Prospective registry-based randomized clinical trials – the Swedish concept for pragmatic clinical trials

Jonas Oldgren, MD PhD

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Uppsala University, Sweden

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Randomized Clinical Trials – RCT

Strengths

- Correctly designed studies with adequate power are gold standard
- Randomization extinguishes confounding

Weaknesses

- Highly selected populations due to exclusion criteria
- Often selected specialized study centers
- Often surrogate endpoints
- Long time to plan and complete
- Expensive
- Often sponsored by industry – only studies of economic interest will be performed

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Big Cost Drivers in Traditional Clinical Trials

- Data collection – size of case report form
- Site monitoring - % source document verification
- Number of study-specific procedures and tests
- Number of study-specific contacts and visits
- Volume and complexity of safety reporting requirements
- Investigational drug storage and accountability
- **Total trial timeline!!!!!**

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ORIGINAL CONTRIBUTION

Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

Robert M. Califf, MD
Deborah A. Zarin, MD
Judith M. Kramer, MD, MS
Rachel E. Sherman, MD, MPH
Laura H. Aberle, BSPH
Asba Tasneem, PhD

Context Recent reports highlight gaps between guidelines-based treatment recommendations and evidence from clinical trials that supports those recommendations. Strengthened reporting requirements for studies registered with ClinicalTrials.gov enable a comprehensive evaluation of the national trials portfolio.

Objective To examine fundamental characteristics of interventional clinical trials registered in the ClinicalTrials.gov database.

Methods A data set comprising 96 346 clinical studies from ClinicalTrials.gov was downloaded on September 27, 2010, and entered into a relational database to analyze aggregate data. Interventional trials were identified and analyses were focused

Conclusion Clinical trials registered in ClinicalTrials.gov are dominated by small trials and contain significant heterogeneity in methodological approaches, including reported use of randomization, blinding, and DMCs.

CLINICAL TRIALS ARE THE CEN-

Journal Editors (ICMJE) announced a policy, which took effect in 2005, of requiring registration of clinical trials as a prerequisite for publication.[6,7] The Food and Drug Administration Amendment Act (FDAAA)[8] expanded the mandate of

randomization and blinding were less frequently reported in earlier-phase, oncology, and device trials.

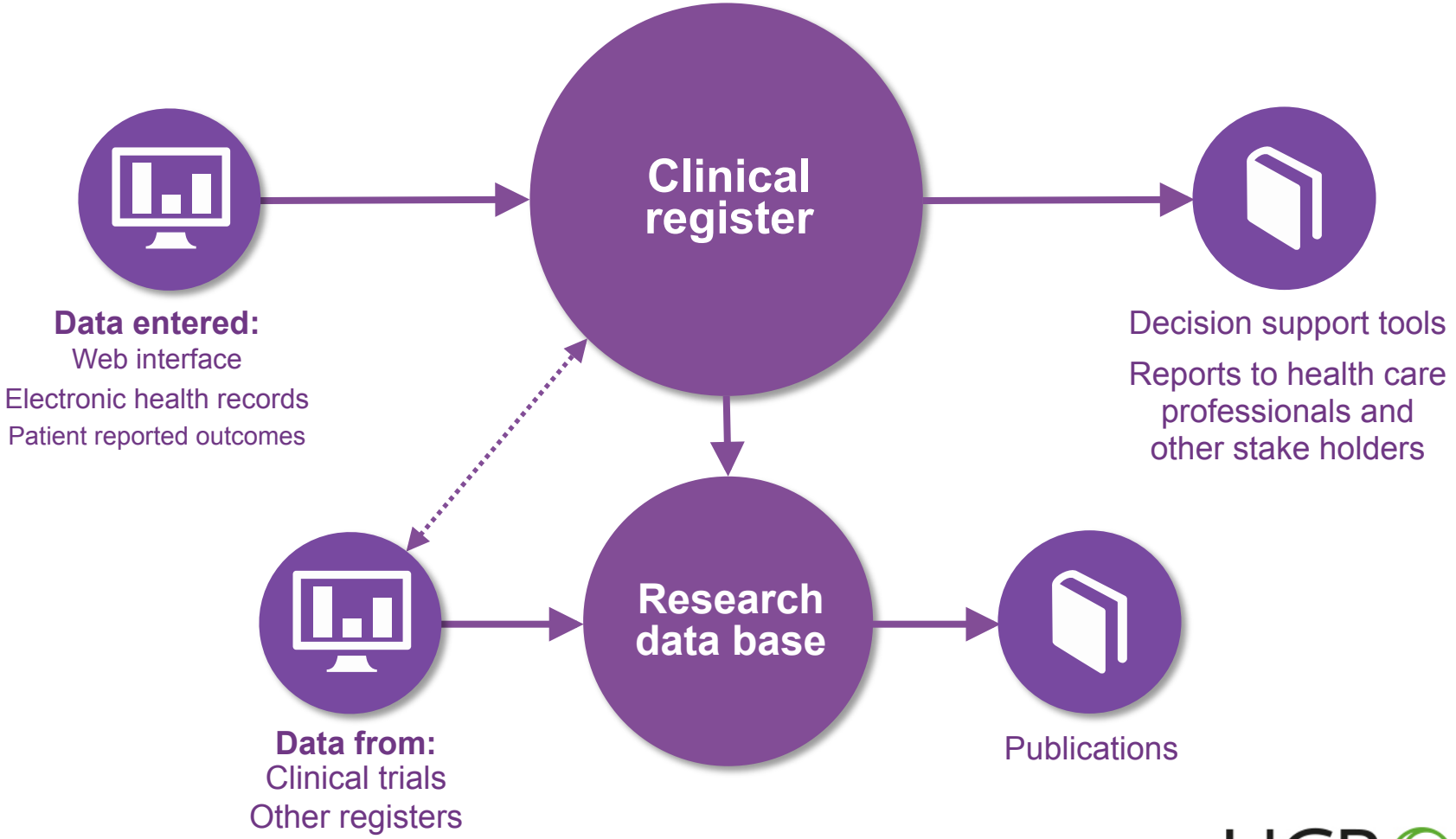
Conclusion Clinical trials registered in ClinicalTrials.gov are dominated by small trials and contain significant heterogeneity in methodological approaches, including reported use of randomization, blinding, and DMCs.

Sweden and clinical registries

- A system of national clinical registries has been established in the Swedish health and medical services during the last three decades.
- Six national competence centers for clinical registers and 96 national registries receive national funding in Sweden.
- UCR is the oldest and largest competence center for clinical registers hosting more than 20 national registers.
- Participation in clinical registers is voluntary. Based on the unique personal identification number given to each Swedish citizen (at birth or immigration) data from clinical registers can be combined with data from mandatory register such as cause of death, patient administrative (with discharge diagnoses), and drug prescription registers

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Clinical registers in Swedish health care



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EUROPEAN SOCIETY OF CARDIOLOGY®

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

CardioPulse

SWEDEHEART: Sweden's new online cardiac registry, the first of its kind

Covering all hospitals in Sweden, SWEDEHEART is unique because it allows long-term follow-up and immediate feedback, says Ulf Stenestrand, MD, PhD, Associate Professor of cardiology and Senior consultant interventional cardiologist, Department of Cardiology, University Hospital, Linköping, Sweden, and President of SWEDEHEART.

SWEDEHEART

Number of cases annually: 80 000

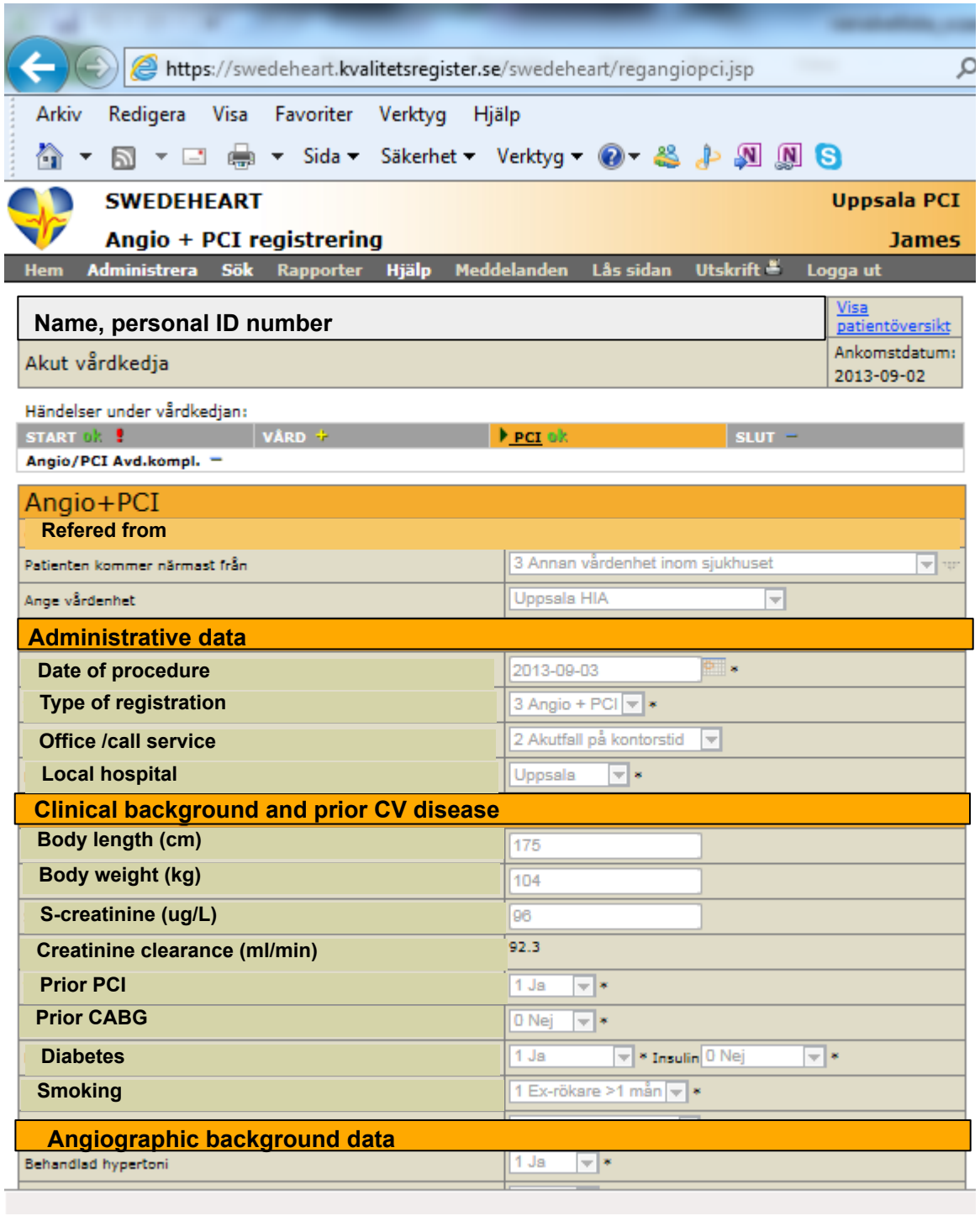
RIKS-HIA	73 CCU hospitals, 100%
SCAAR	30 PCI hospitals, 100%
Percutaneous valves	7 hospitals, 100%
Heart surgery	7 hospitals, 100%
Secondary prevention	65 hospitals, 85%
Cardiogenetic registry	New

>200 variables

(Baseline data, procedural and outcome measures)

At monitoring: 95-96% agreement between files and registry.

