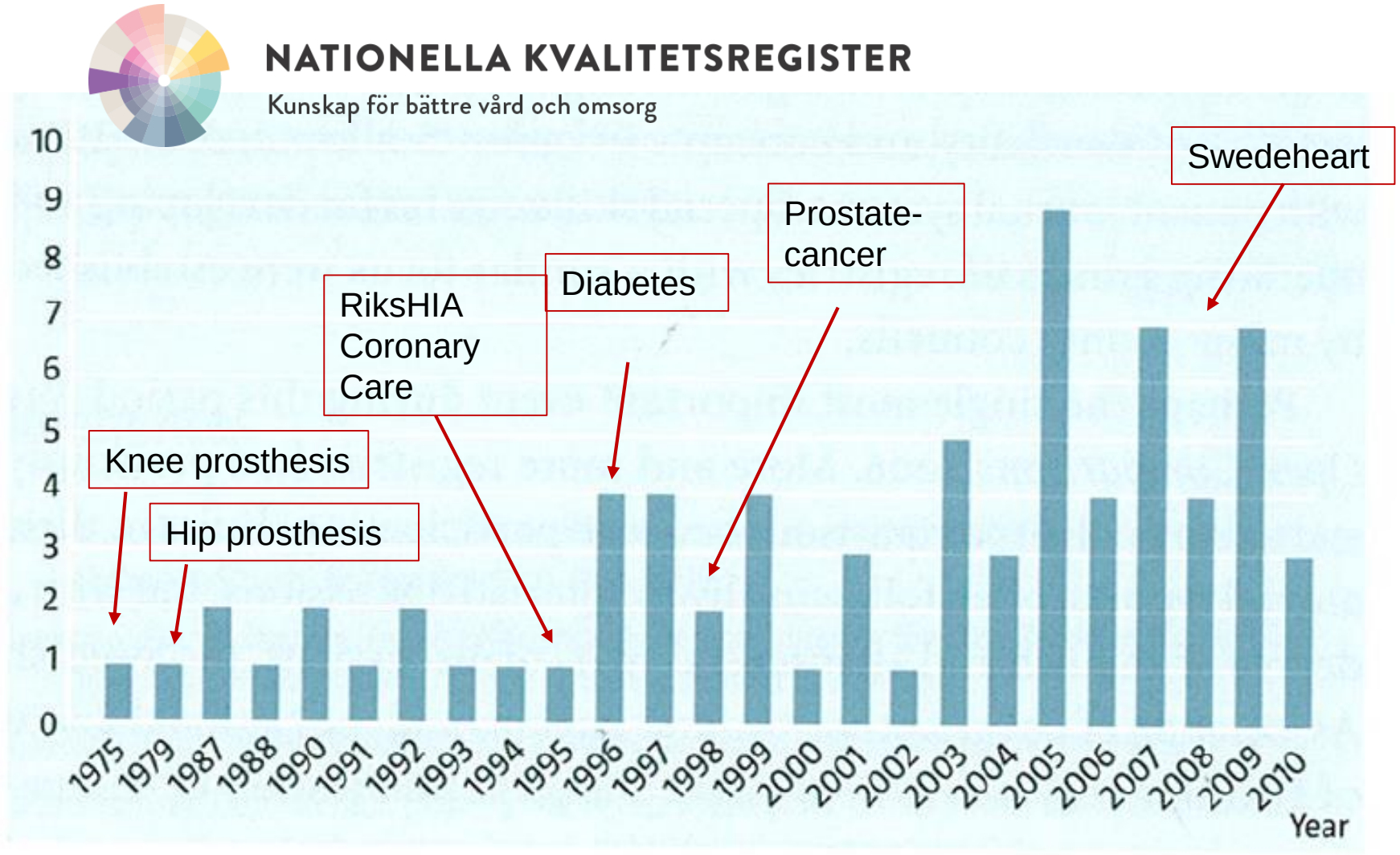

Figure 1. National Quality Registries by starting year. 2010 registries. Source: Applications for 2010 national quality registries.

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

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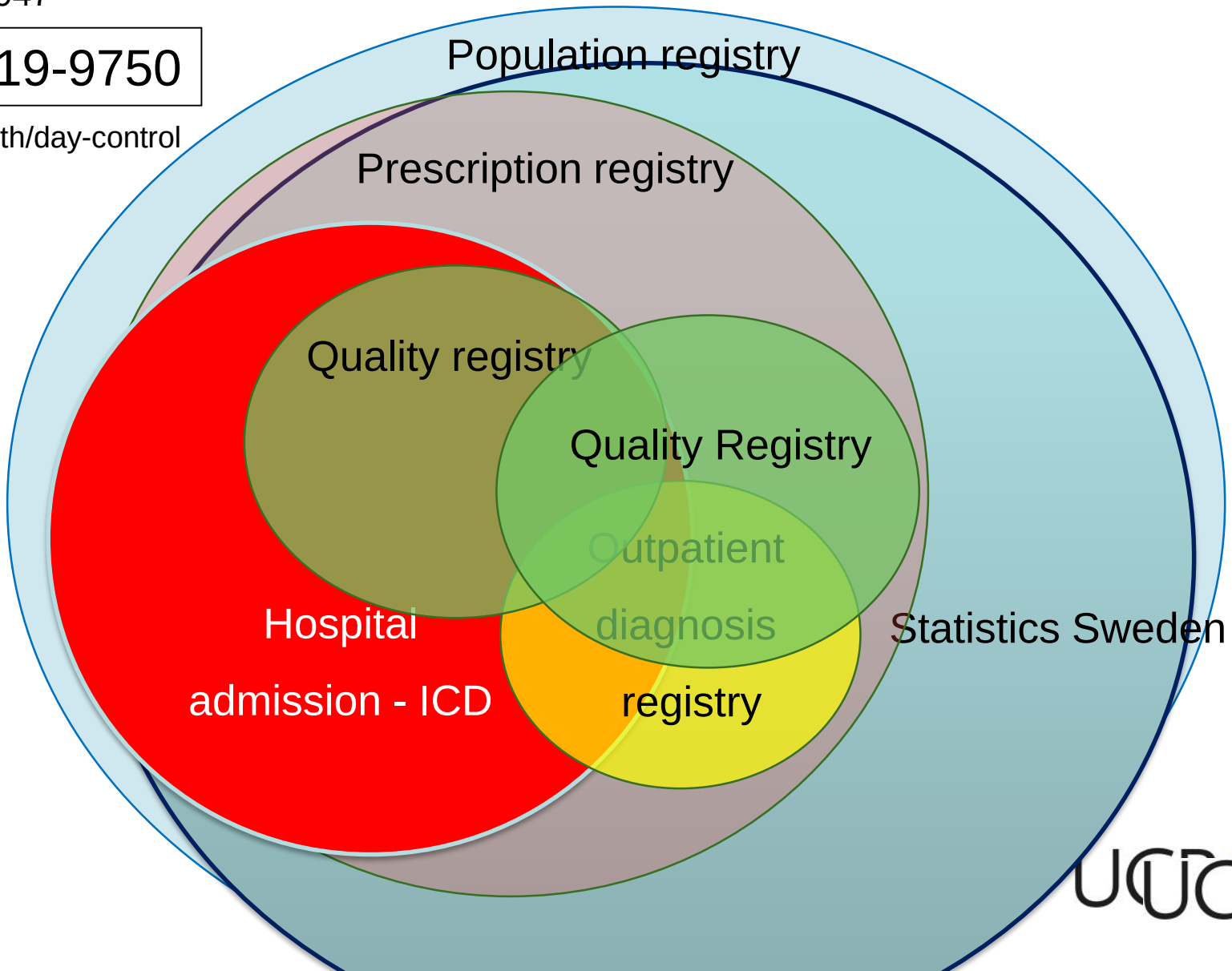
Year/month/day-control



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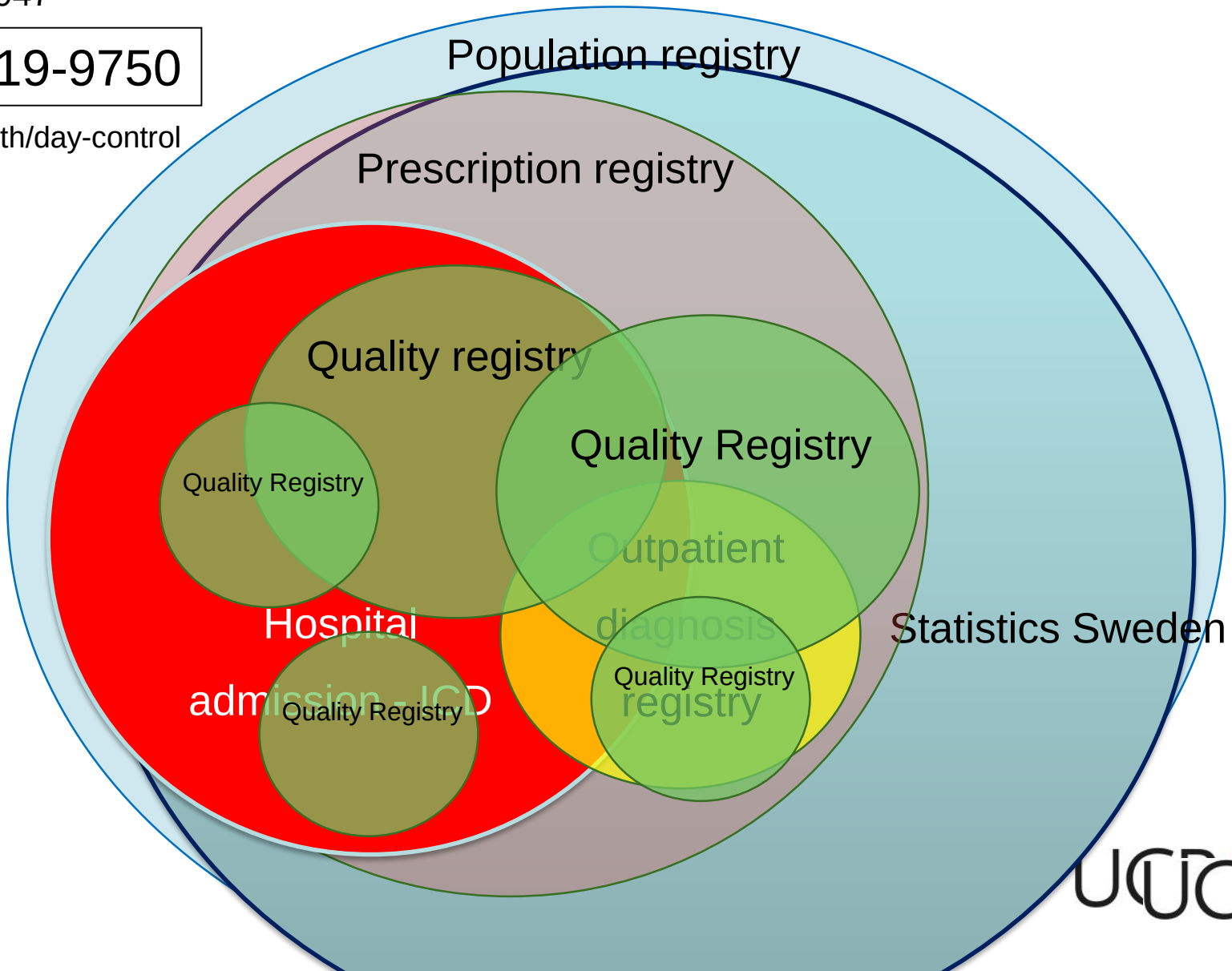

