ESC Paris, Sept. 1, 2019

Registry-based randomised clinical trials - An innovative trial paradigm

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Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Sanofi - speakers fees)

Background

85% of the money spent on clinical trial research every year is wasted [1)]

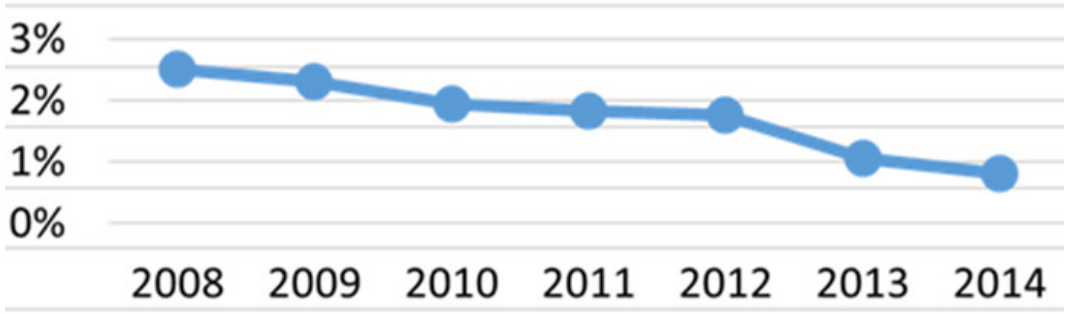
Wrong research questions are chosen, studies are poorly designed, and information on trials' methods and results is often not available [2)]

Half of all clinical trials are never published [3)]

1) Chalmers I. Lancet 2009; 374: 86 2) Chan A-W. Lancet 2014; 383: 257
3) Goldacre B. BMJ 2018;362:k3218