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SWEDEHEART

Data entry on line by the operator

Automatic linkage with population registry to provide name, sex

Automated data checks

Auto populated fields from previous registrations

Calculated variables

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Thrombus aspriration in ST-elevation myocardial infarction (STEMI)

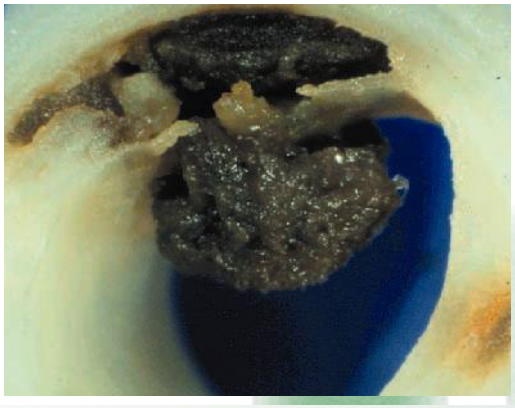
RCT vs registry data

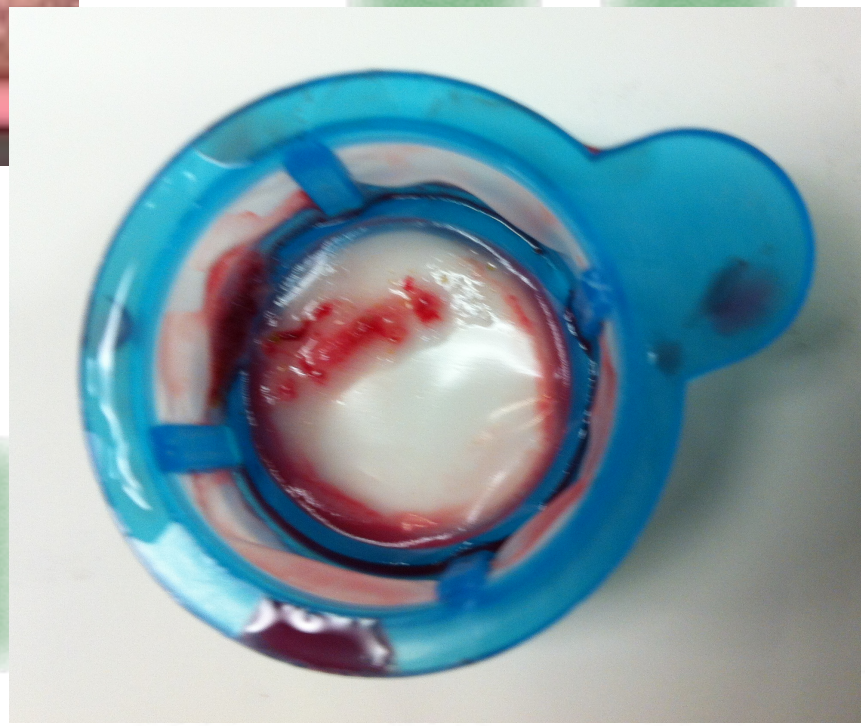
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Thrombus aspiration in STEMI

SCAAR
SWEDE HEART





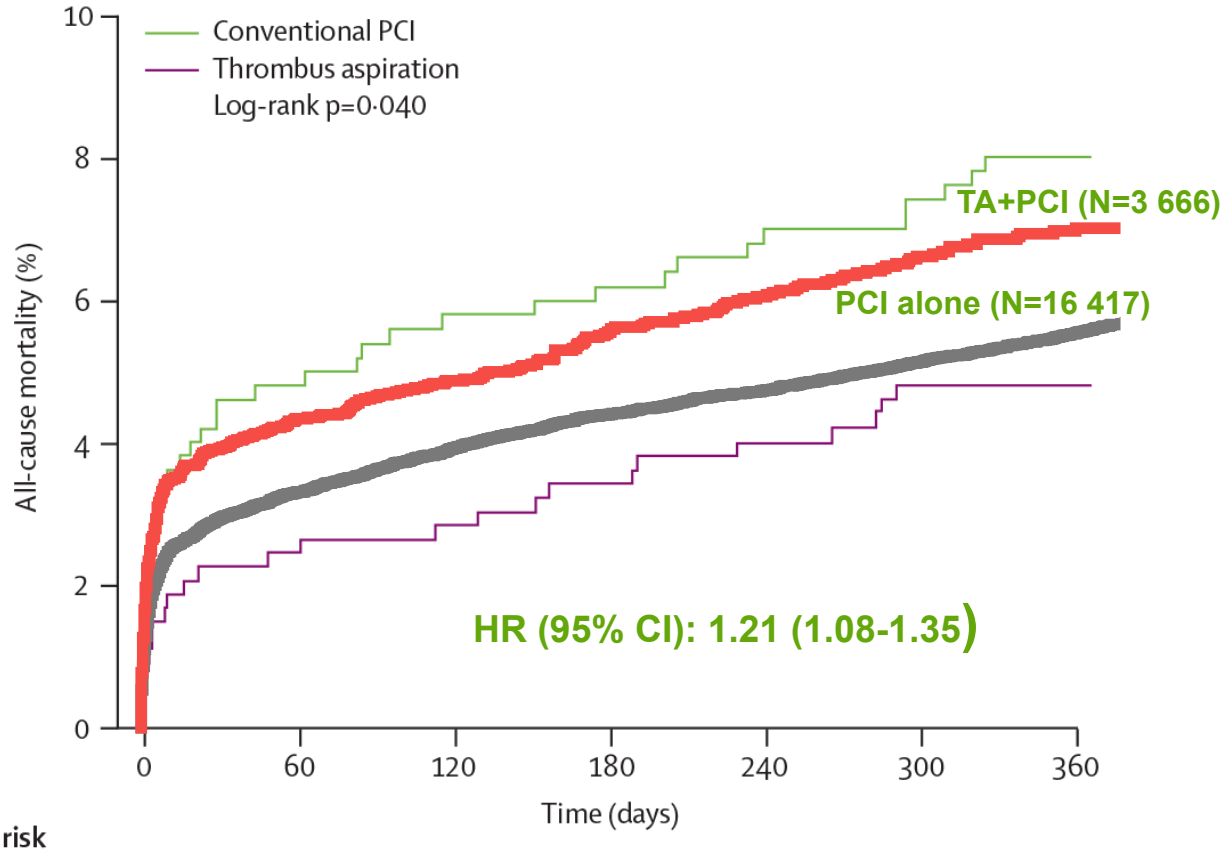


Thrombus aspiration in Sweden

SCAAR
SWEDE HEART



TAPAS / Swedish registry data



Number at risk							
Conventional PCI	536	506	501	499	495	494	489
Thrombus aspiration	535	519	517	514	510	506	505
Total	1071	1025	1018	1013	1005	1000	994