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Chair Tomas Jernberg

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, 90%
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.

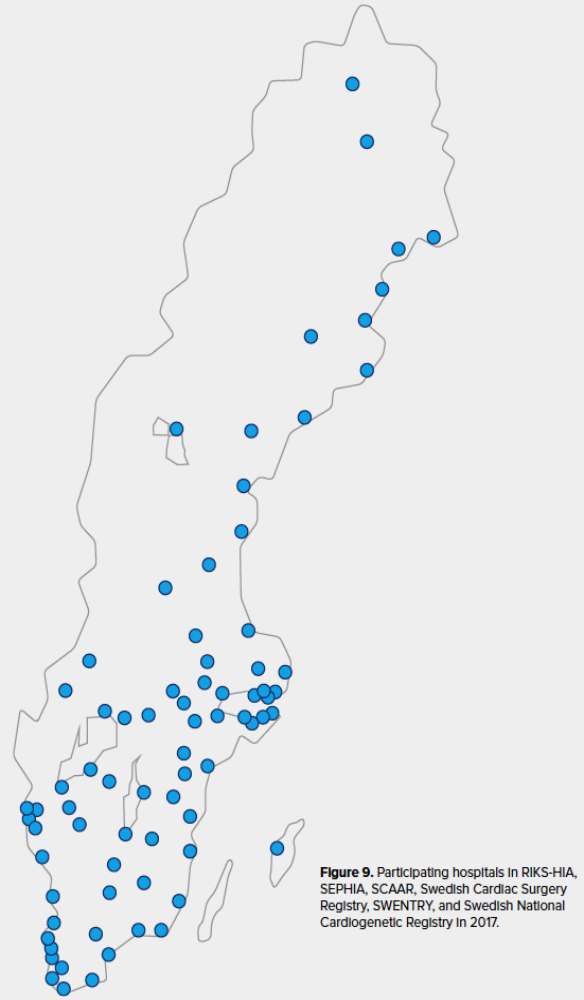


Figure 9. Participating hospitals in RIKS-HIA, SEPHIA, SCAAR, Swedish Cardiac Surgery Registry, SWENTRY, and Swedish National Cardiogenetic Registry in 2017.

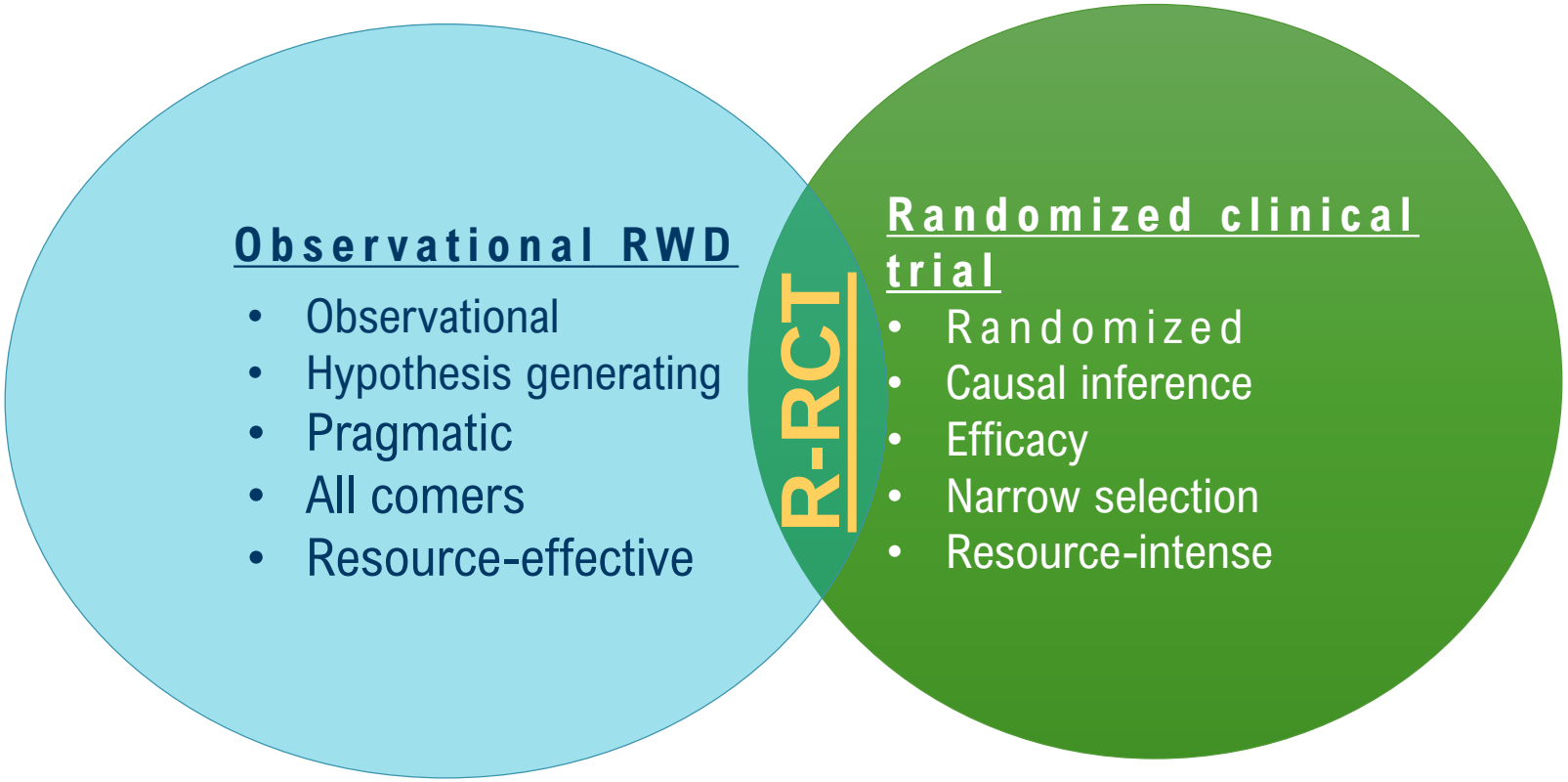
EuroHeart – The Project

EuroHeart is an ESC coordinated and sponsored programme that:

- Covers the common disease areas ACS-PCI, valve disease, heart failure and atrial fibrillation.
- Starts with development of standardised data sets and quality indicators for diseases and devices.
- During the pilot phase, it tests the system in 2 – 4 countries.
- Will develop a data science centre localised with options for remote data access.
- Will include representatives from the interested countries in the development and in all subcommittees.