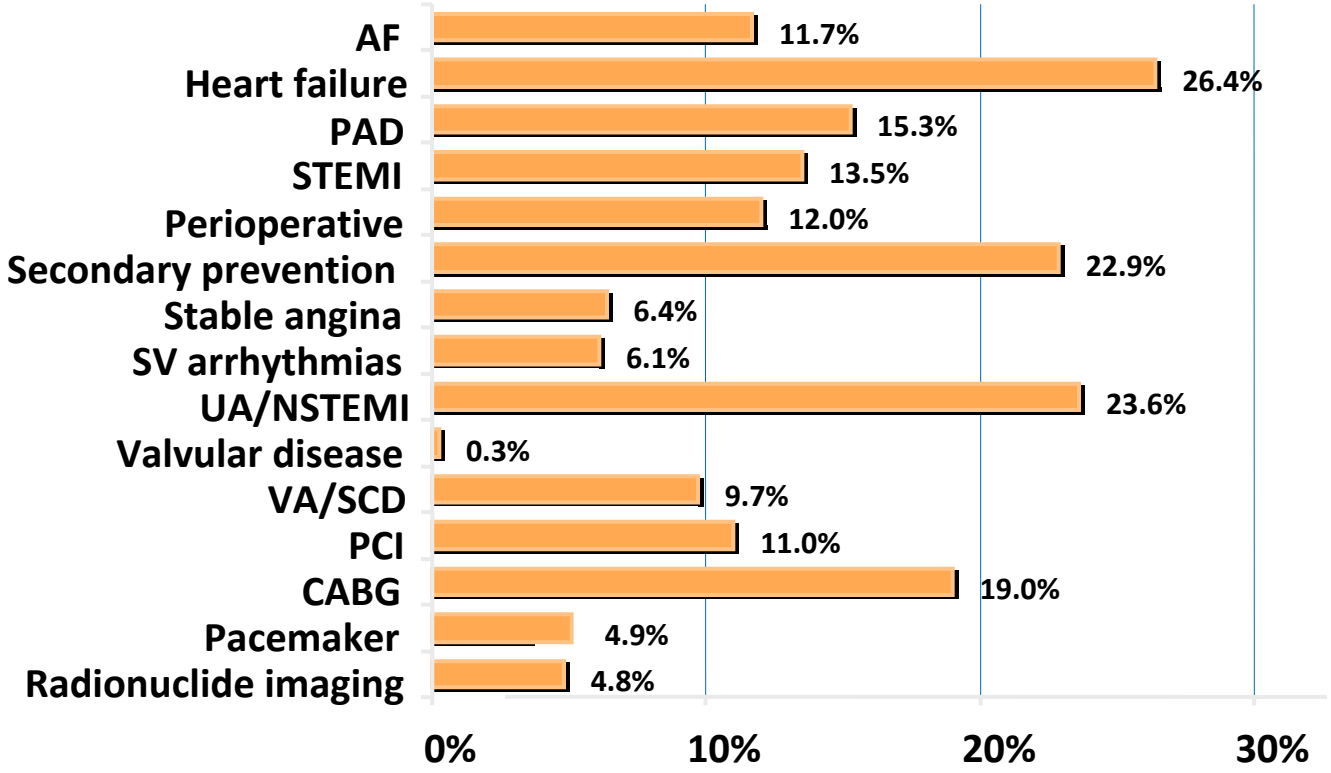
MI patients in clinical trials

Proportion of patients with MI enrolled in a clinical trial



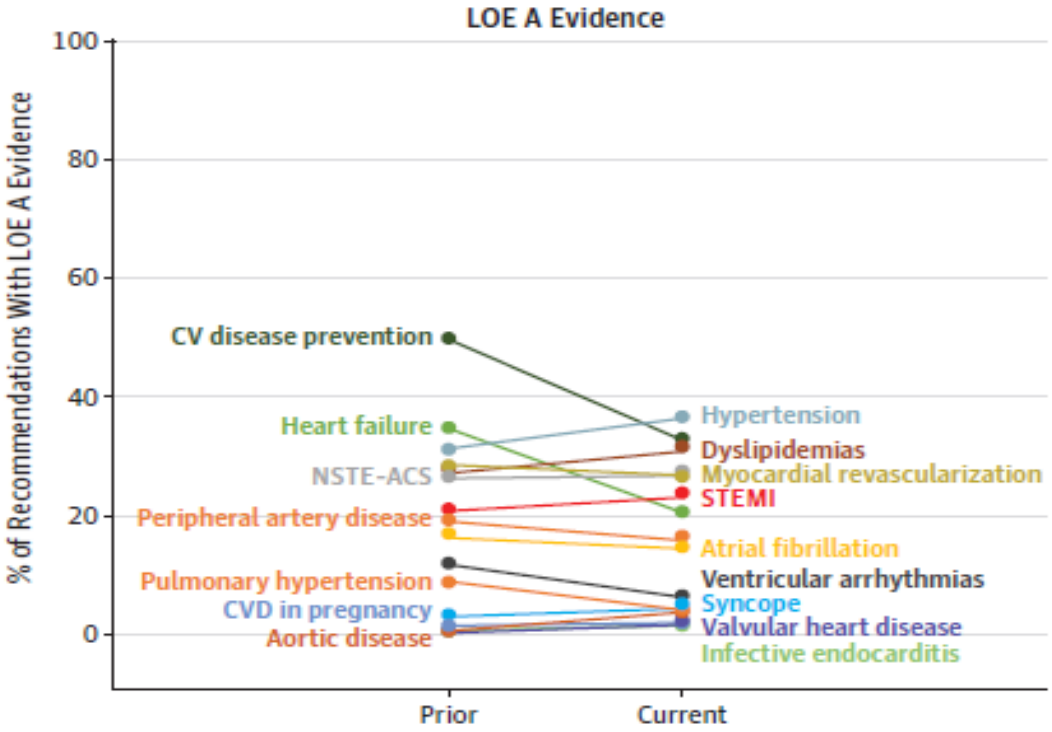
Fanaroff, AC. Am. Heart J 2019; 214: 184

Level of evidence A in cardiology guidelines



Adapted from Tricoci, P. JAMA 2009; 301:831

Level of evidence A, ESC guidelines 2008-2019 - from 17.6% to 15.1%



Fanaroff, A.C. JAMA 2019; 321:1069

Randomized Clinical Trials - RCTs

Gold standard
Eliminates confounding

BUT

Highly selected patients and centers

Surrogate endpoints

Long time to plan and complete

Expensive

Economic incentive and not patients' interests

Not applicable to real-world patients

Registries

Unselected populations – findings may be generalized

“Hard endpoints”