SWEDE HEART

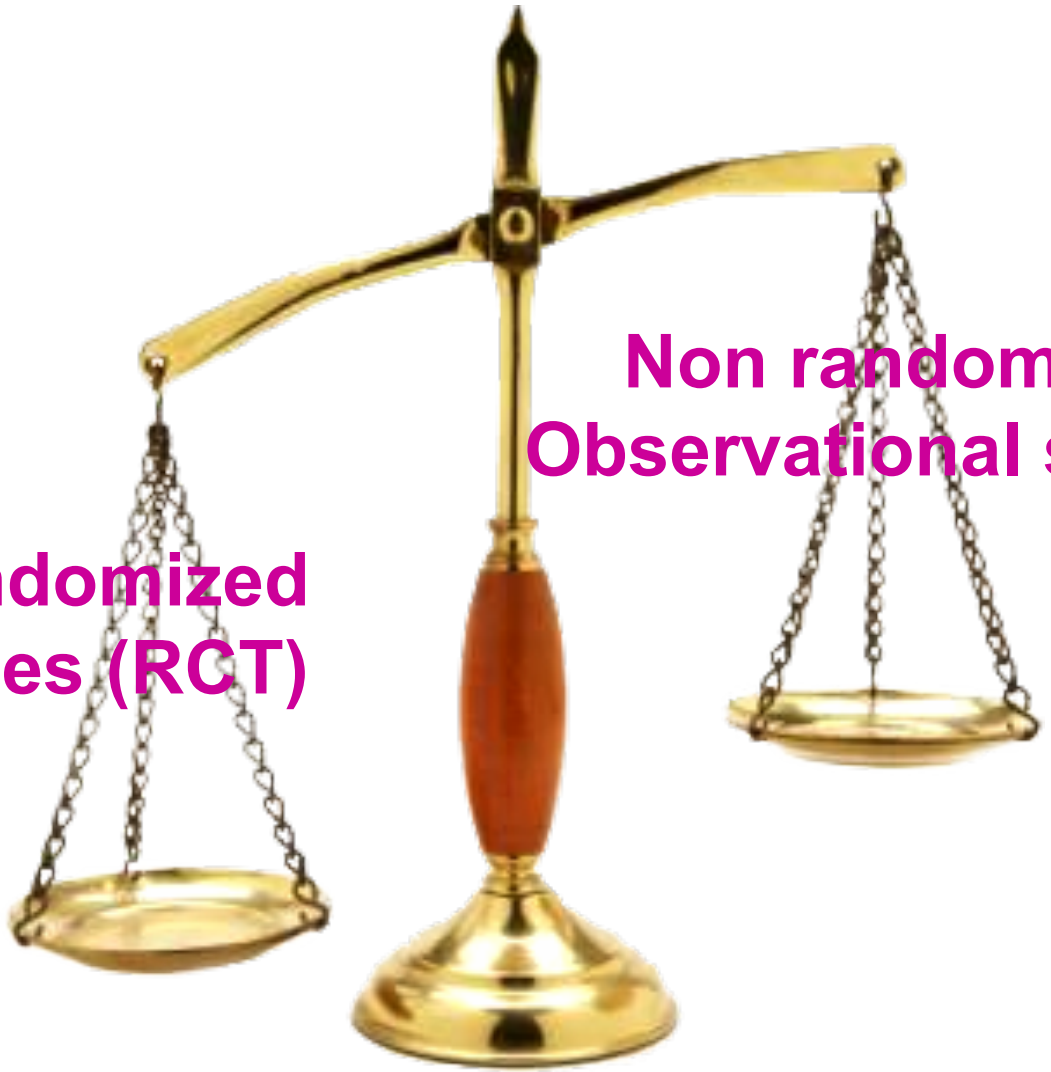
TASTE

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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Randomized Controlled/Clinical Trials - RCT



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Utilizing clinical registers for randomized clinical trials

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Register-based Randomized Clinical trials (R-RCT)

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

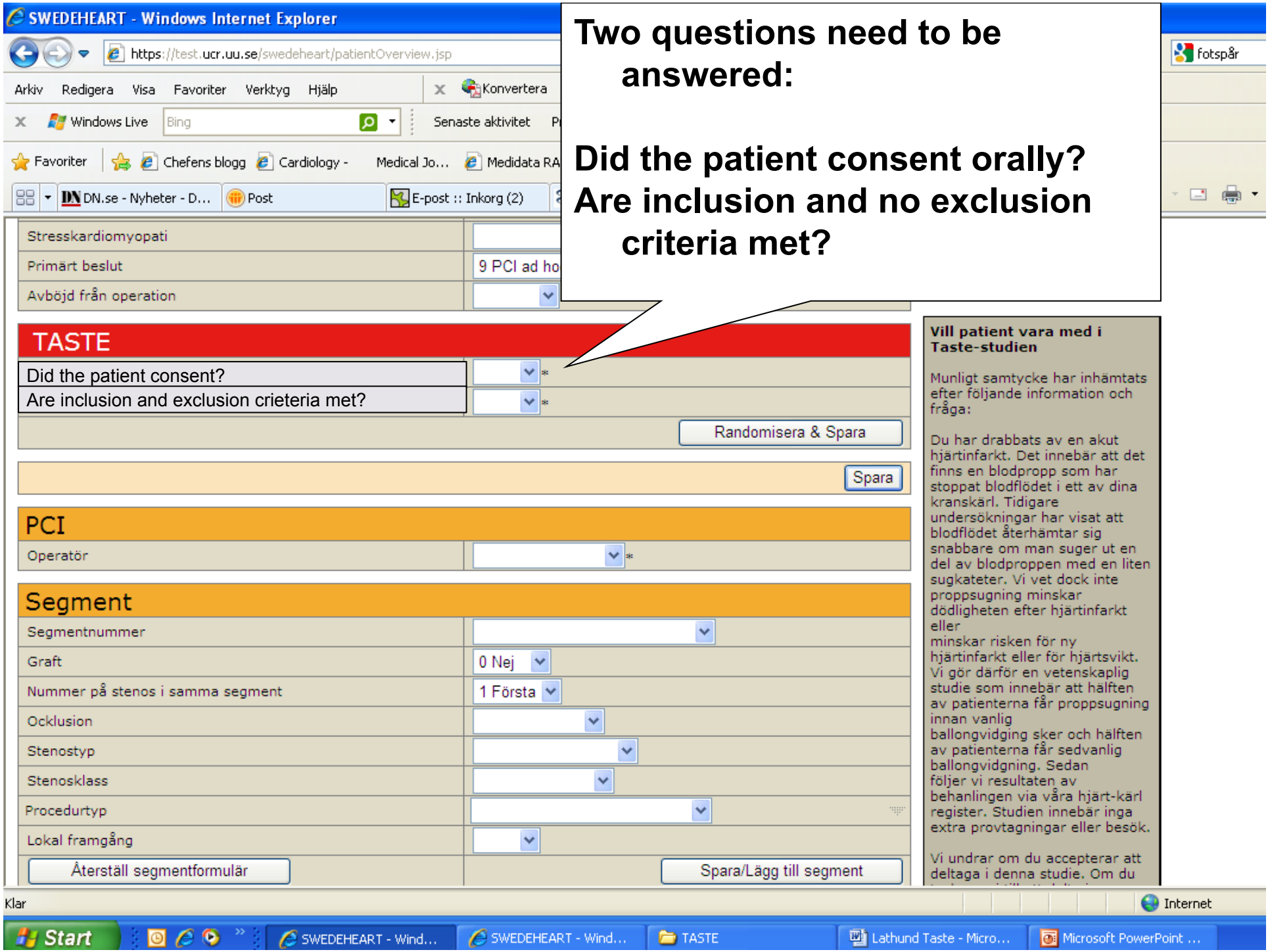
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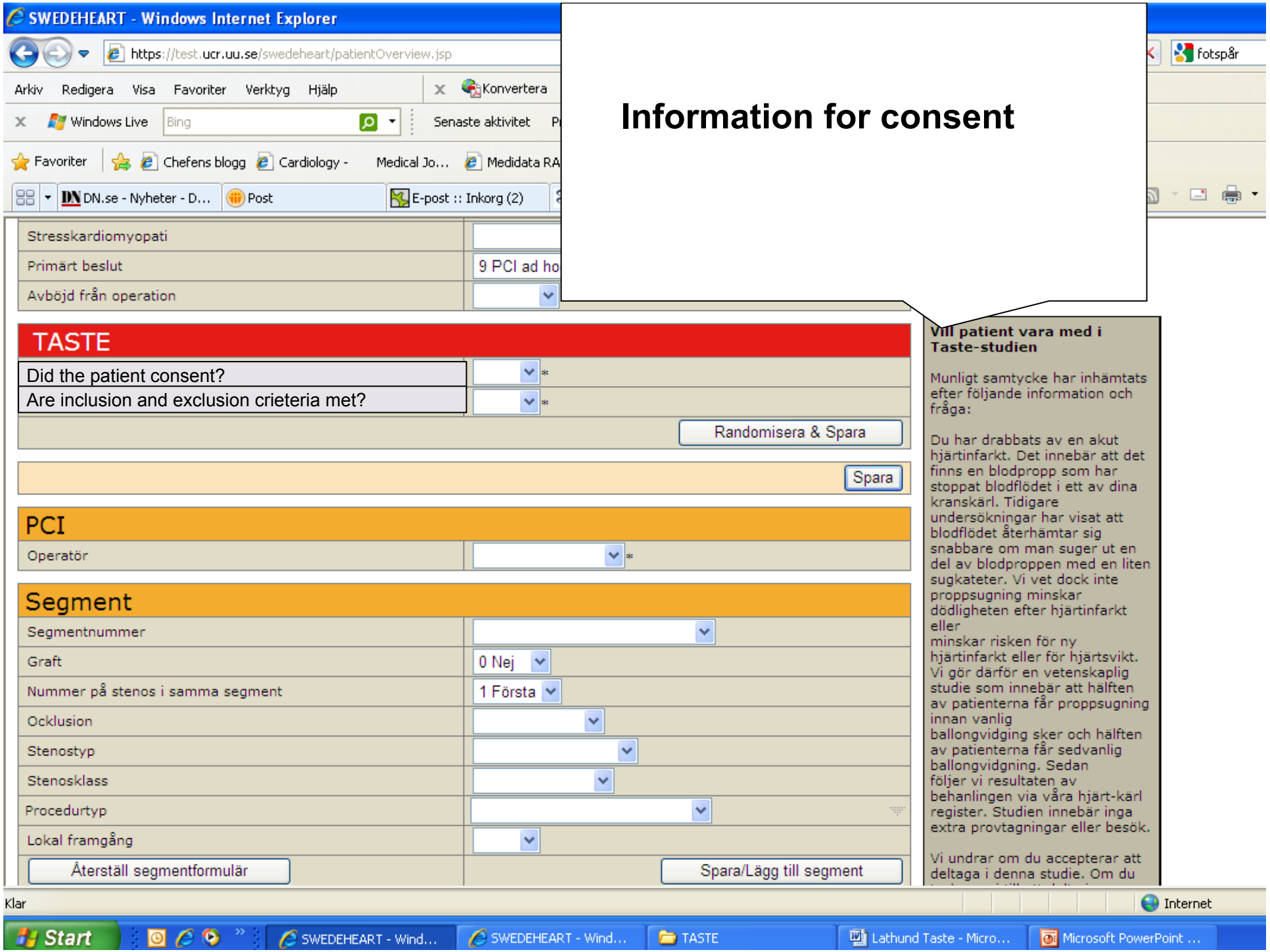
How can a registry be utilized in a RCT?