Registry-based Randomized Clinical Trial - R-RCT

”A prospective randomized trial that uses a clinical registry for one or several major functions for trial conduct and outcomes reporting” (*Uppsala Clinical Research definition)*



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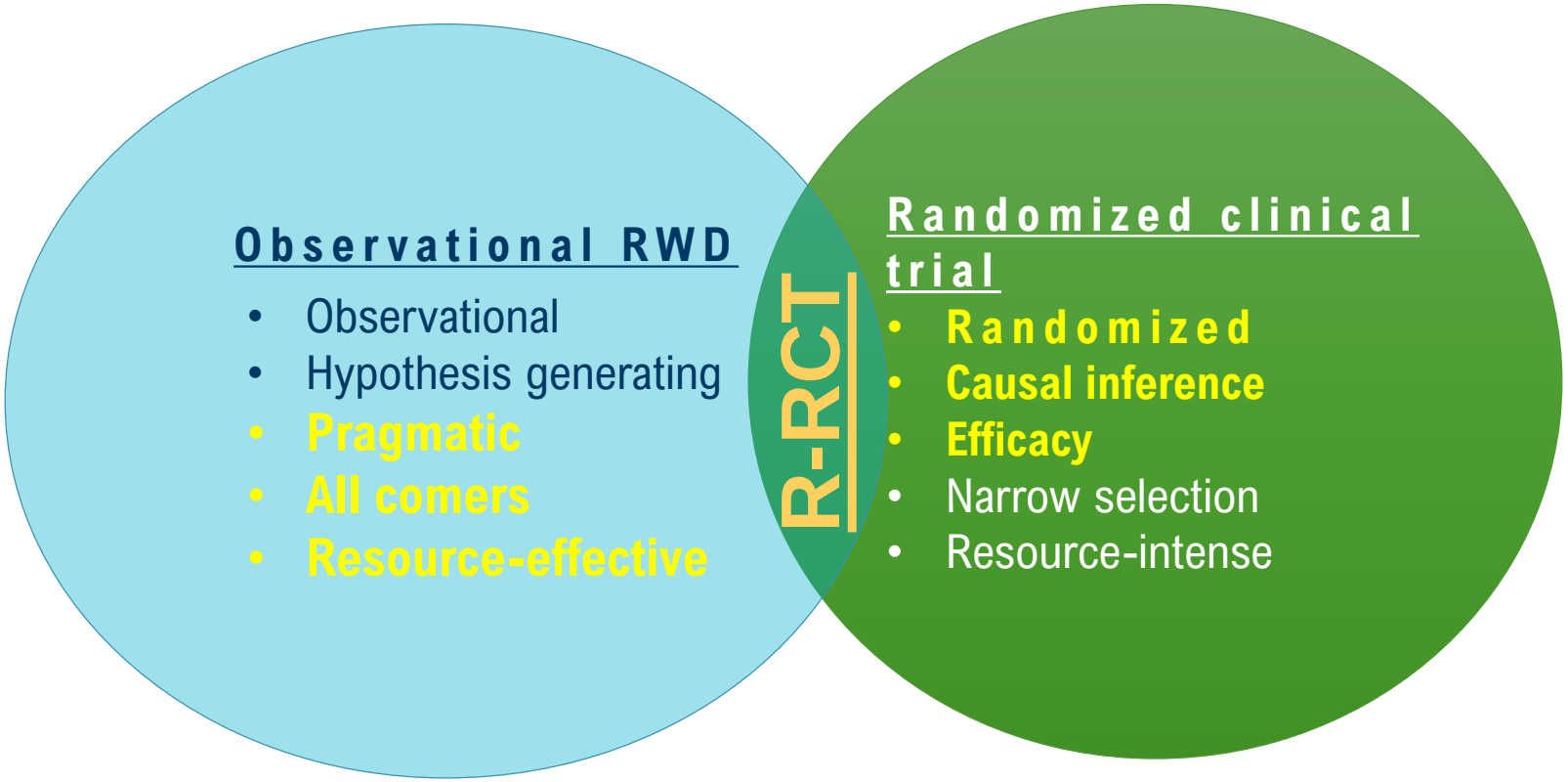

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Register based Randomized Clinical trials- R-RCT

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

PERSPECTIVES

OPINION

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

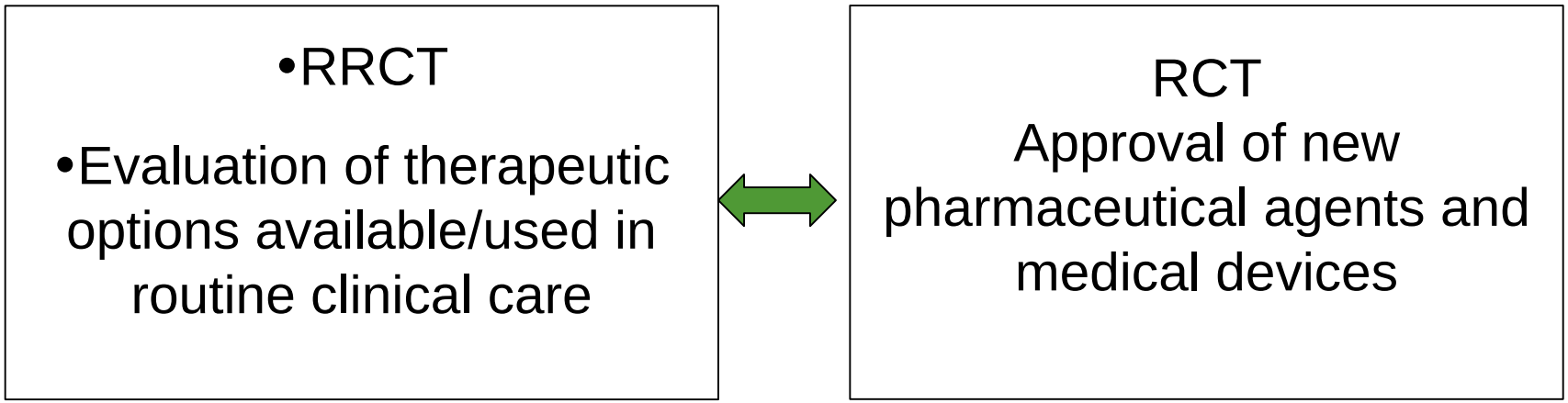
Stefan James, Sunil V. Rao and Christopher B. Granger

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/nrcardio.2015.33

R-RCT vs. classical RCT

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



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Pre-requisits for modern R-RCTs

Registry	Contents
Swedish Population Registry	Place of residency; country of own and parents' birth; marital status
Swedish Censuses	Socioeconomic group
Swedish National Insurance Agency	Sick leave, pensions
Swedish Education Registry	Highest education
Swedish 9th Grade Registry	Junior high school gra
Swedish Multi-Generation Registry	Number of children a
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Swedish Cancer Registry (since the 50's)	All cancer diagnoses
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Swedish Out-Patient Registries (since 2005)	Hospital-based -> mandatory; primary care -> voluntary

European Heart Journal (2009) **30**, 2165–2173
doi:10.1093/eurheartj/ehp299

CardioPulse

eden's new online cardiac
its kind

WEDEHEART is unique because
mmediate feedback, says Ulf
rofessor of cardiology and Senior
ist, Department of Cardiology,
University Hospital, Linköping, Sweden, and President of
SWEDEHEART.

What can a registry do?

Some or all parts of trial

- Identify patients
- Randomize
- Collect baseline and procedure characteristics (CRF)
- Assist with and collect consent forms
- Identify clinical endpoints (endpoint detection)
- Control clinical outcome events (adjudication, CEC)

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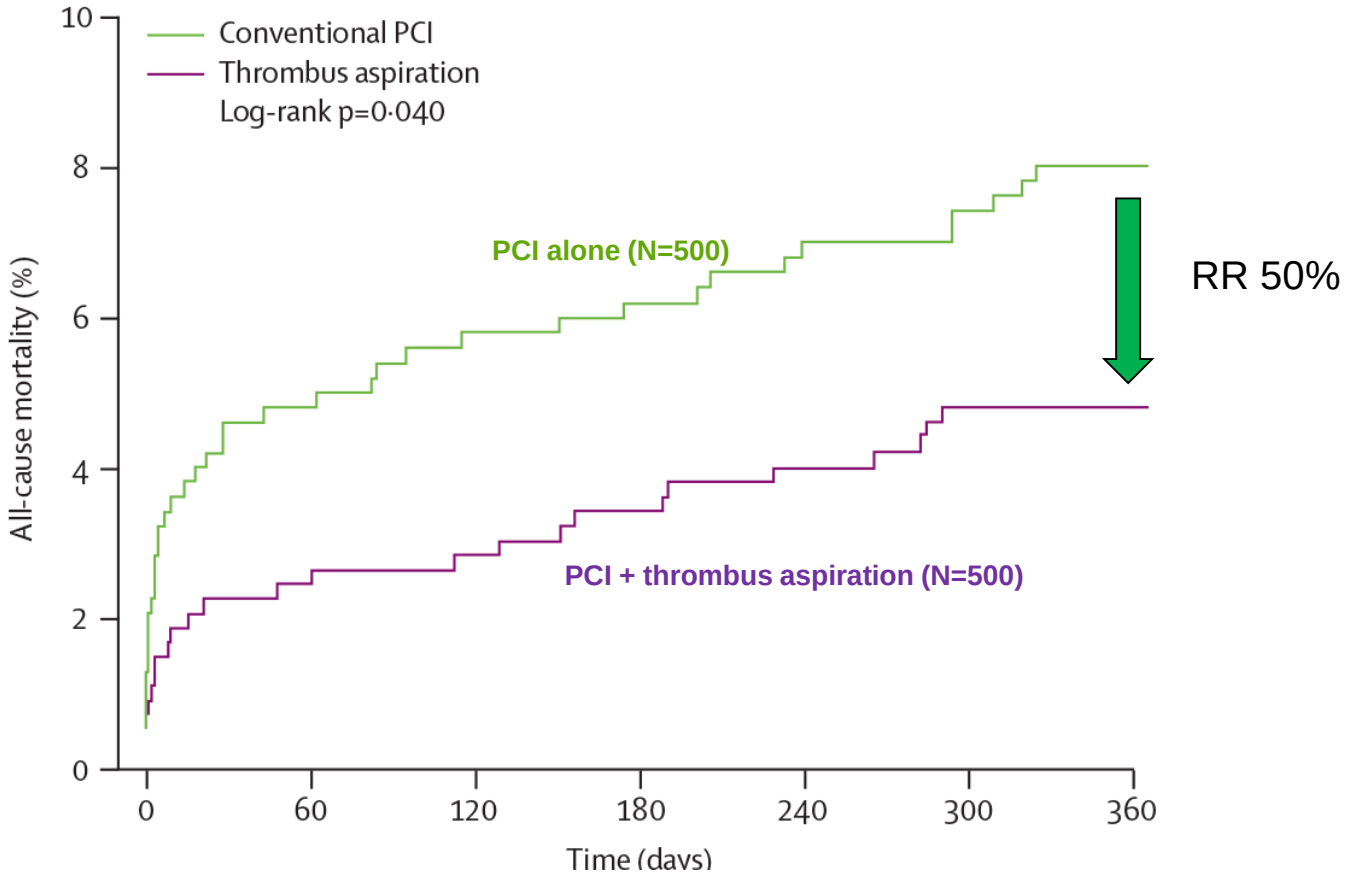
TASTE