Large consecutive cohorts

Inexpensive

BUT

Data quality issues

Missing variables

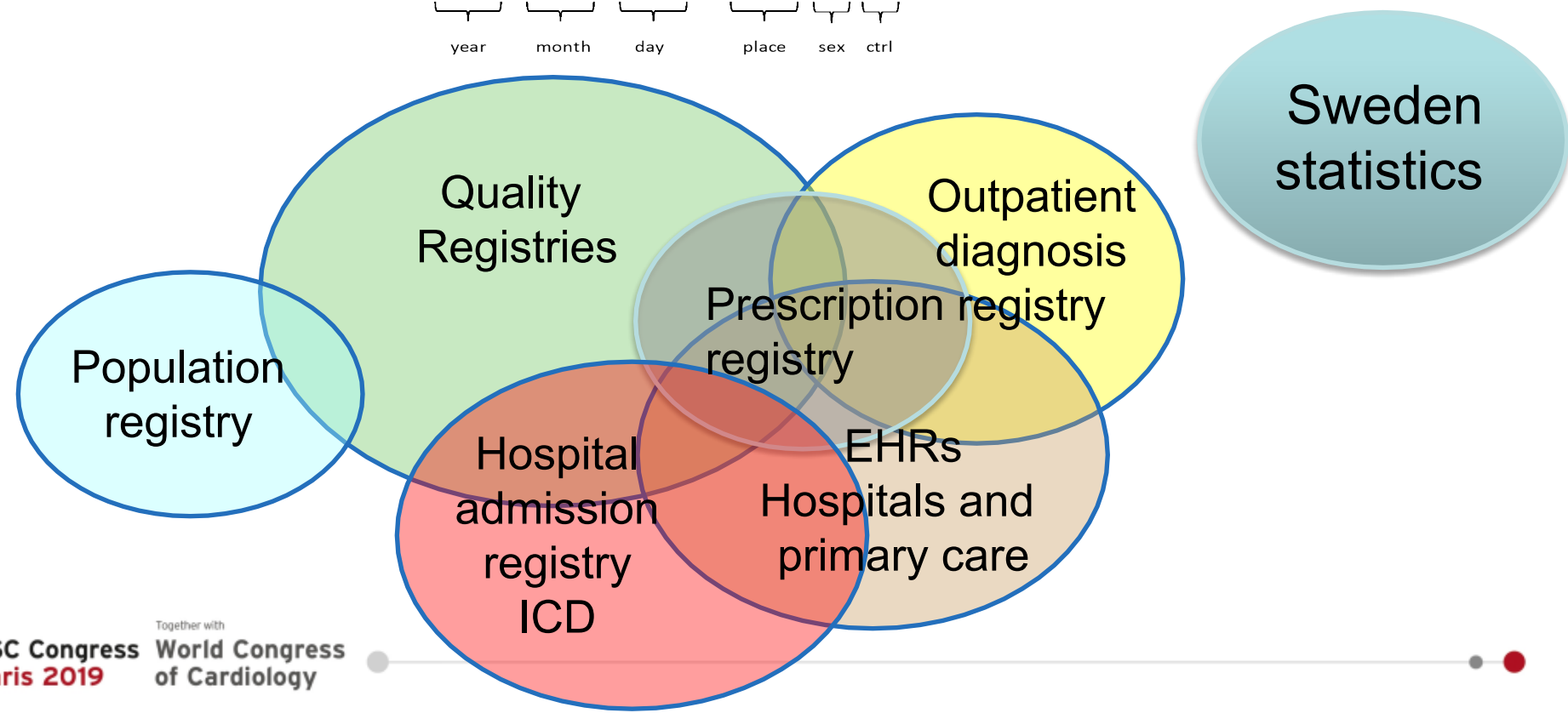
Confounding factors

Multivariable statistics - difficult to interpret

Databases for baseline characteristics and outcomes in Sweden

Personal ID number 540219-9750

year month day place sex ctrl



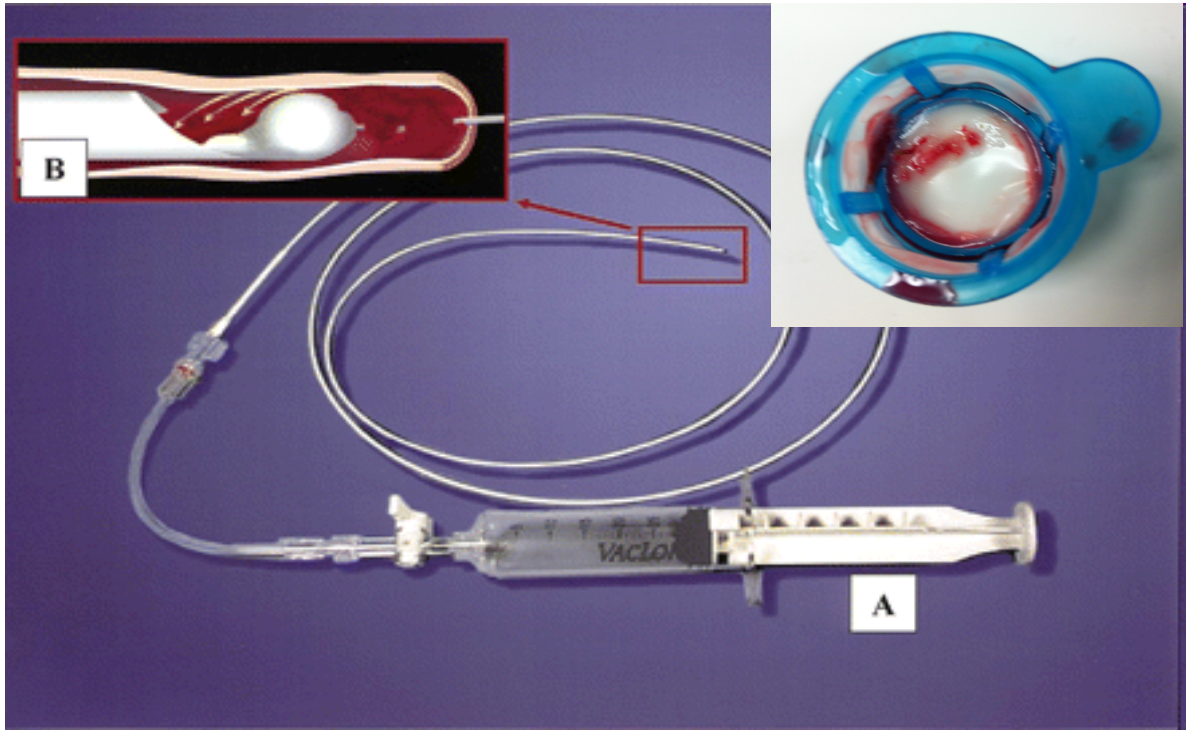
Number of cases annually: 80 000

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%

>150 variables – baseline, procedural and outcome data

Monitoring: >95% agreement between patient records and registry data