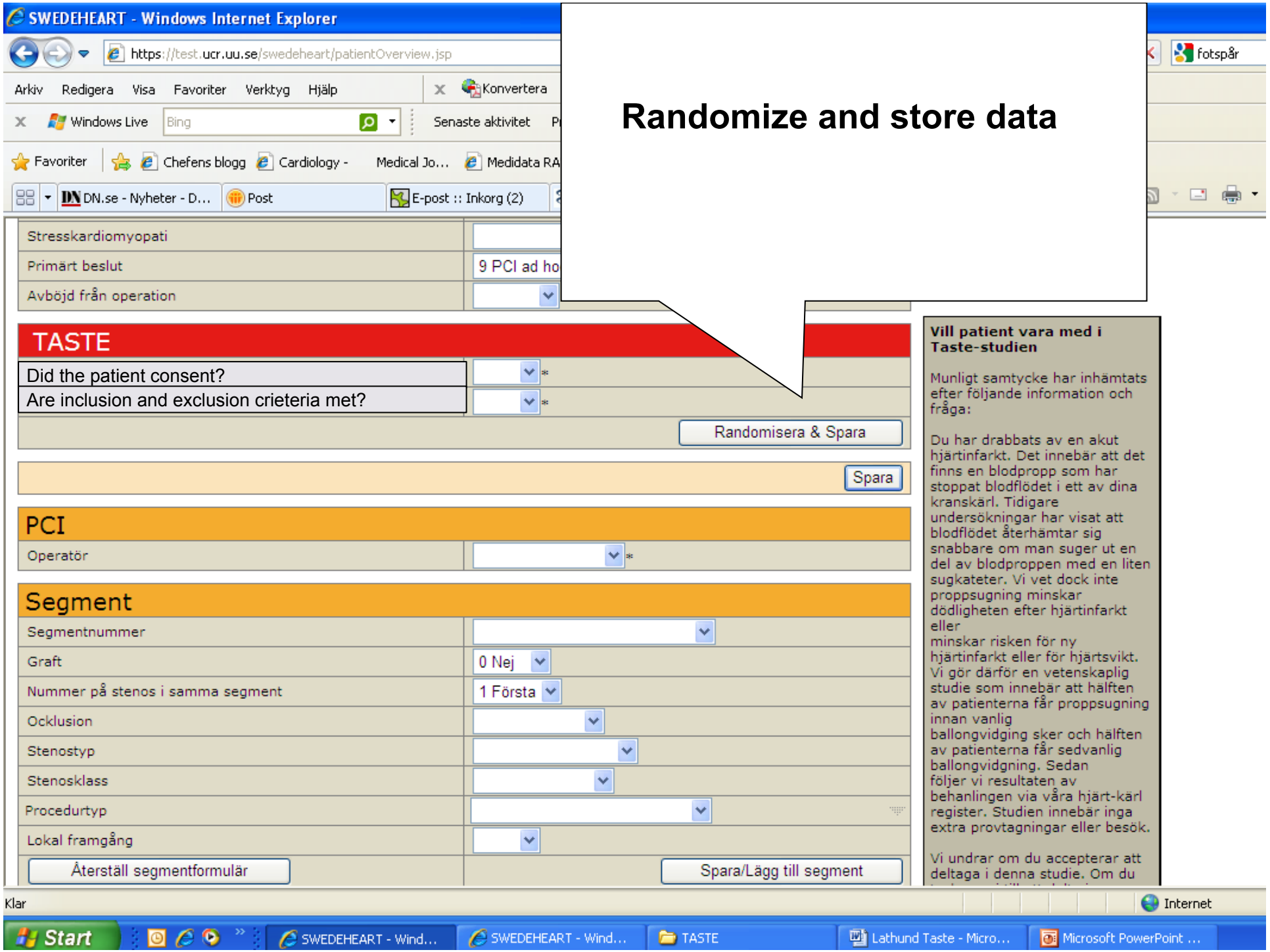
For some or all parts of trial

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

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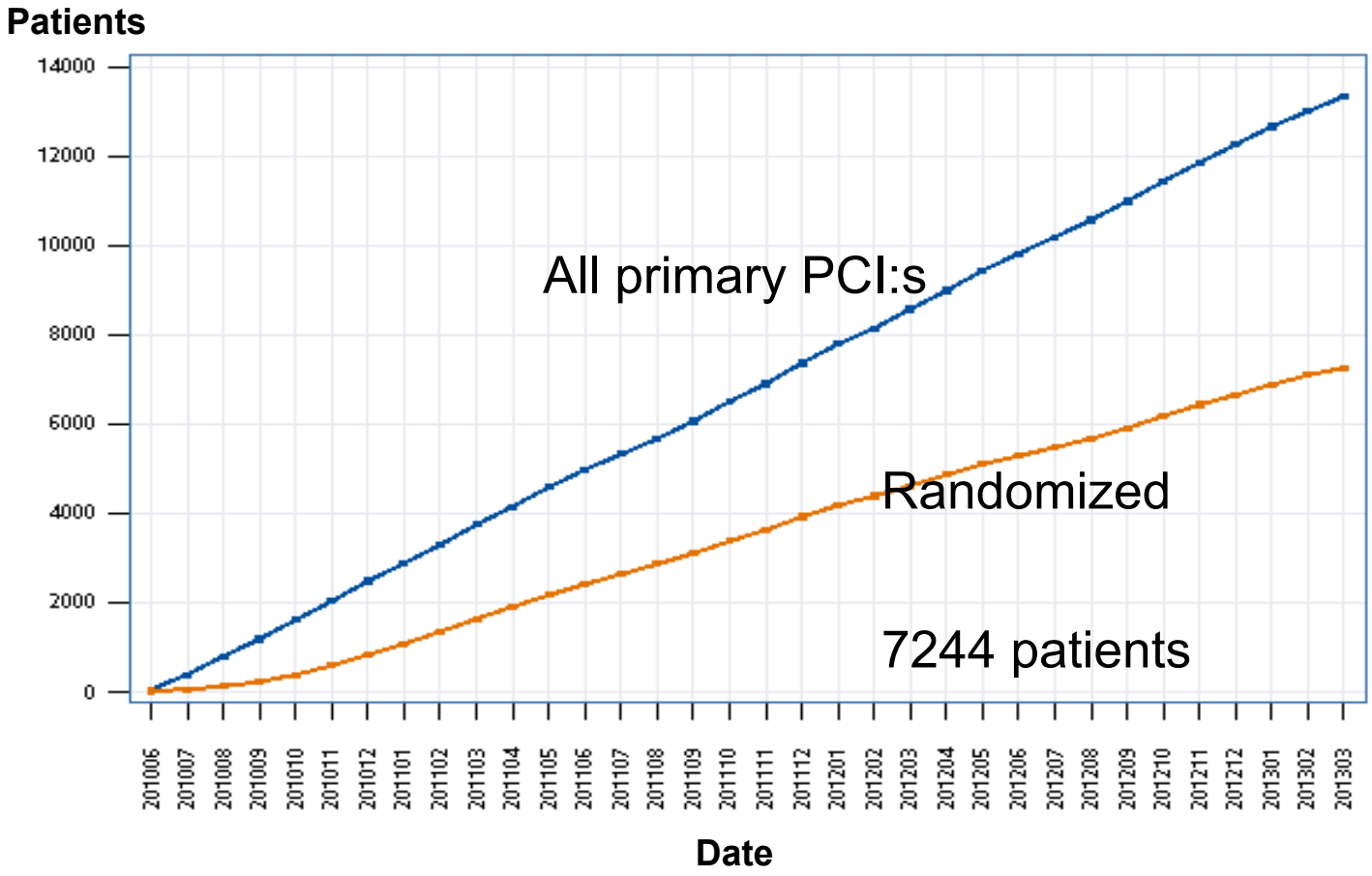

SWEDEHEART - Windows Internet Explorer
https://test.ucr.uu.se/swedeheart/patientOverview.jsp
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Cardiology -
Medical Jo...
Medidata RA
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fotspår
Two questions need to be answered:
Did the patient consent orally?
Are inclusion and no exclusion criteria met?
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
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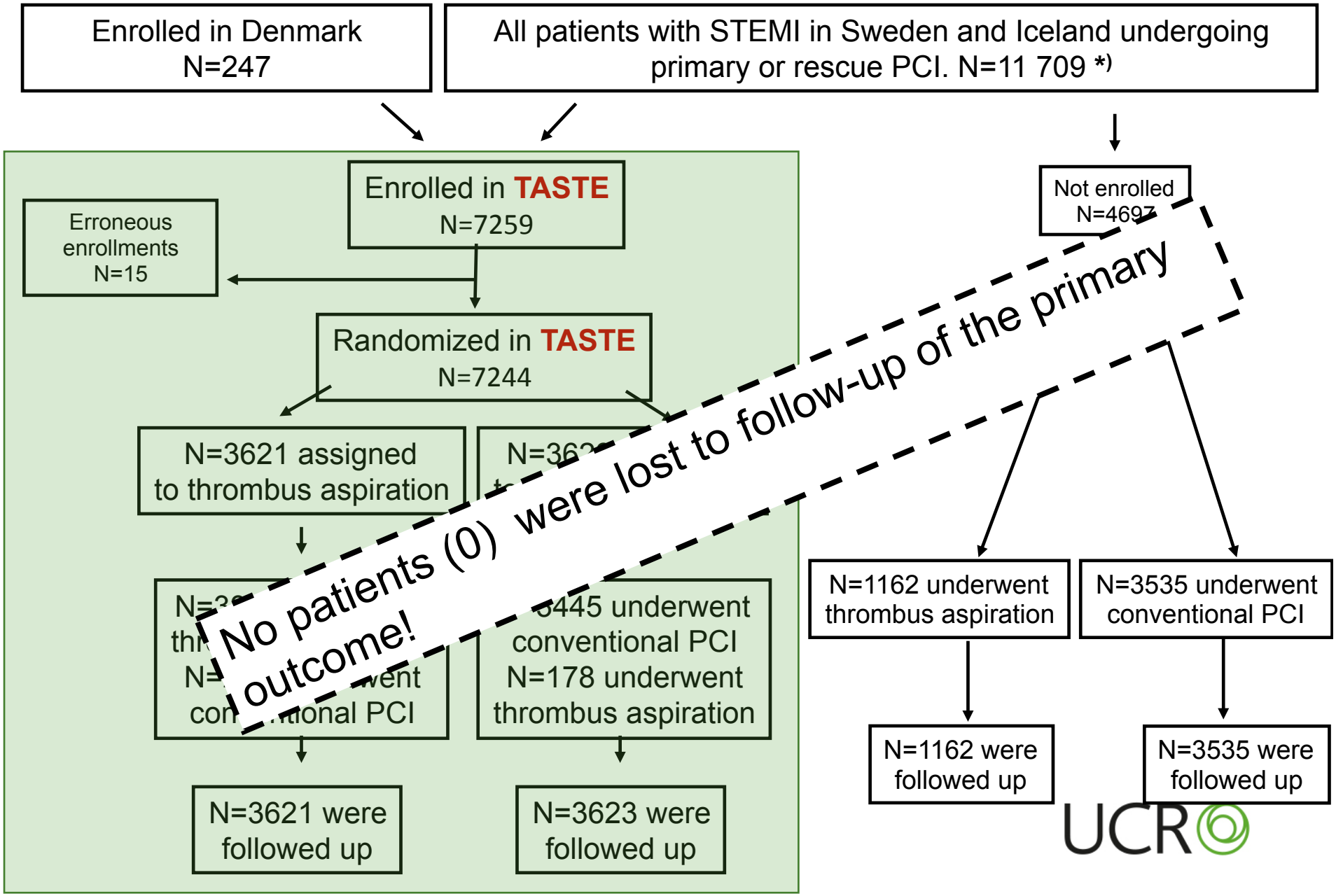
TASTE inclusion rate