Thrombus aspiration



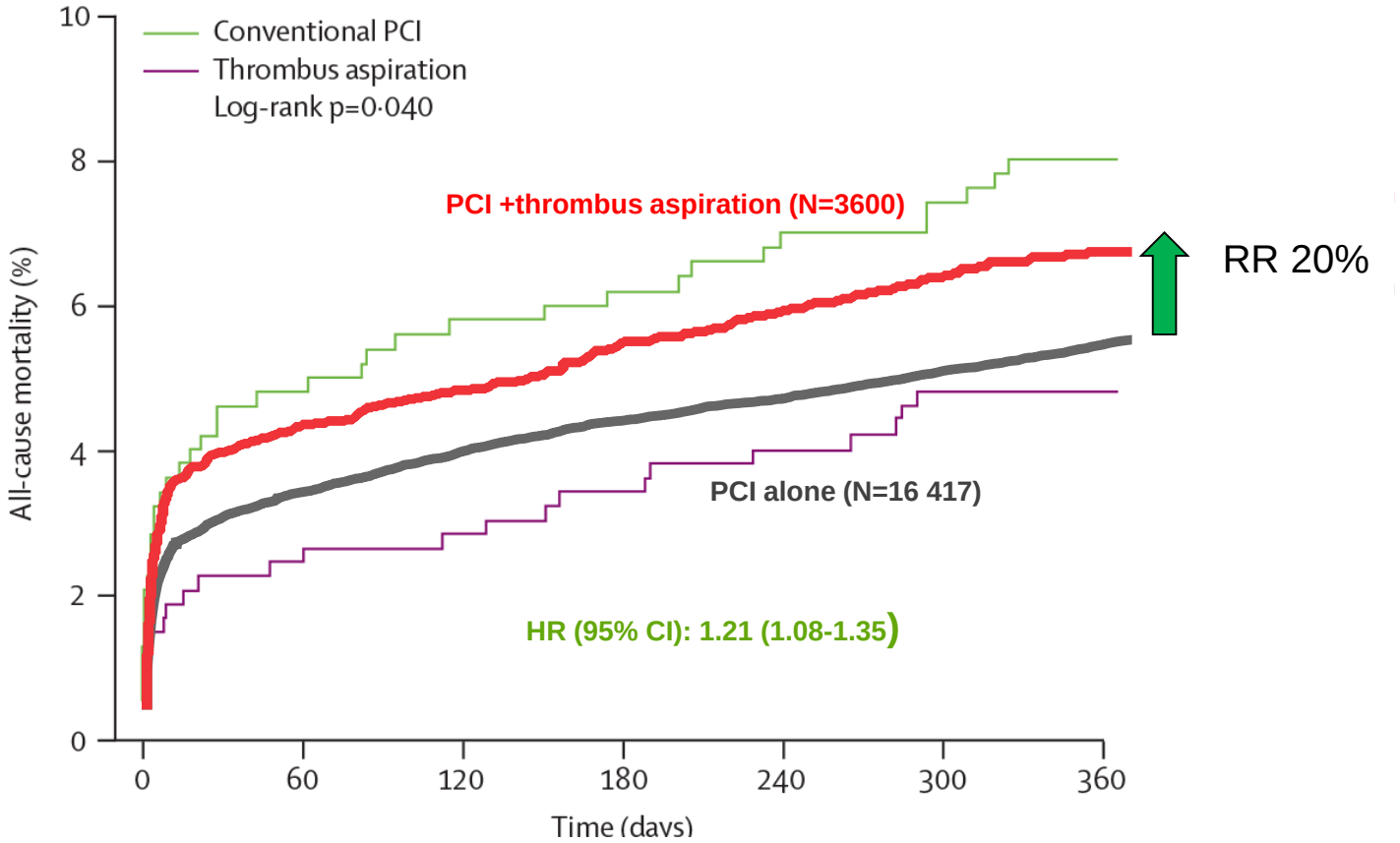
Vlaar, P.J. et al. The Lancet 2008; 371:1915-20

UCR

SWEDE HEART

TASTE

Thrombus aspiration



Vlaar, P.J. et al. The Lancet 2008; 371:1915-20

Fröbert, O. et al. Int J Cardiol. 2010; 145:572-3

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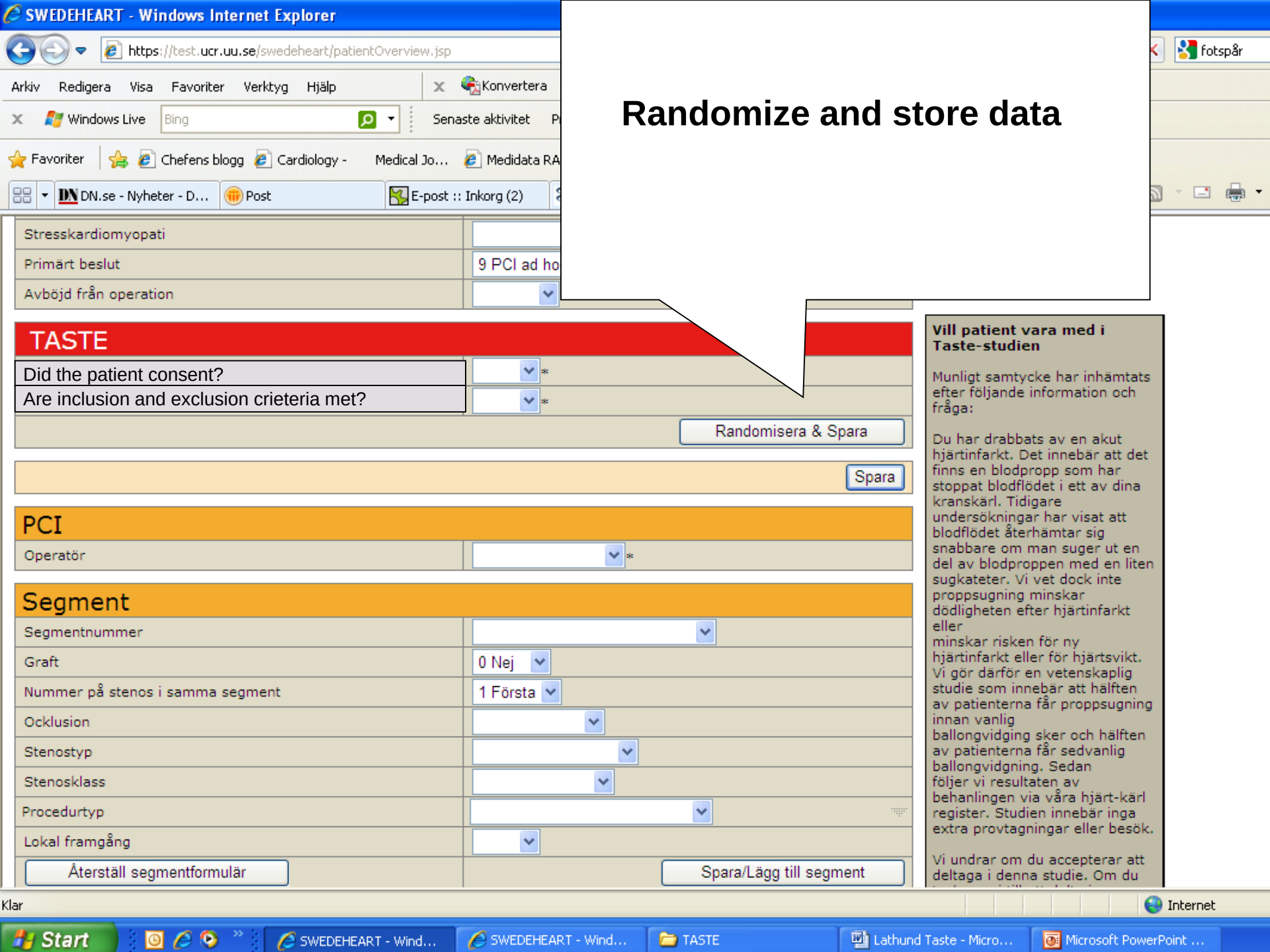
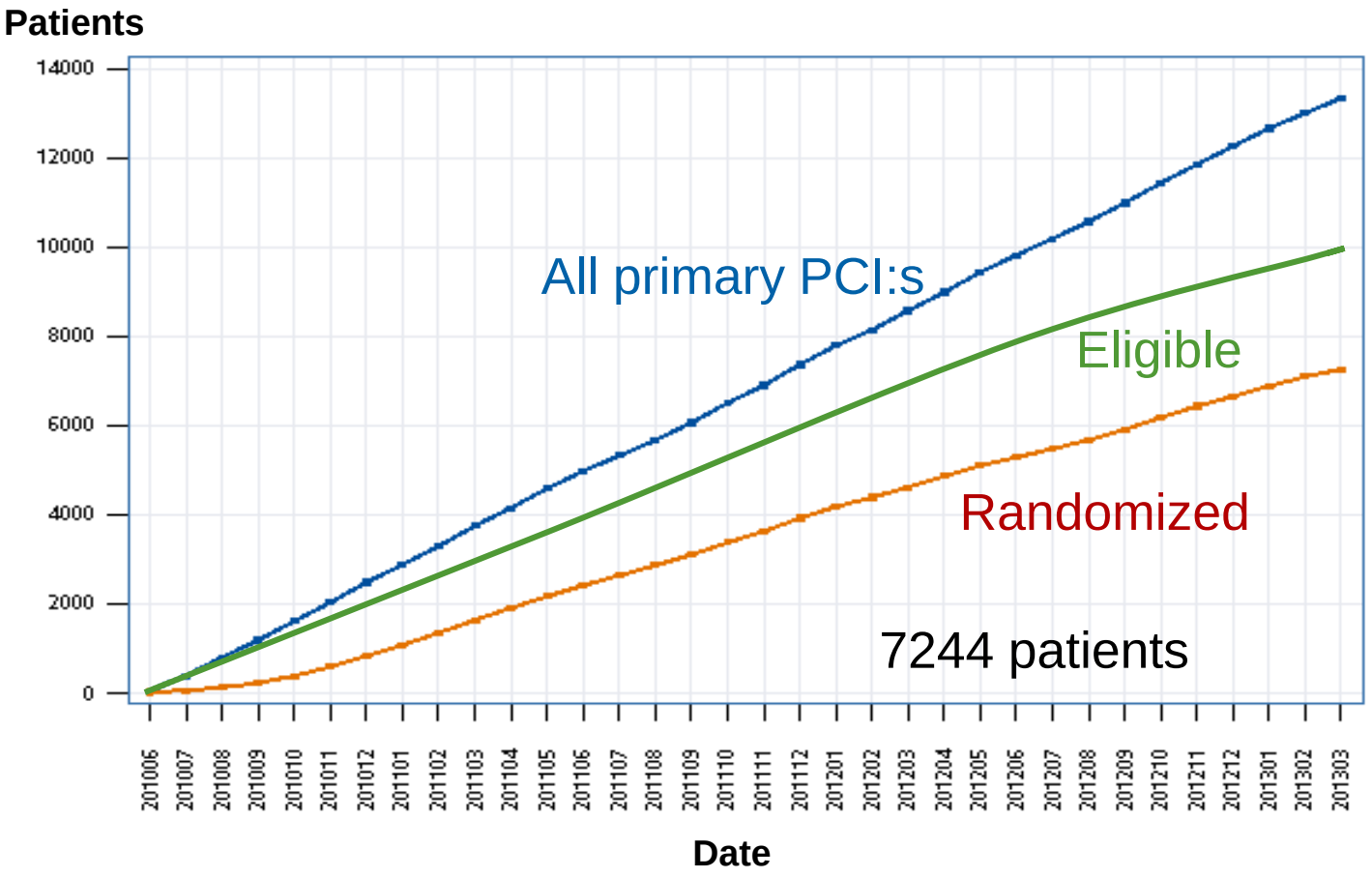