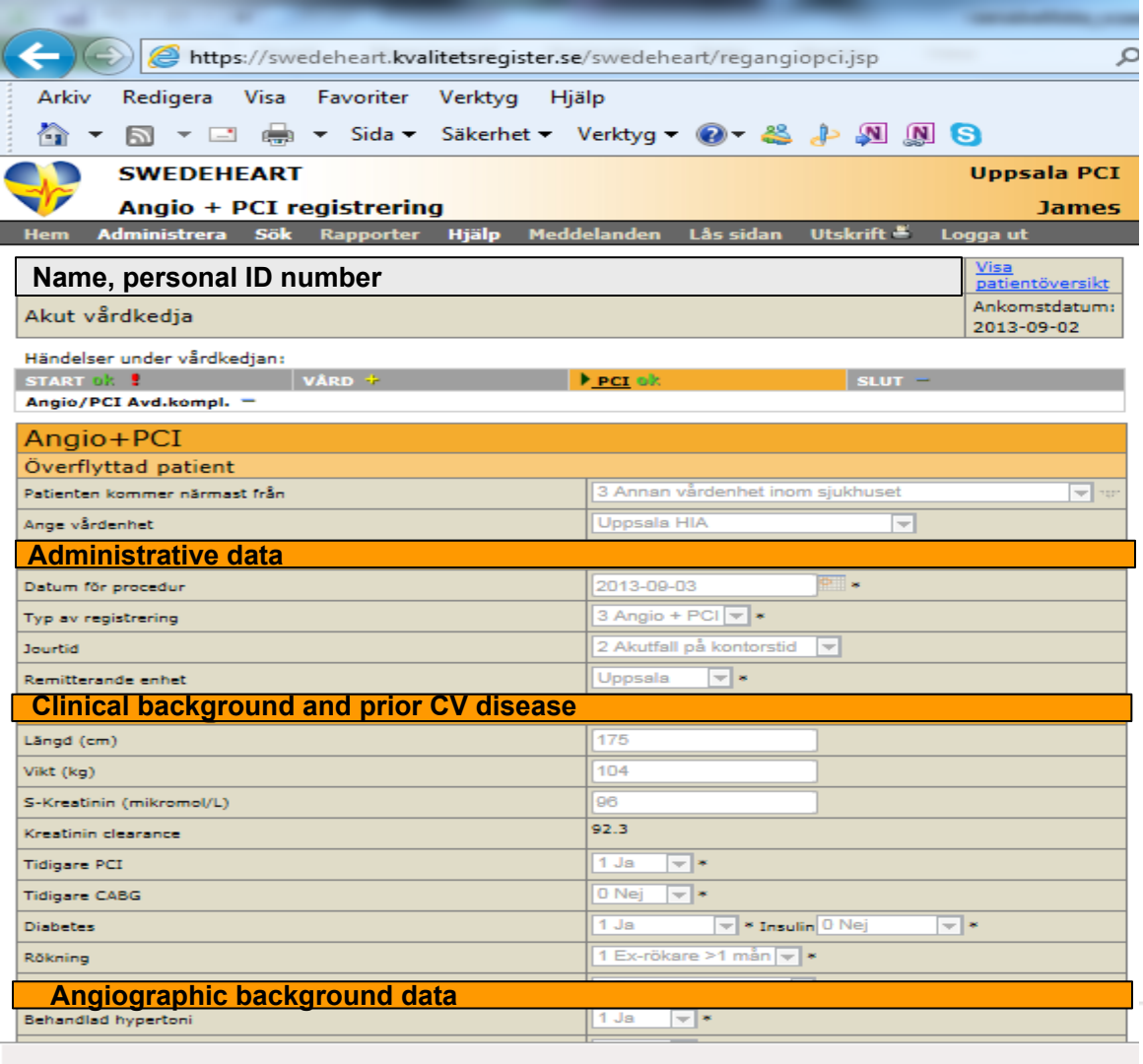
Thrombus aspiration: a simple technique, previously widely used with little evidence



Methods

TASTE *Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia*

- All 29 Swedish, one Icelandic and one Danish PCI center
- Inclusion criteria
  - STEMI and oral consent
  - <24 h symptoms
  - correspondence between ECG and angiography
- Exclusion criteria
  - need for emergency by-pass operation
  - <18 years
  - previous randomization in **TASTE**
- Primary endpoint: time to all-cause death at 30 days