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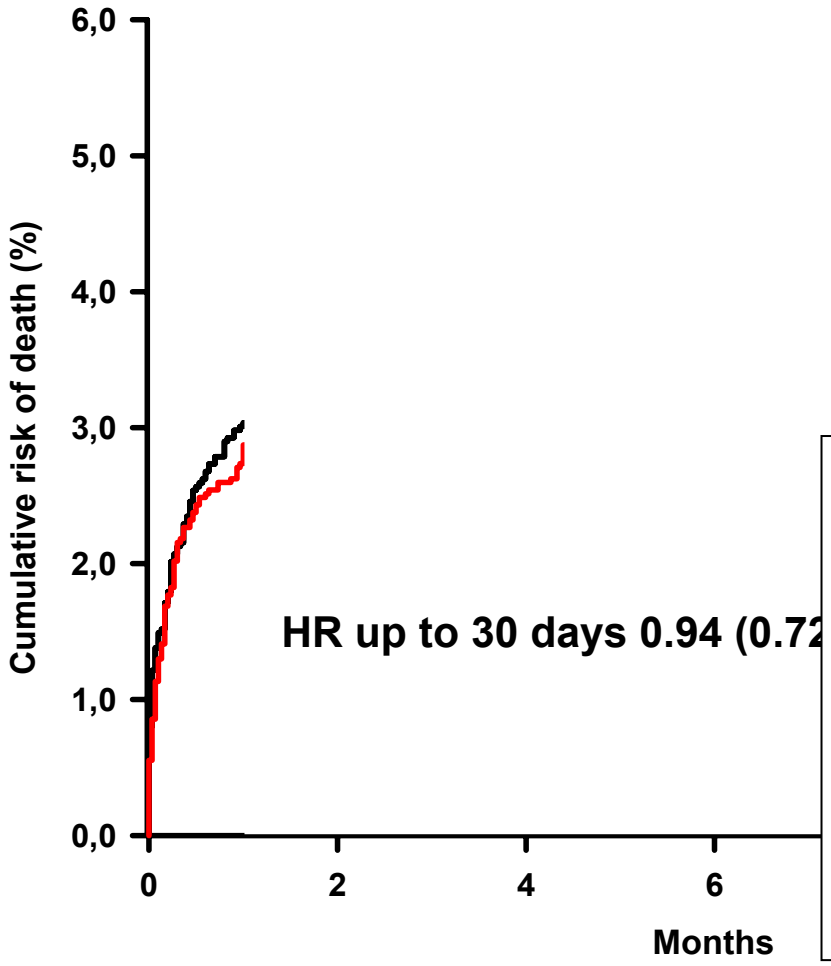
TASTE trial enrollment flow chart



TASTE

All-cause mortality up to 1 year

SWEDE HEART



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.,

The NEW ENGLAND JOURNAL of MEDICINE

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

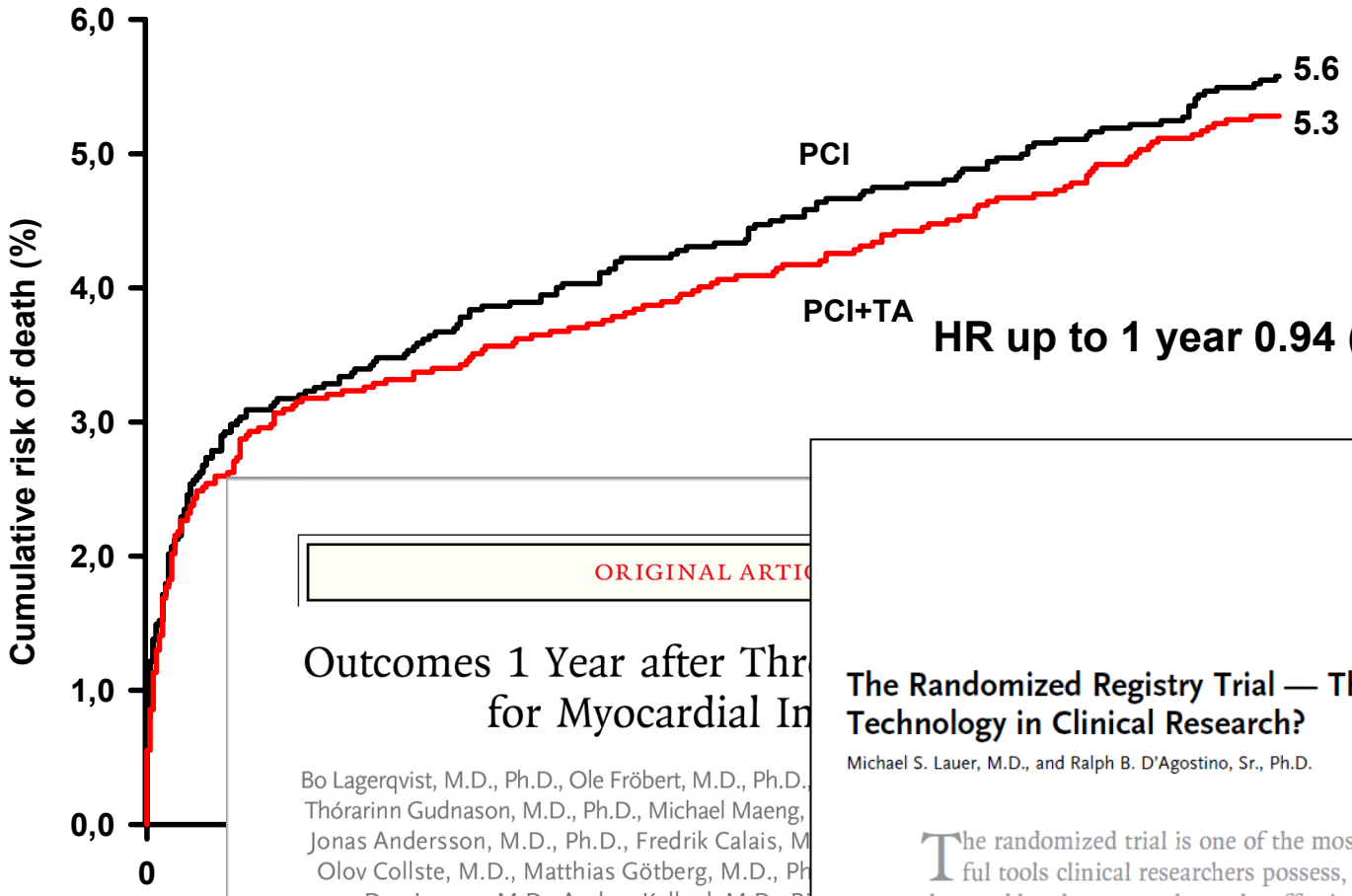
United States and abroad have collected vast amounts of data from patients with acute coronary syndromes, stable coronary disease, and heart failure, as well as

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TASTE

All-cause mortality up to 1 year

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HR up to 1 year 0.94 (0.78 – 1.15), P=0.57

ORIGINAL ARTI

Outcomes 1 Year after Thr
for Myocardial In

Bo Lagerqvist, M.D., Ph.D., Ole Fröbert, M.D., Ph.D.,
Thórarinn Gudnason, M.D., Ph.D., Michael Maeng,
Jonas Andersson, M.D., Ph.D., Fredrik Calais, M
Olov Collste, M.D., Matthias Götberg, M.D., Ph
Dan Ioanes, M.D., Anders Kallryd, M.D., Ri
Anders Lundin, M.D., Jacob Odenstedt, M.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.