SWEDEHEART - Windows Internet Explorer
https://test.ucr.uu.se/swedeheart/patientOverview.jsp
Arkiv Redigera Visa Favoriter Verktyg Hjälp
Konvertera
Windows Live
Bing
Senaste aktivitet
Favoriter
Chefens blogg
Cardiology -
Medical Jo...
Medidata RA
DN.se - Nyheter - D...
Post
E-post :: Inkorg (2)
fotspår
Randomize and store data
Stresskardiomyopati
Primärt beslut
9 PCI ad ho
Avböjd från operation
TASTE
Did the patient consent?
Are inclusion and exclusion crieteria met?
Randomisera & Spara
Spara
PCI
Operatör
Segment
Segmentnummer
Graft
0 Nej
Nummer på stenos i samma segment
1 Första
Ocklusion
Stenostyp
Stenosklass
Procedurtyp
Lokal framgång
Återställ segmentformulär
Spara/Lägg till segment
Vill patient vara med i Taste-studien
Munligt samtycke har inhämtats efter följande information och fråga:
Du har drabbats av en akut hjärtinfarkt. Det innebär att det finns en blodpropp som har stoppat blodflödet i ett av dina kranskärl. Tidigare undersökningar har visat att blodflödet återhämtar sig snabbare om man suger ut en del av blodproppen med en liten sugkateter. Vi vet dock inte proppsugning minskar dödligheten efter hjärtinfarkt eller
minskar risken för ny hjärtinfarkt eller för hjärtsvikt. Vi gör därför en vetenskaplig studie som innebär att hälften av patienterna får proppsugning innan vanlig
ballongvidging sker och hälften av patienterna får sedvanlig ballongvidgning. Sedan följer vi resultaten av behanlingen via våra hjärt-kärl register. Studien innebär inga extra provtagningar eller besök.
Vi undrar om du accepterar att deltaga i denna studie. Om du
Klar
Internet
Start
SWEDEHEART - Wind...
SWEDEHEART - Wind...
TASTE
Lathund Taste - Micro...
Microsoft PowerPoint ...

TASTE

TASTE inclusion rate



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The simplest and most pragmatic design

TASTE

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Pragmatic Trials

Ian Ford, Ph.D., and John Norrie, M.Sc.

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.

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

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.

Registry based Patient Follow-up

STEMI Thrombectomy Story

TASTE

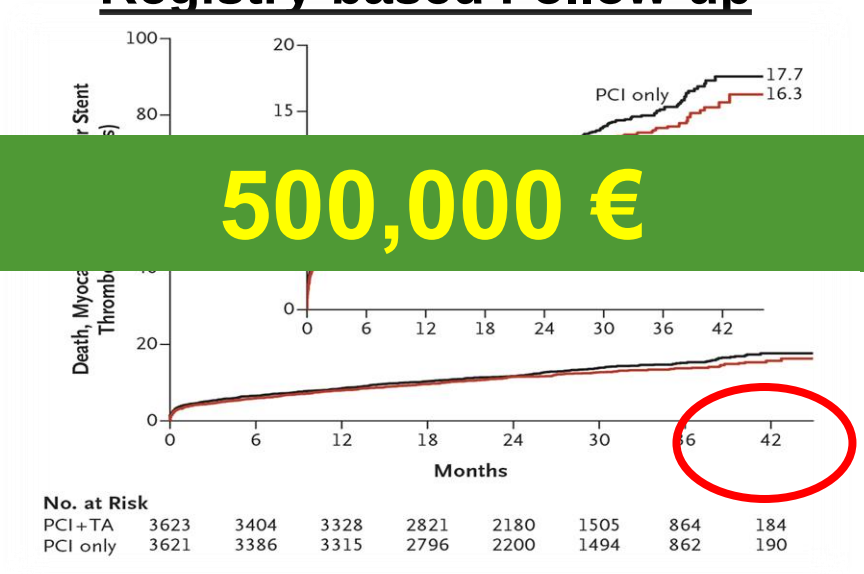
TOTAL

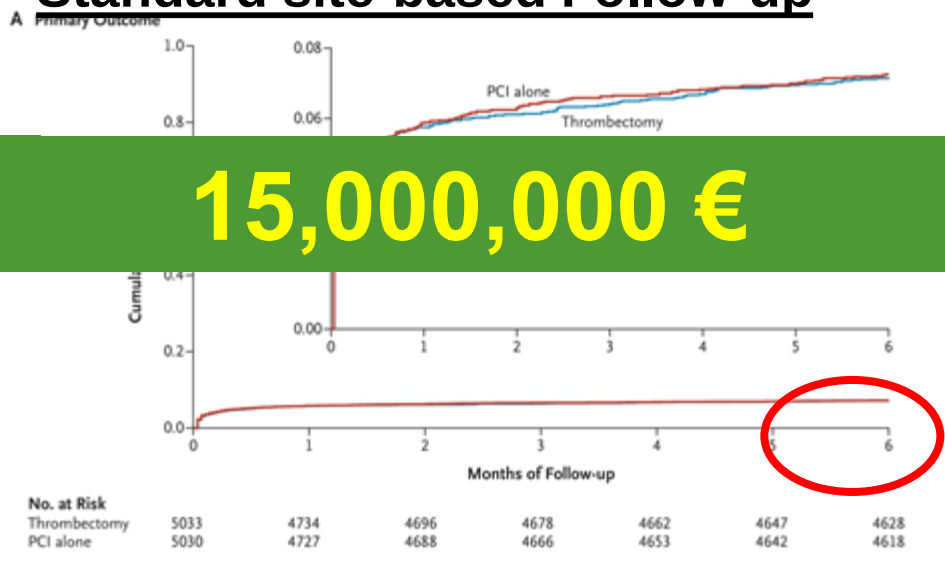
Registry-based Follow-up

Standard site-based Follow-up

500,000 €

15,000,000 €





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

1st patient: August 2010
87 centers
48 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