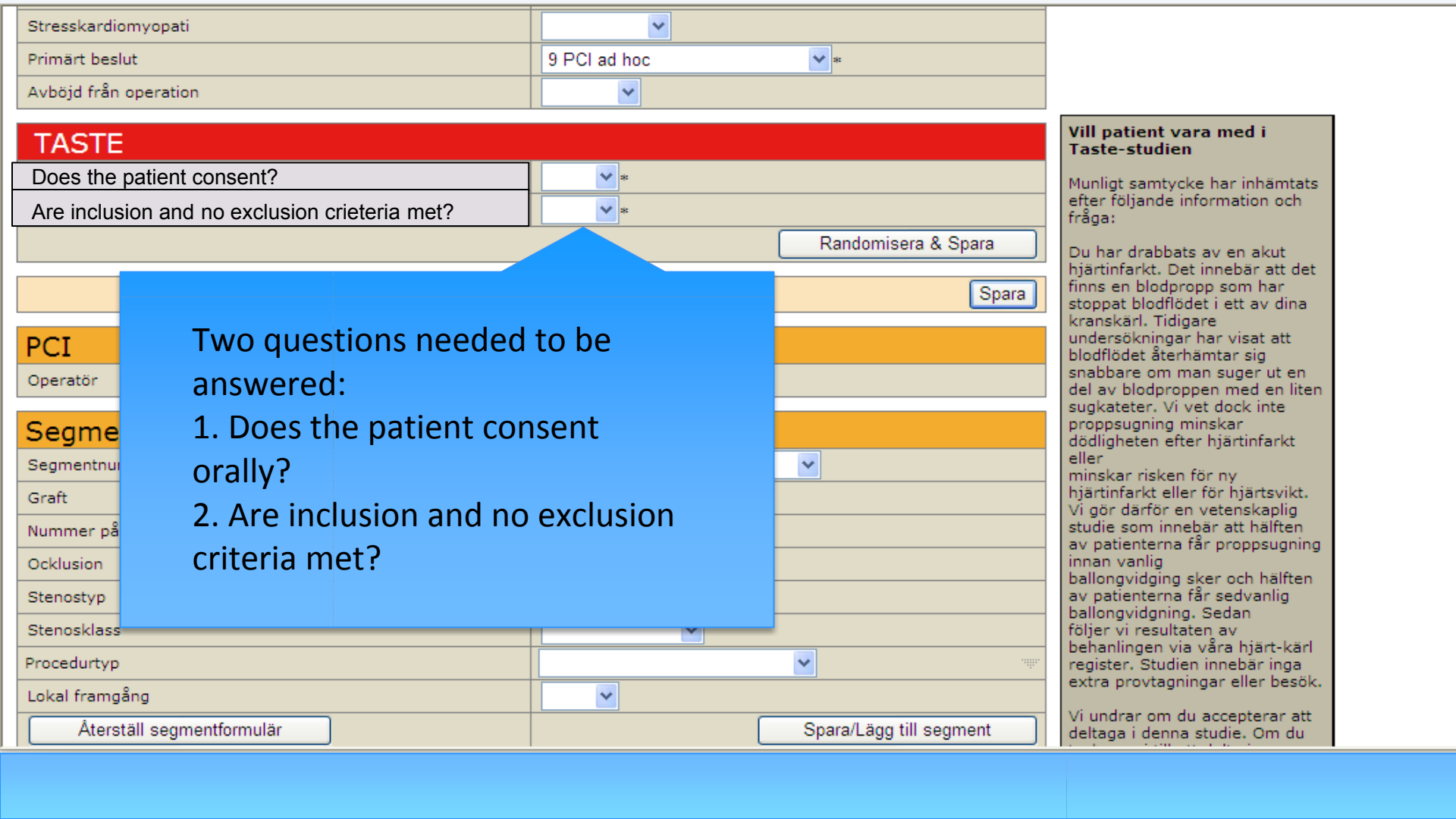


The SWEDEHEART Registry

Data entry online

Automatic linkage with population registry

Automated data checks


Stresskardiomyopati
Primärt beslut
9 PCI ad hoc
Avböjd från operation
TASTE
Does the patient consent?
Are inclusion and no exclusion crieteria met?
Randomisera & Spara
Spara
PCI
Operatör
Segme
Segmentnu
Graft
Nummer på
Ocklusion
Stenostyp
Stenosklass
Procedurtyp
Lokal framgång
Återställ segmentformulär
Spara/Lägg till segment
Two questions needed to be answered:
1. Does the patient consent orally?
2. Are inclusion and no exclusion criteria met?
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

Stresskardiomyopati	
Primärt beslut	9 PCI ad hoc *
Avböjd från operation	

TASTE

Does the patient consent?

Are inclusion and no exclusion crieteria met?

Information for consent

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
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Vi undrar om du accepterar att deltaga i denna studie. Om du

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

Stresskardiomyopati	
Primärt beslut	9 PCI ad hoc *
Avböjd från operation	

TASTE

Does the patient consent?	*
Are inclusion and no exclusion crieteria met?	*

Randomisera & Spara

Spara

PCI

Operatör	

Segment

Segmentnummer	
Graft	
Nummer på stenos i samma segment	1 Första
Ocklusion	
Stenostyp	
Stenosklass	
Procedurtyp	
Lokal framgång	