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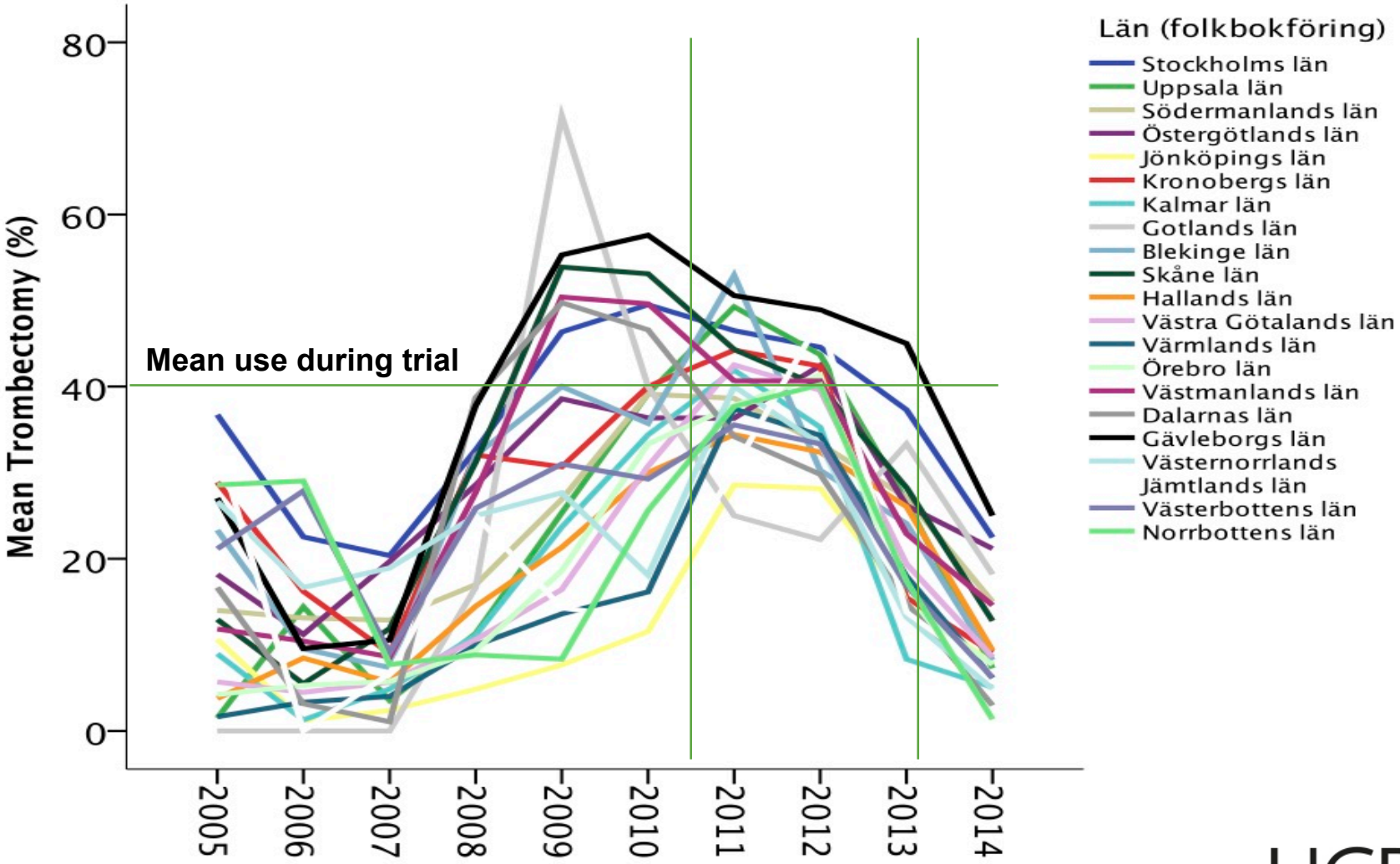
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Thrombus aspiration pre/post Taste

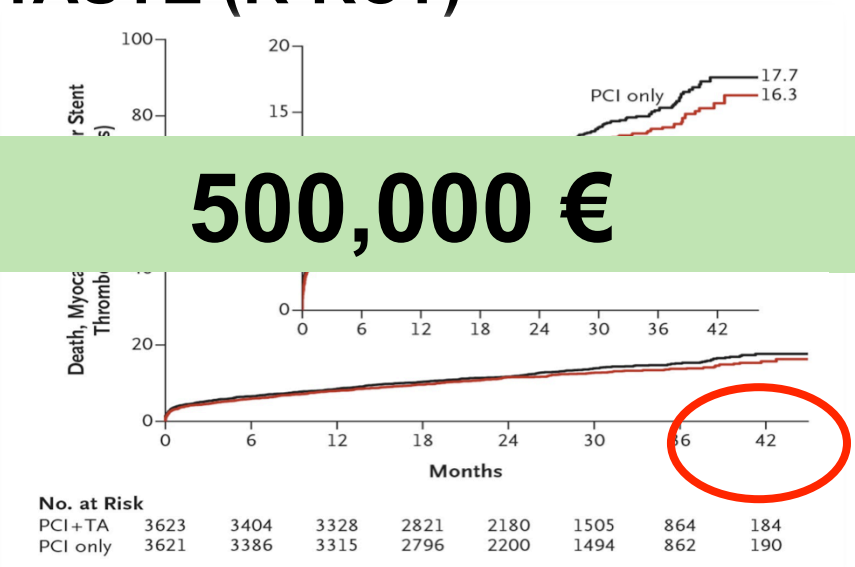


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R-RCT vs. RCT

STEMI Thrombectomy Story

TASTE (R-RCT)

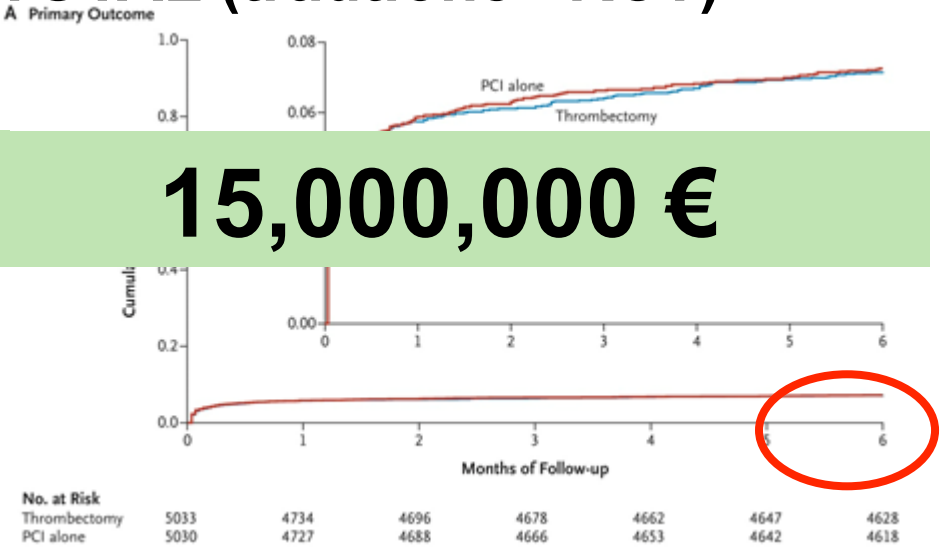


500,000 €

1st patient: June 2010
30 centers
33 months to full enrollment
7,244 patients

Lagerqvist B et al. N Engl J Med 2014;371:1111-1120

TOTAL (tradtionell RCT)



15,000,000 €

1st patient: August 2010
87 centers
48 months to full enrollment
10,732 patients

Jolly SS et al. N Engl J Med 2015;371:1389-1398

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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 considered in selected patients	IIb	A
2015 ACC/AHA focused update PPCI	JACC	Routine thrombectomy not useful	III	A
2015 ACC/AHA focused update PPCI	JACC	Selective and bailout Thrombectomy 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

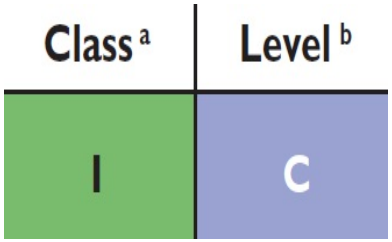
DETermination of the role of OXygen in suspected Acute Myocardial Infarction



Robin Hofmann, MD
Karolinska Institutet
Department of Clinical Science and Education
Division of Cardiology, Södersjukhuset
Stockholm, Sweden

Background (1)

- Oxygen therapy has been used for more than a century and is widely recommended by guidelines despite limited evidence*



- Rationale: Increased oxygen delivery to the ischemic myocardium reduces infarct size and subsequent complications

*Roffi M, et al. Eur Heart J 2016; 37: 267-315.
Steg PG, James SK, et al. Eur Heart J 2012; 33: 2569-619.

Background (2)

European Heart Journal (2013) **34**, 1630–1635
doi:10.1093/eurheartj/eht110

REVIEW

Controversies in cardiovascular medicine

Oxygen therapy in acute coronary syndrome: are the benefits worth the risk?

Mony Shuvy[1]*, Dan Atar[2,3], Philippe Gabriel Steg[4], Sigrun Halvorsen[2], Sanjit Jolly[5], Salim Yusuf[5], and Chaim Lotan[1]

[1]Heart Institute, Hadassah Hebrew University Medical Center, PO Box 12000, Jerusalem, Israel; [2]Department of Cardiology, Oslo University Hospital Ulleval; [3]Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [4]Université Paris-Diderot, INSERM U-698 and Hôpital Bichat, AP-HP, Paris, France; and [5]McMaster University and the Population Health Research Institute, Hamilton Health Sciences, Hamilton, ON, Canada

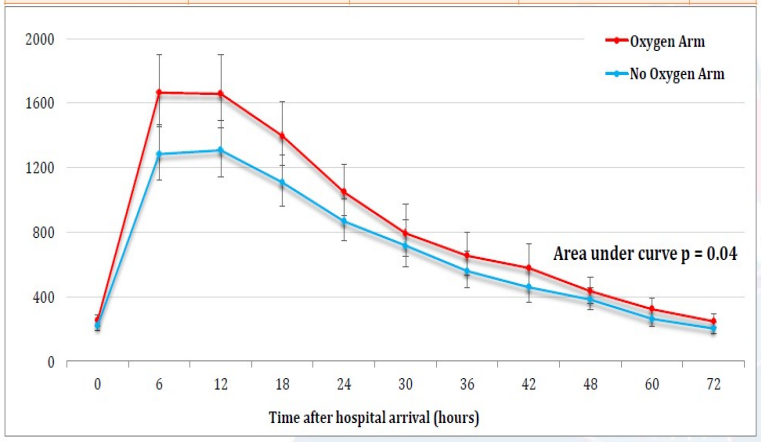
Received 31 August 2012; revised 22 October 2012; accepted 26 February 2013; online publish-ahead-of-print 3 April 2013

A randomized controlled trial of oxygen therapy in acute myocardial infarction Air Verses Oxygen In myocarDial infarction study (AVOID Study)

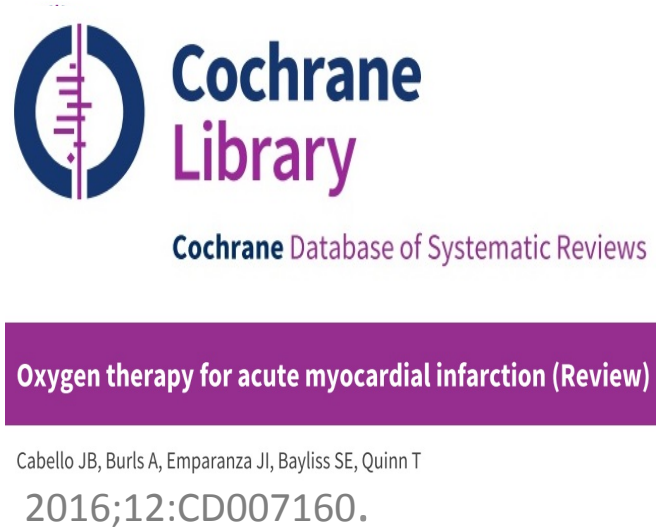
Dion Stub, MBBS,[a,b,c,f,g] Karen Smith, BSc(Hons) PhD,[b,d,f,g] Stephen Bernard, MBBS MD,[a,b,g] Janet E. Bray, RN, PhD,[b,d,g] Michael Stephenson, RN, BHlthSc, Grad, Dip (MICA),[d,g] Peter Cameron, MBBS, MD,[a,b,g] Ian Meredith, BSc, MBBS, PhD,[b,d,e,g] and David M. Kaye, MBBS, PhD[a,b,c,g] *Melbourne, Australia*