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

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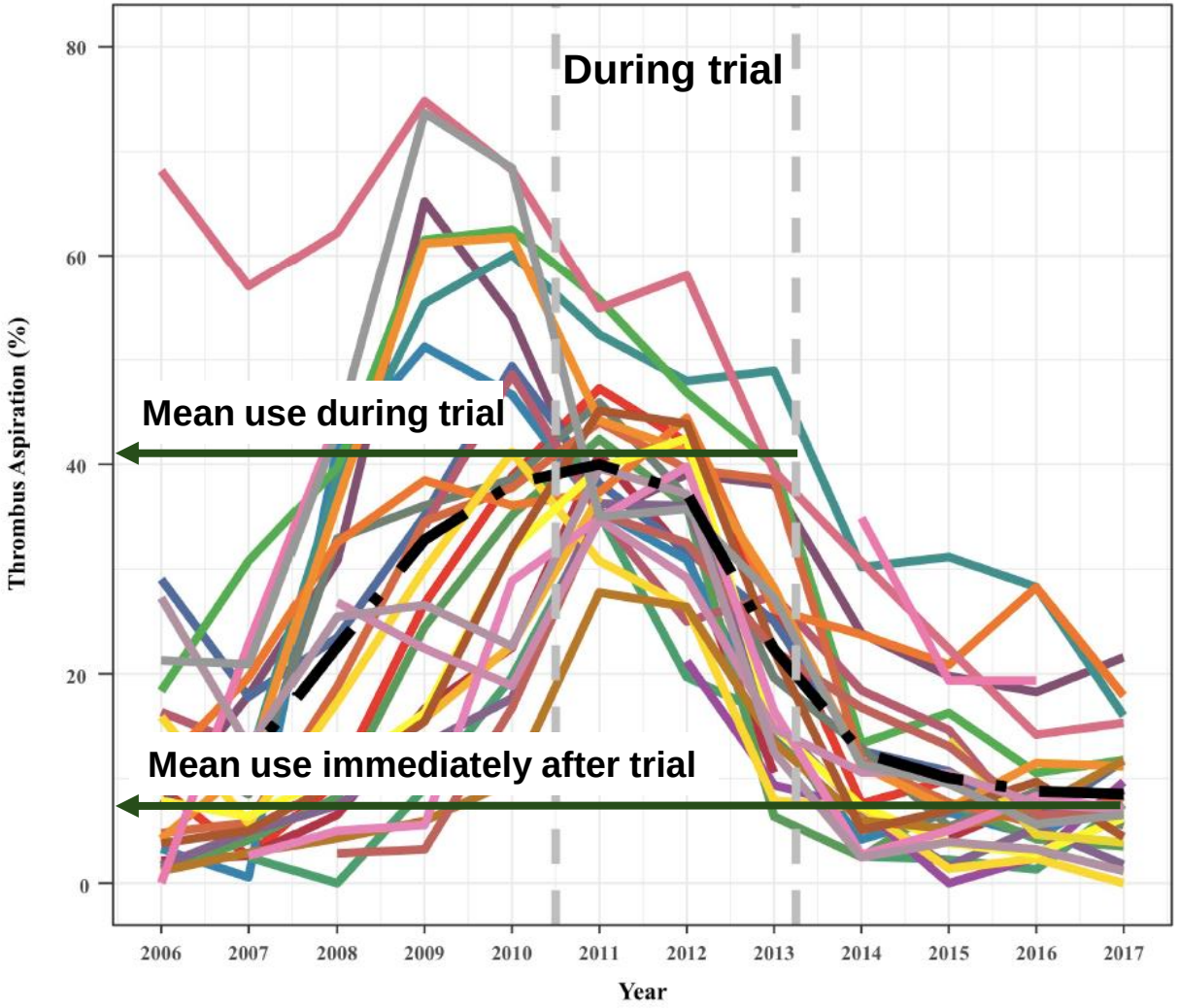
Guidelines

Title	Citation		Class	LOE
2012 ESC Guidelines ST-segment elevation myocardial infarction .	European Heart Journal 2012 Oct;33(20):2569-619	Routine aspiration should be considered	IIa	B
2014 ESC/EACTS guidelines on myocardial revascularization	Eur Heart J. 2014 Oct 1;35(37):2541-619	May be con red in selected pa s	IIb	A
2015 ACC/AHA focused update PPCI	JACC	Routine thro ectomy not useful	III	A
2015 ACC/AHA focused update PPCI	JACC	Selective ar ailout Thrombecto not well established	IIb	C
2017 ESC Guidelines ST-segment elevation myocardial infarction	European Heart Journal 2017	Routine use of thrombus aspiration is not recommended.	III	A

ORIGINAL ARTICLE

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

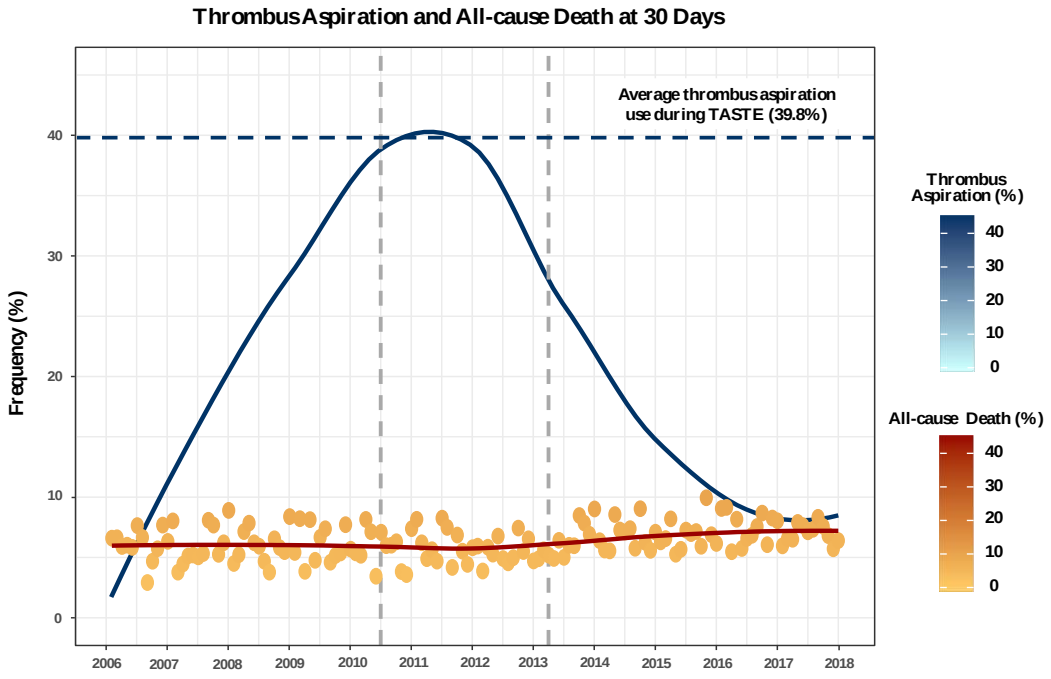
The TASTE Trial in Perspective



SWEDE HEART

Bucceri Circ CV Int 2019

Trombsugning – före, under, och efter TASTE



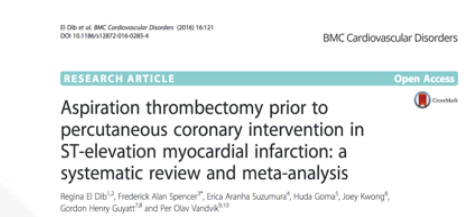
Buccheri S. et al. Circ. Cardiovasc. Intv. 2019;12:e007381

Evidence Ecosystem reducing waste

Thrombus aspiration for MI
Loop 2 2014-2017

Synthesized new evidence

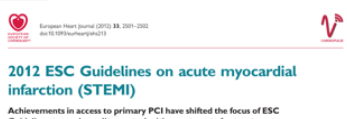
2015: High quality systematic reviews (20 trials, 21660 patients)
Moderate certainty evidence (4 fewer MI, 6 more strokes)



data

Updated and disseminated guidance

2015: ACC/ AHA guidelines
2017: ESC guidelines
Strong recommendations against

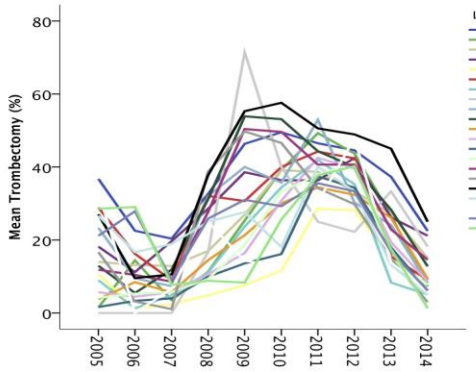


data

SWEDE HEART

De-implemented and evaluated in Sweden, what about the rest of the world?

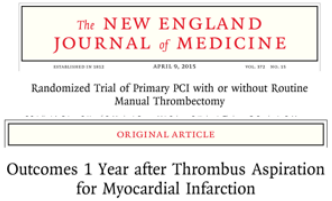
2014-2015: Swedish national online registry rapid de-implementation of thrombus aspir of PCI patients), immediately following TAS before systematic review and guidelines up