Återställ segmentformulär

Spara/Lägg till segment

Randomize and save data

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
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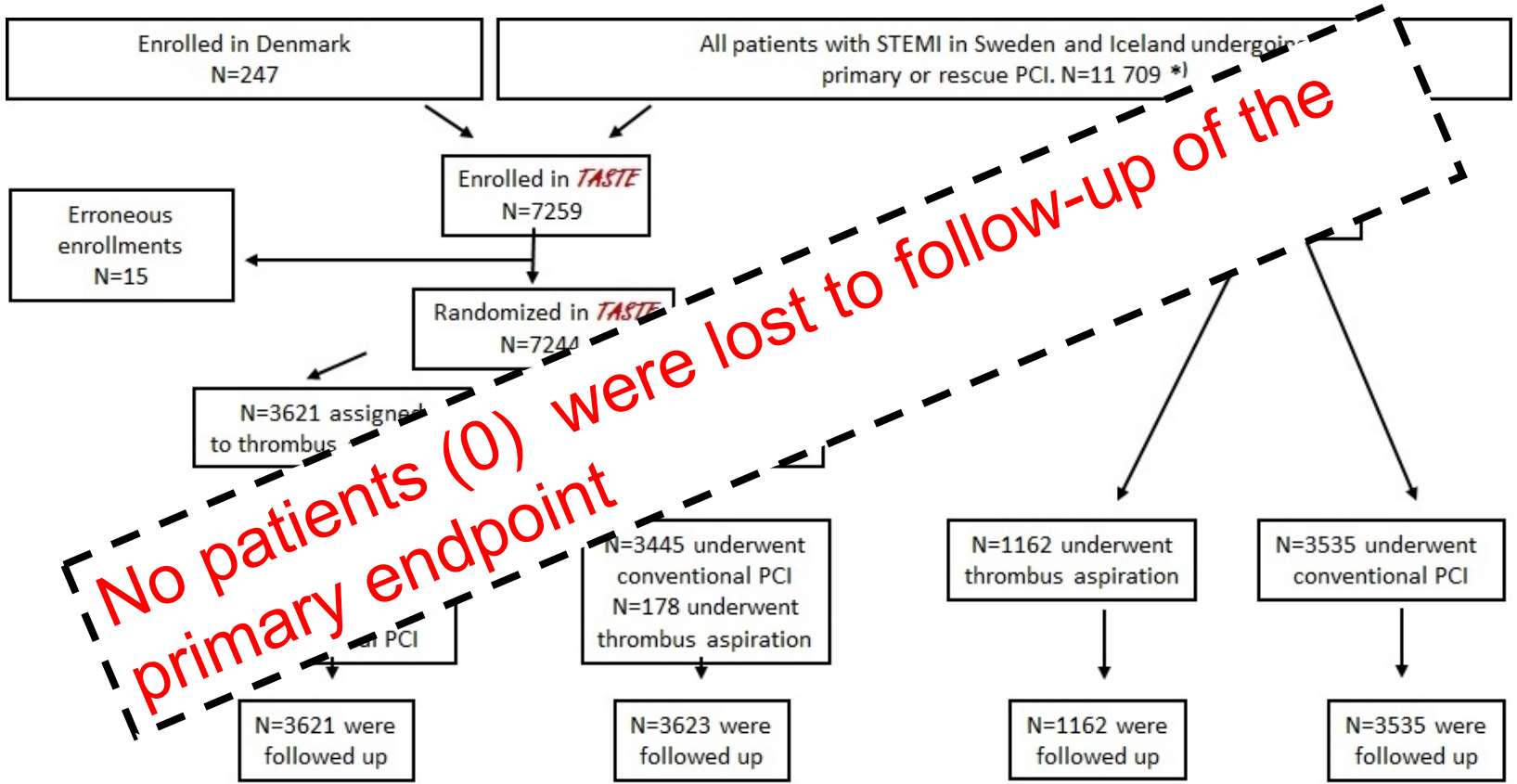
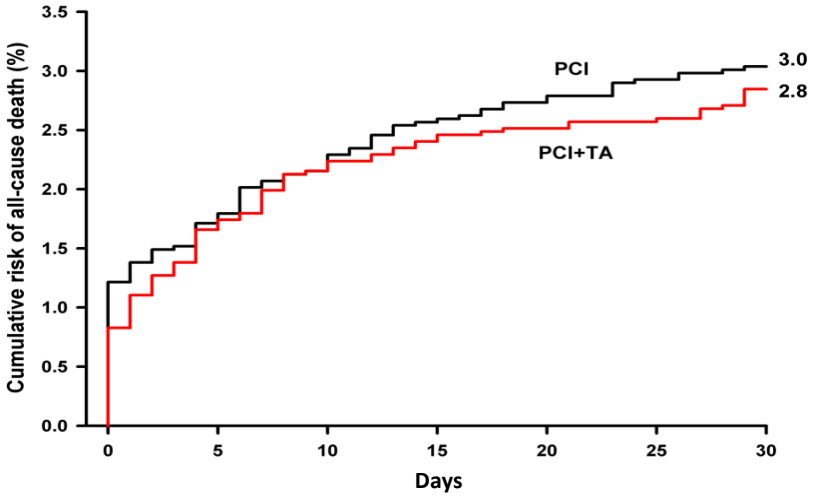
Vi undrar om du accepterar att deltaga i denna studie. Om du