Primary Endpoint Infarct Size on Cardiac Enzymes

Creatine kinase, U/L	Oxygen Arm N=217	No Oxygen Arm N=222	Ratio of means (Oxygen/No Oxygen)	P-value
Geometric Mean Peak (95% CI)	1948 (1721 – 2205)	1543 (1341 – 1776)	1.26 (1.05 – 1.52)	0.01
Median Peak (IQR)	2073 (1065, 3753)	1727 (737, 3598)		0.04

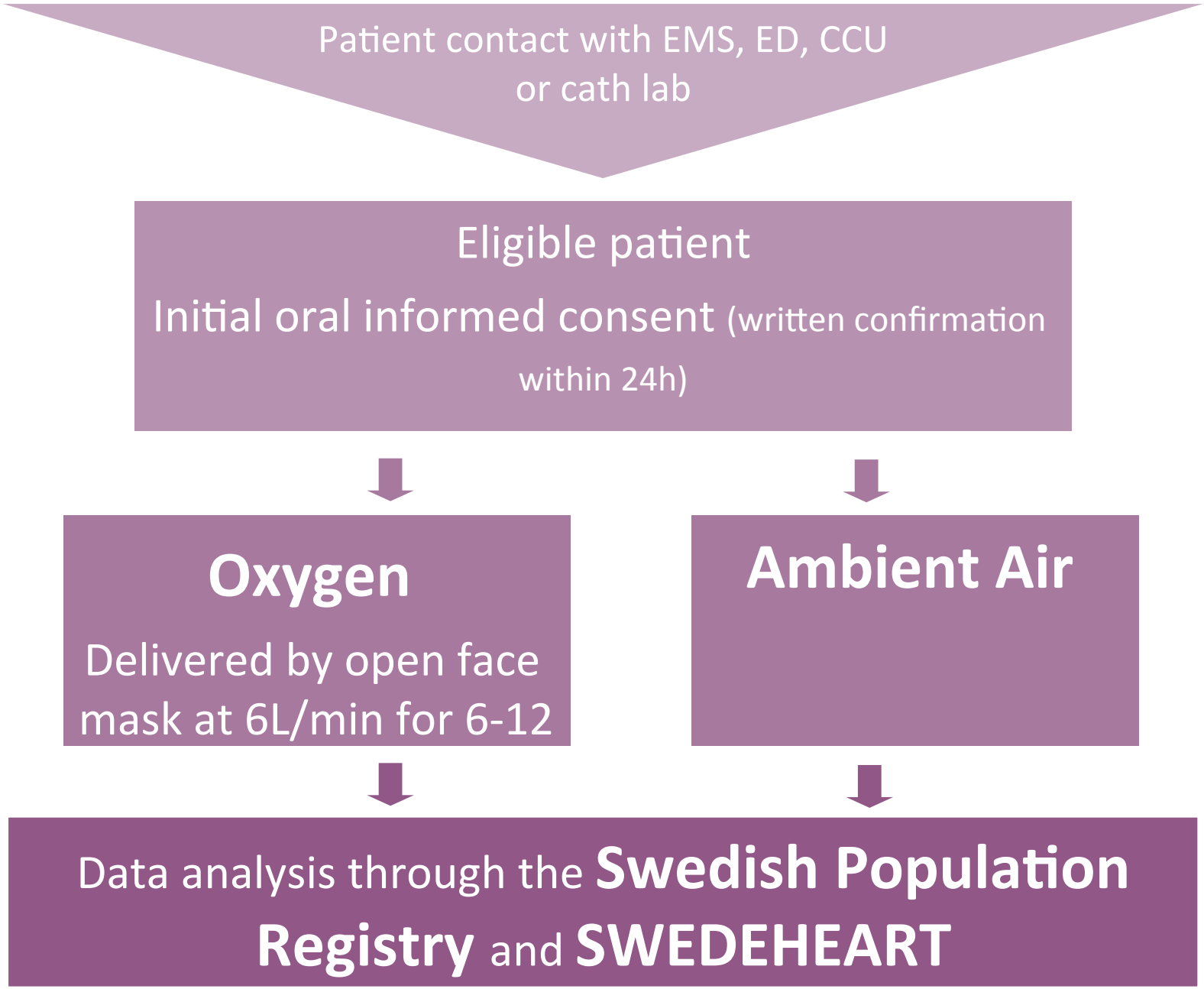


Background (3)

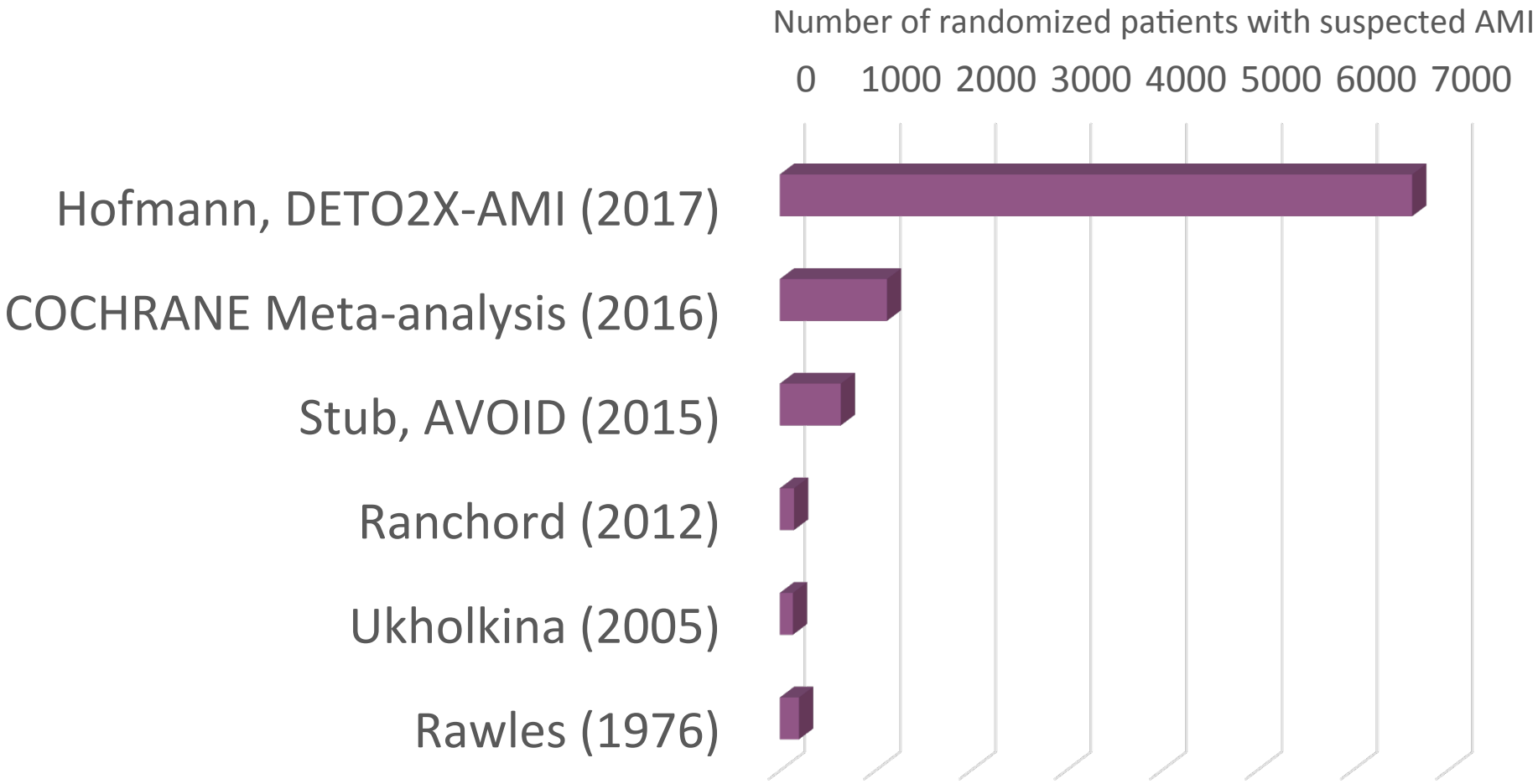


- No high quality data from large RCTs available
- The clinical effect of routine oxygen therapy in normoxemic patients with suspected AMI remains uncertain