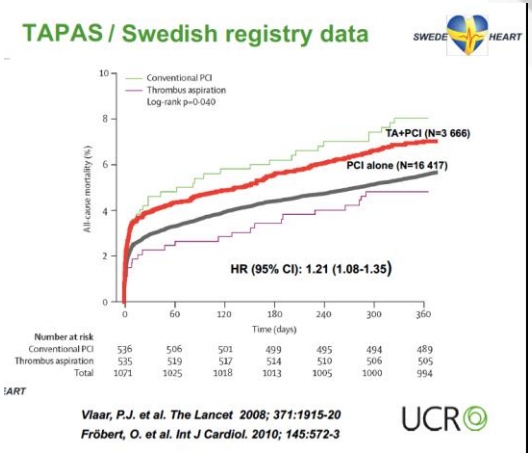
data

Produced more reliable and relevant evidence

2014: TASTE (n=7244)
2015: TOTAL (n= 10732)
Negative results

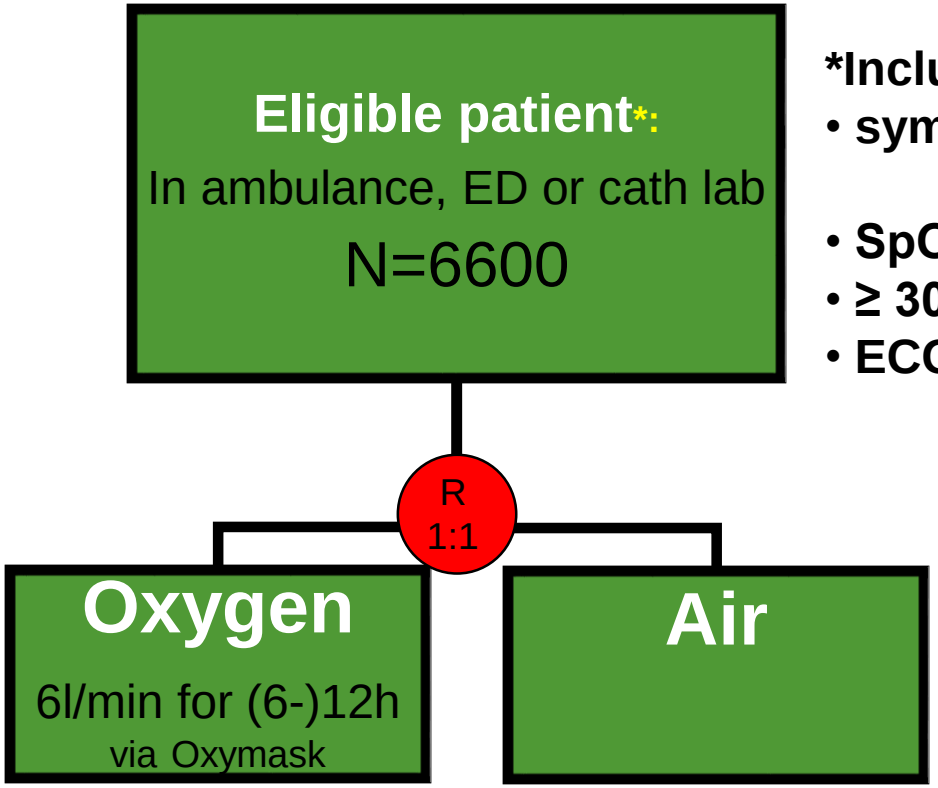


data



data

DETO2X – AMI



***Inclusion criteria:**

- **symptoms suggestive of AMI within 6h**
- **SpO2 ≥ 90%**
- **≥ 30y**
- **ECG changes indicating ischemia and/or elevated troponin levels**

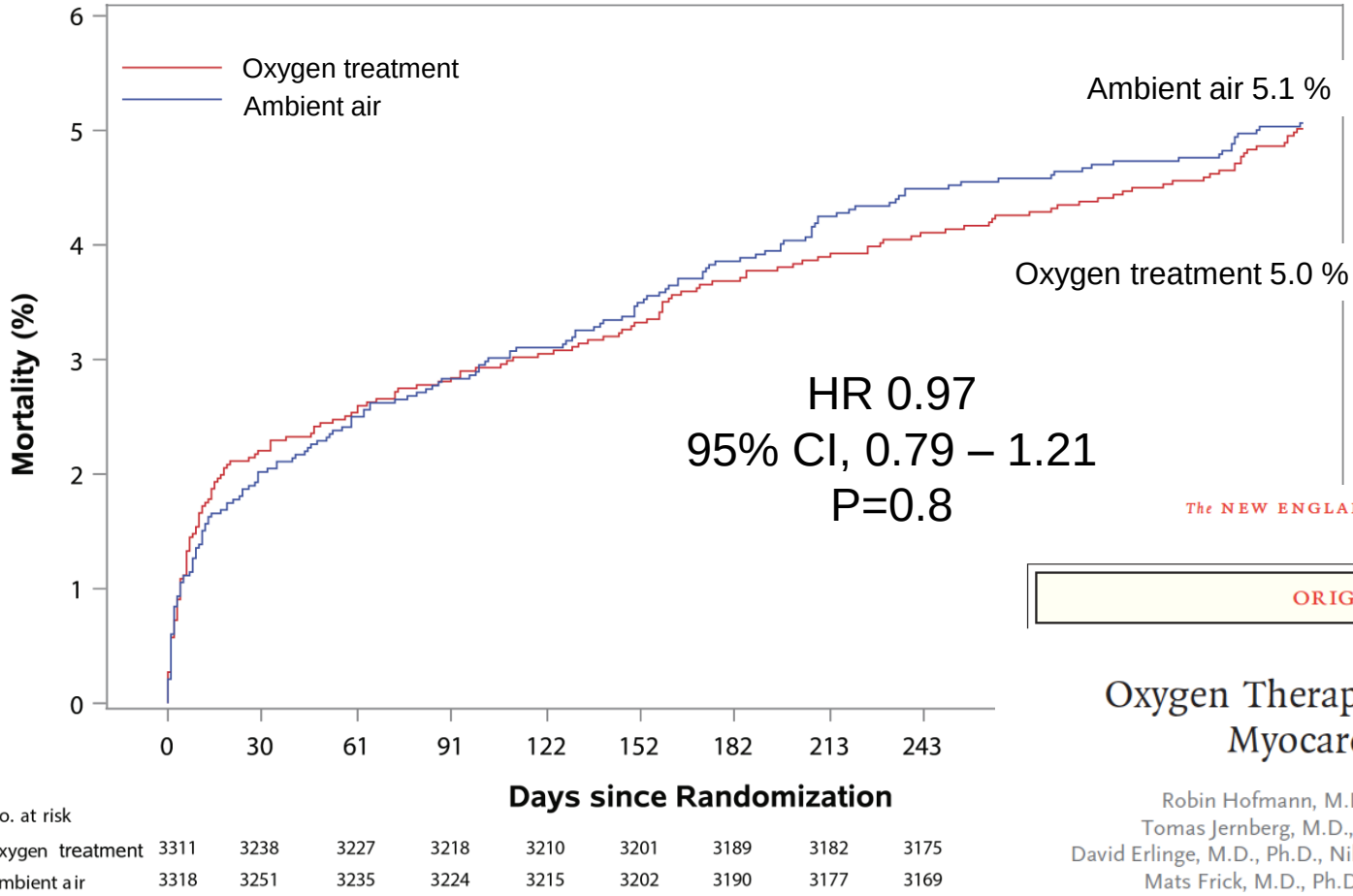
Primary Endpoint: 1-year total mortality

Additional secondary endpoint and sub studies

Data analysis through **SWEDEHEART** registry and **national mortality registry**

Funding: Swedish Research council (VR)