TASTE trial enrollment chart

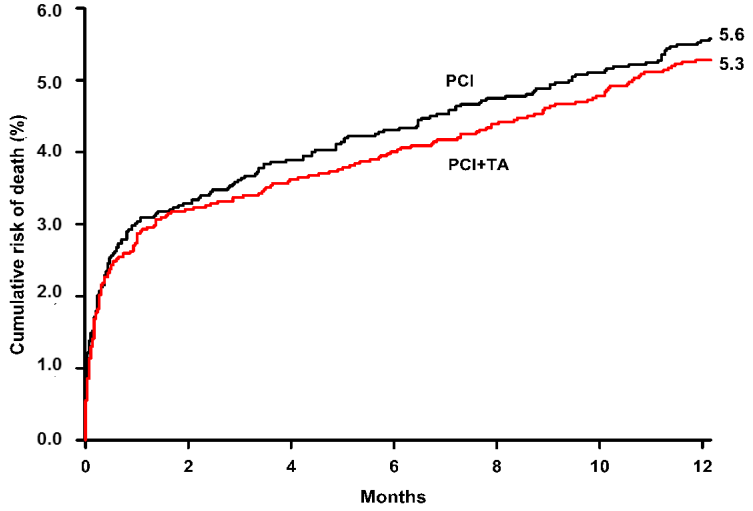


All-cause mortality at 30 days and 1 year

HR 0.94 (0.72 - 1.22), P=0.63



HR 0.94 (0.78 – 1.15), P=0.57



Fröbert, O. et al. N Engl J Med. 2013, 369:1587

Lagerqvist, B. et al. N Engl J Med. 2014, 371:1111

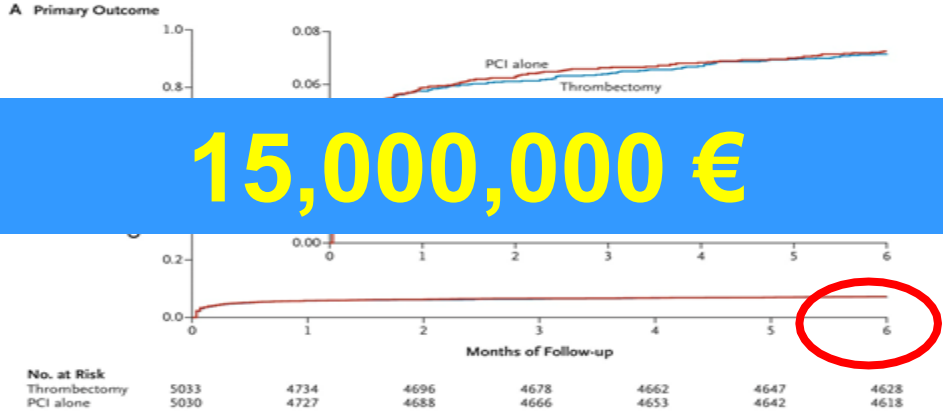
Registry based Patient Follow-up

STEMI Thrombectomy Story

TASTE

Registry-based Follow-up

Standard site-based Follow-up



350,000 €

15,000,000 €

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

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

Fröbert O et al. N Engl J Med 2013;369:1587
Lagerqvist B et al. N Engl J Med 2014;371:1111
Jolly SS et al. N Engl J Med 2015;372:1389