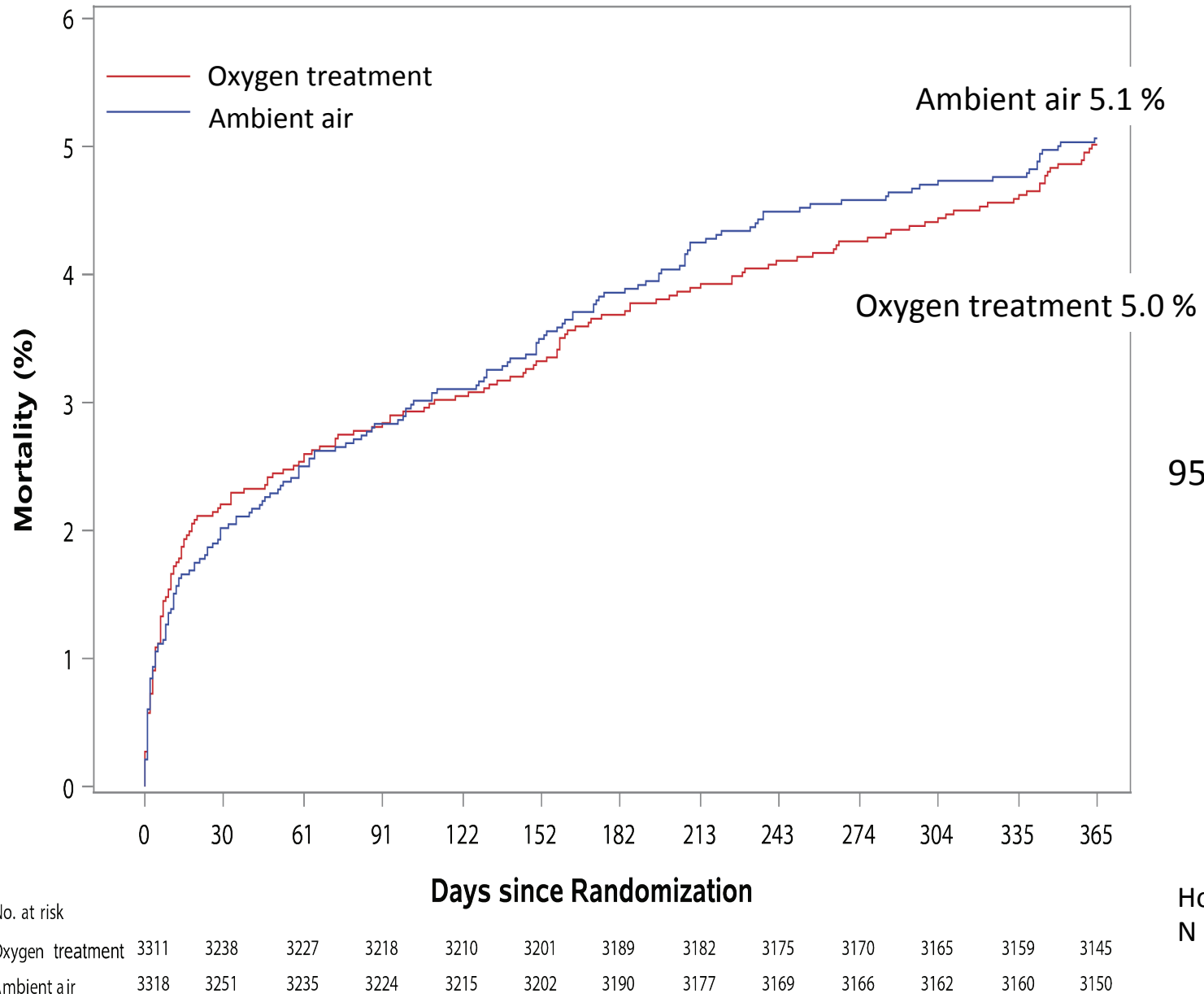
Study Enrollment



DETO2X-AMI compared to other studies



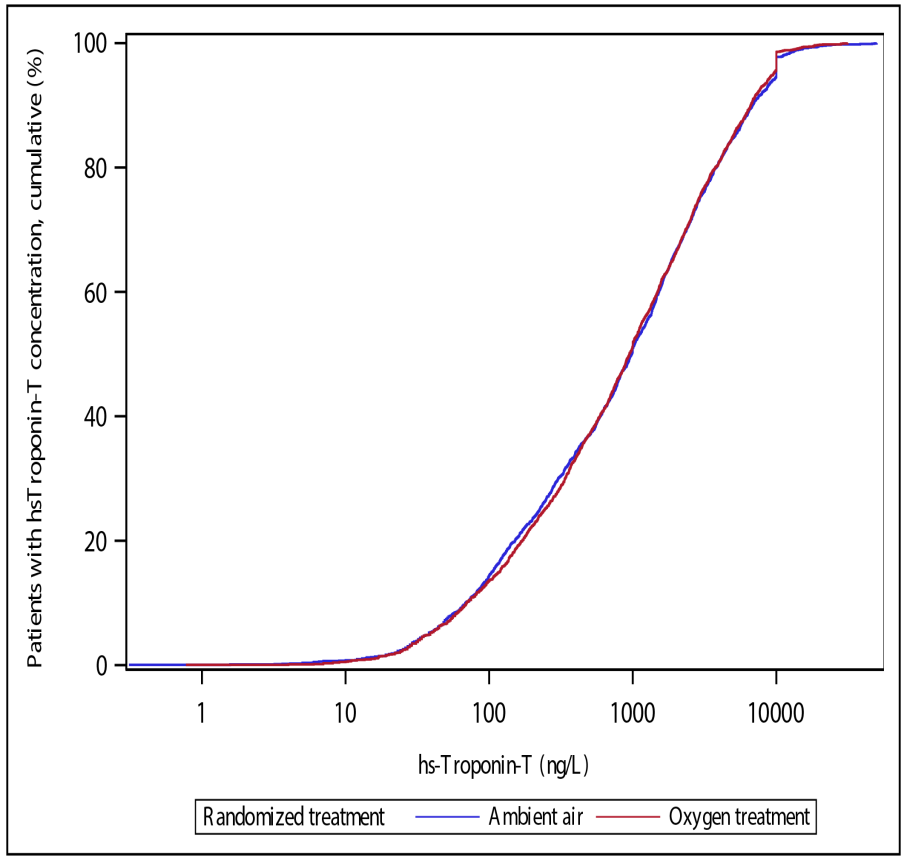
Primary Endpoint up to 365 days



HR 0.97
95% CI, 0.79 – 1.21
P=0.8

Hofmann, et al.
N Engl J Med. 2017 Aug 28

Myocardial injury by Troponin T



Cumulative distribution of hs-Cardiac Troponin T according to treatment group

hs-cardiac Troponin T	Oxygen (N=1998)	Ambient air (N=1978)	P Value
ng/L* - median** (IQR)	946.5 (243-2884)	983.0 (225-2931)	0.97

* Confirmed AMI
**Highest measured value during hospitalization

Hofmann, et al.
N Engl J Med. 2017 Aug 28

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*

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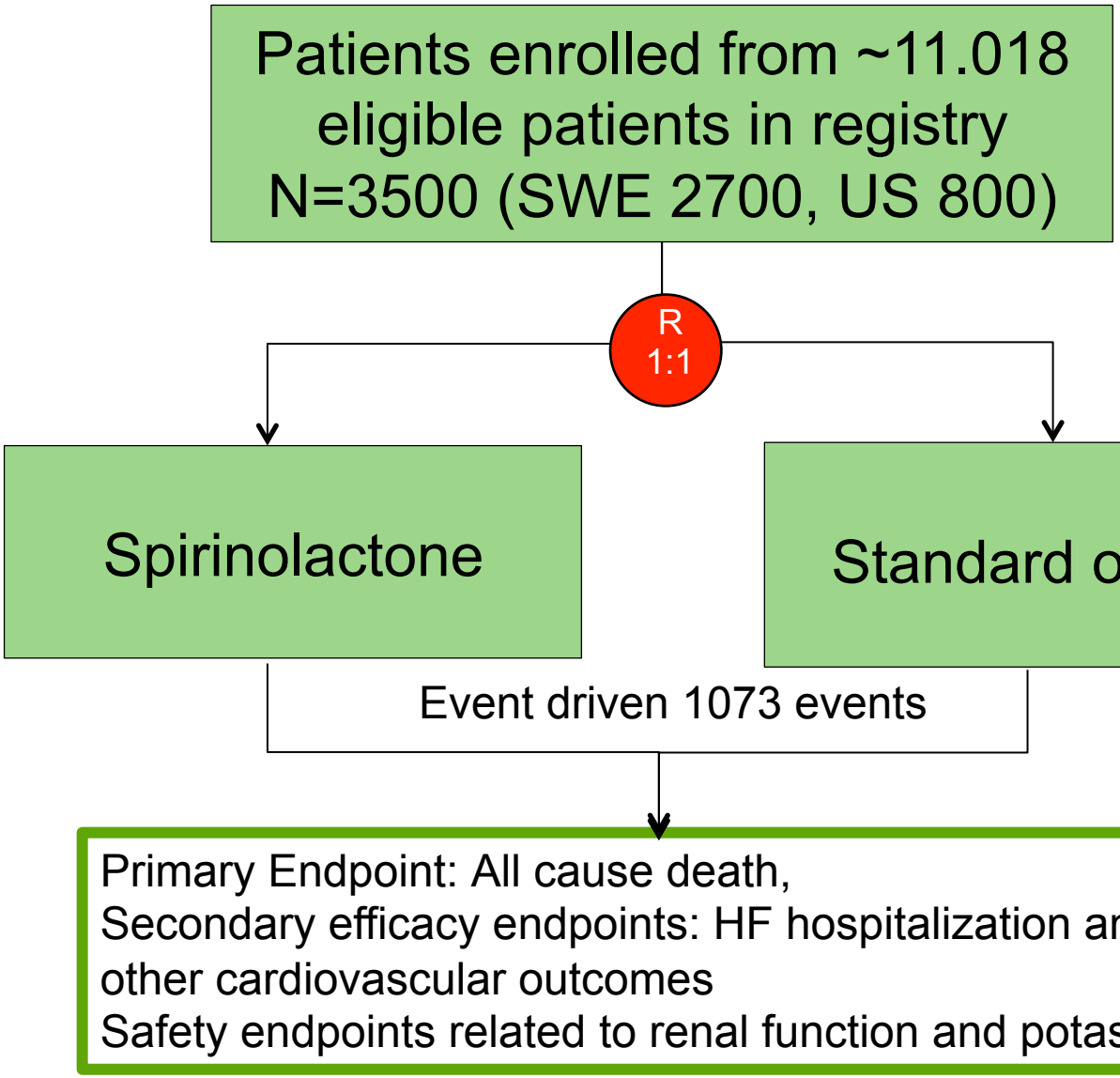
The NEW ENGLAND JOURNAL of MEDICINE

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

SPIRRIT- HFPEF



- Stable chronic HF
- Age ≥ 50 years
- EF ≥ 40%
- NT-proBNP
  - > 300 (sinus rhythm);
  - > 750 (AF)

Planned start
Q4 2017

Funded by
Swedish Heart Lung foundation
National Institute of Health, US

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."



"Prospectively designed registries and cohort studies in the context of clinical practice are highly valuable, and **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

UCR



Uppsala Clinical Research Center

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