Primary Endpoint up to 365 days



HR 0.97
95% CI, 0.79 – 1.21
P=0.8

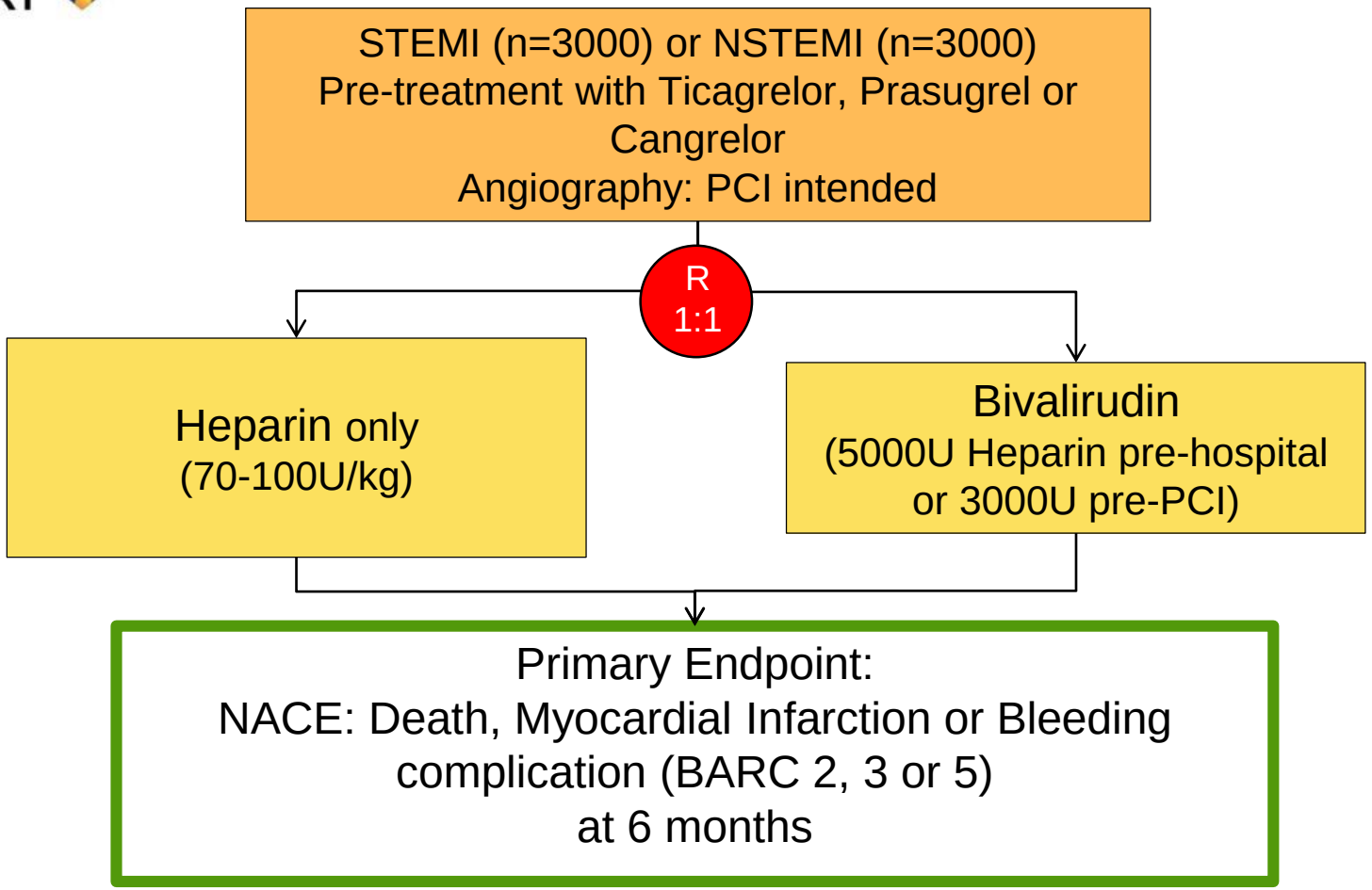
The NEW ENGLAND JOURNAL of MEDICINE

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*

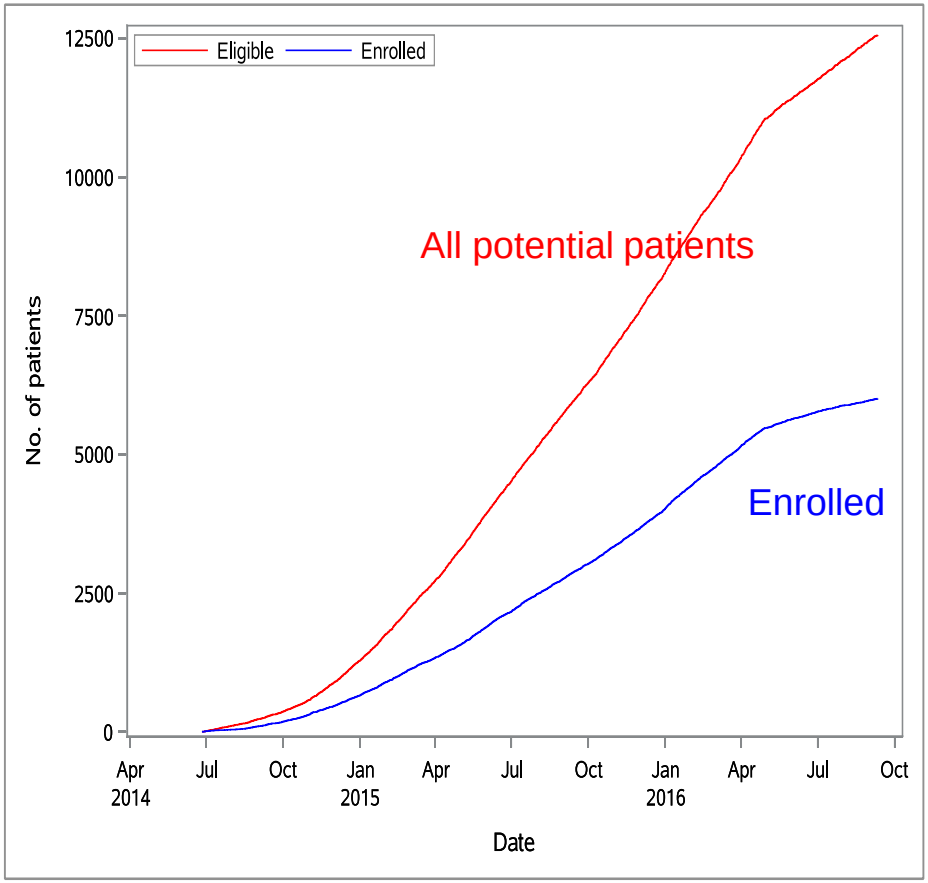
VALIDATE (R-RCT)



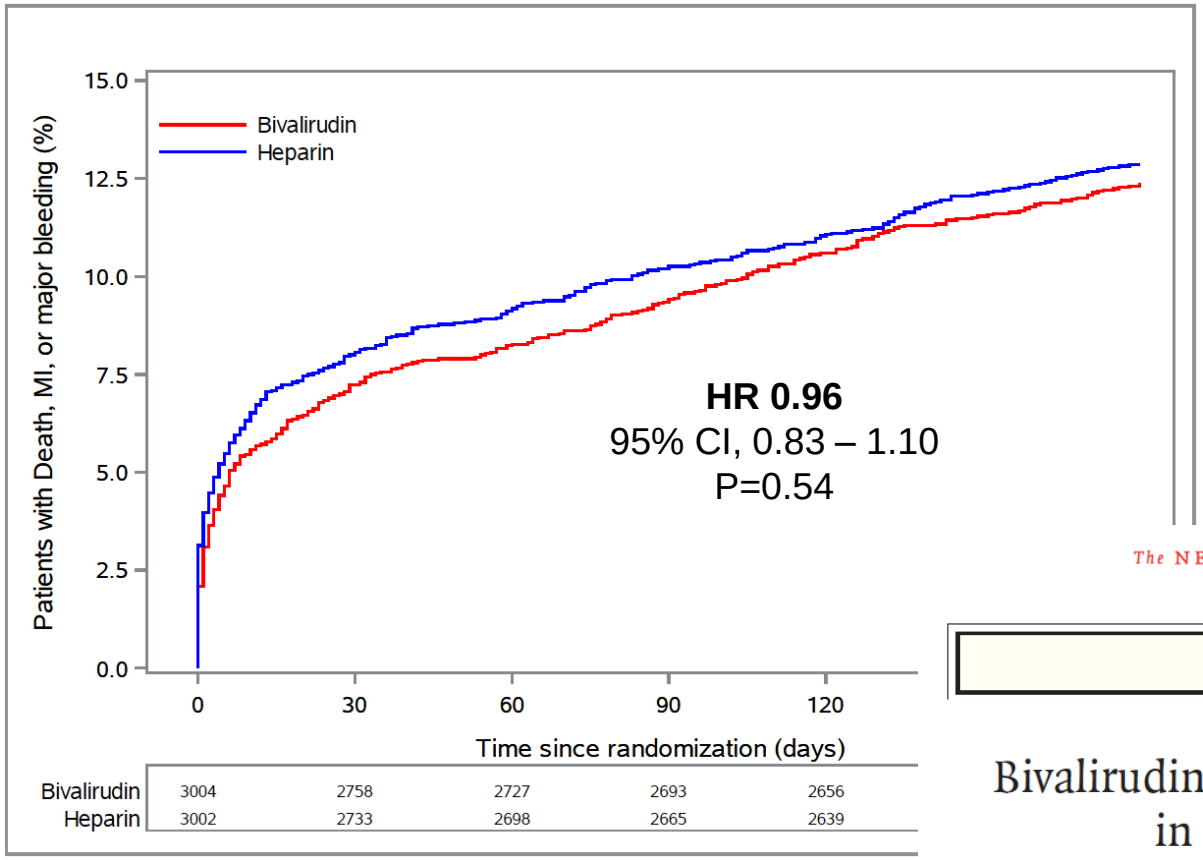
- FU: Register data, combined with phone call endpoint follow up and CEC
- Funding: Heart-lung foundation. Swedish research council, Astra Zeneca, The Medicines company.

Included NSTEMI/STEMI in relation to possible eligible patients in Sweden

- 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.



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

Swedeheart RRCT

Guidelines

TASTE

VALIDATE SWEDEHEART

DETO2X

iFR-SWEDEHEART

	Guideline	Reco	Guideline	Reco
Thrombus aspiration	2012 Routine thrombus aspiration should be considered	IIa B	2017 Routine use of thrombus aspiration is not recommended	III A
Bivalirudin	2012 Bivalirudin (GP IIb/IIIa blocker restricted to bailout) is recommended over heparin and a GP IIb/IIIa blocker	I B	2018 Bivalirudin may be considered as an alternative to UFH	IIb A
Oxygen	2012 Oxygen is indicated if hypoxia (SaO2 <95%), breathlessness, or acute heart failure.	I C	2017 Routine oxygen is not recommended if SaO2 > 90%	III B
iFR	2014 FFR to identify haemodynamically relevant coronary lesion(s) in stable patients when evidence of ischaemia is not available.	I A	2019 When evidence of ischaemia is not available, FFR or iFR are recommended to assess the haemodynamic relevance of intermediate-grade stenosis.	I A

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Swedeheart RRCT

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Assessing the Nationwide Impact of a Registry-Based Randomized Clinical Trial on Cardiovascular Practice.
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R-RCTs in Sweden

Cardiology

TASTE	**(n=7200)**	**Thrombus aspiration in primary PCI**	**NEJM**
iFR	**(n=2018)**	**iFR vs FFR in stable angina or ACS**	**NEJM**
VALIDATE	**(n=6006)**	**Bivalirudin vs UFH for PCI in ACS**	**NEJM**
DETO2X	**(n=6629)**	**Oxygen therapy in myocardial infarction**	**NEJM**
FULL-REVASC	**(n=4000)**	**FFR-guidance in myocardial infarction**	***Ongoing***
PROSPECT-2	**(n=1200)**	**Near infrared spectroscopi**	***Ongoing***
IAMI	**(n=4400)**	**Influenza vaccination After Myocardial Infarction**	***Ongoing***
SPIRRIT HFpEF	**(n=3200)**	**Spironolactone for HFpEF**	***Ongoing***
REDUCE	**(n=6600)**	**Betablocker post MI in patients**	***Ongoing***
ABC AF	**(n=6500)**	**Biomarker score based treatment strategies**	***Ongoing***

Stroke

TIMING	**(n=3000)**	**Treatment after ischemic stroke in atrial fibrillation**	***Ongoing***

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R-RCTs in Sweden

Cardiothorasic Surgery

Swedegraft	**(n=800)**	**Vein grafts for CABG surgery**	***Ongoing***
TACSI	**(n=2048)**	**Medication after CABG**	***Ongoing***

Obesity Surgery

SLITS	**(n=2507)**	**Gastric by pass operation**	**Lancet**
BEST	**(N=4000)**	**Obesity surgery**	***Ongoing***

Vascular Surgery

SWEDEPAD	**(N=2400)**	**Drug Elution trial in Peripheral Arterial Disease,**	***Ongoing***

Gynecology/Labor

SWEPIS	**(n=10 000)**	**Post-term Induction of labour**	***Stopped***

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Conclusions

We need more trials- more affordable, generalizable and clinically informative trials

Integrating trials with simple questions into clinical registries is one way of conducting large trials in clinical reality

Euroheart will be an opportunity to conduct RRCT in Cardiology across Europe

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