TASTE – clinical impact

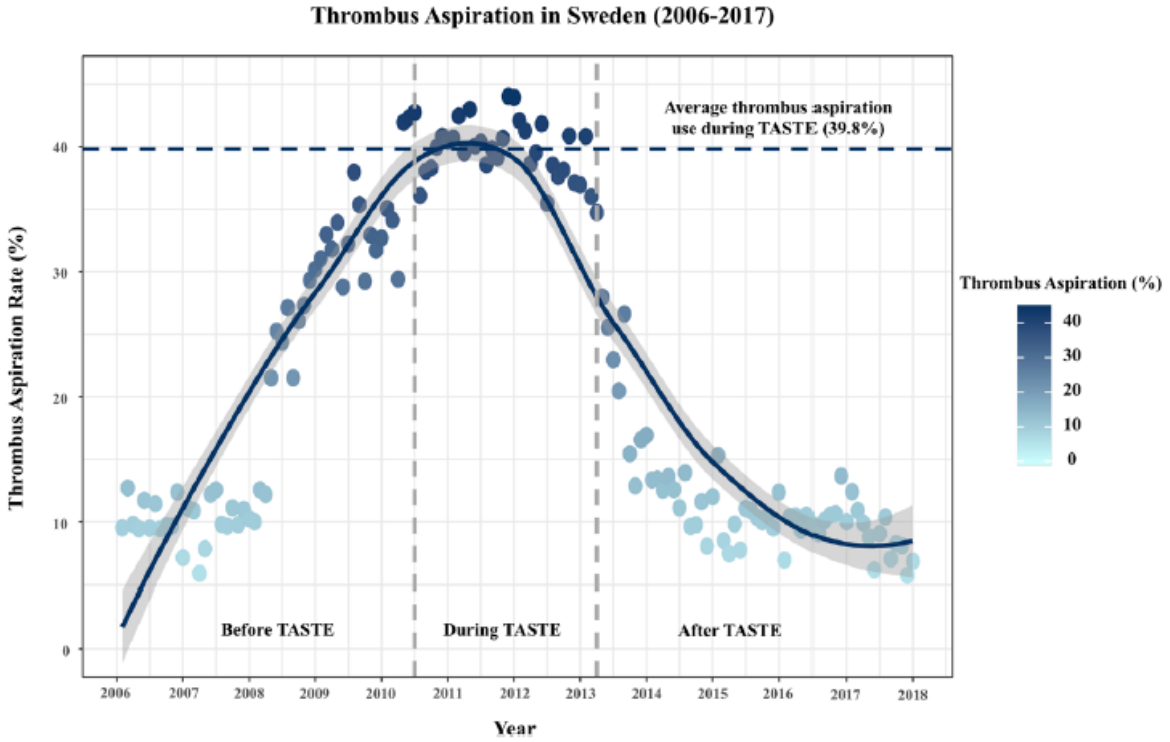
Thrombus aspiration

downgraded in ACC/AHA and

ESC guidelines from:

IIa (reasonable to consider)

to: IIIa (not recommended)



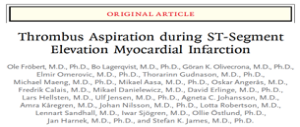
Buccheri, S. et al. Circ Cardiovasc Int. 2019, 12:e007381

RRCT vs. RCT

	RCT	RRCT
Treatment strategy		+
Device – CE marked, in use		+
Device, first in man	+	

Four finalized RRCTs – all guideline changing

TASTE
Thrombus aspiration in ST-elevation myocardial infarction, N=7244
(N Engl J Med. 2013, 369:1587 and N Engl J Med. 2014, 371:1111)

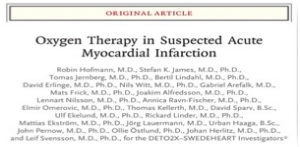

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction


ORIGINAL ARTICLE
Outcomes 1 Year after Thrombus Aspiration for Myocardial Infarction

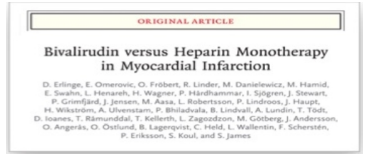
iFR-SWEDEHEART
Comparison of two invasive diagnostic methodologies, N=2037
(N Engl J Med. 2017 376:1813)


ORIGINAL ARTICLE
Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI

DETO2X-AMI
Determination of the role of oxygen in acute myocardial infarction, N=6629
(N Engl J Med. 2017; 377:1240)


ORIGINAL ARTICLE
Oxygen Therapy in Suspected Acute Myocardial Infarction

VALIDATE-SWEDEHEART
Bivalirudin versus Heparin in NST and ST- Elevation myocardial infarction in patients on modern antiplatelet therapy, N=6006 *(N Engl J Med. 2017; 377:1132)*


ORIGINAL ARTICLE
Bivalirudin versus Heparin Monotherapy in Myocardial Infarction

Impact on Swedish health economy

TASTE

Cost of study:	350 000 €
Cost reduction for health care system:	220 000 €/year

DETO2X-AMI

Cost of study:	950 000 €
Cost reduction for health care system:	3 800 000 €/year

VALIDATE-SWEDEHEART

Cost of study:	1 600 000 €
Cost reduction for health care system:	4 700 000 €/year

Some ongoing RRCTs in Sweden

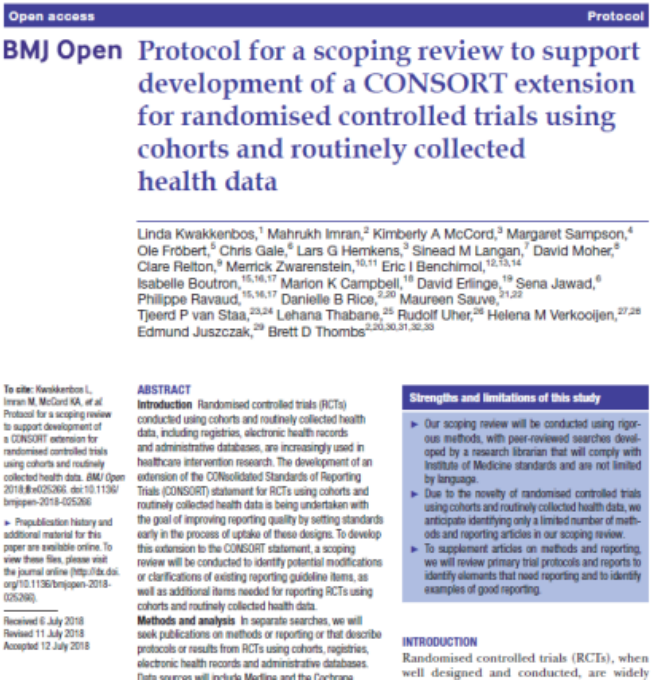
- IAMI: Influenza vaccine/placebo post-MI, n=4400
- REDUCE: Open label beta blocker post-MI, n= 7000
- MINOCA: Open label beta blocker/ACE post-MINOCA, n=3500

RRCT advantages and limitations

Advantages

- No need for purpose built data collection system
- Fast recruitment of large cohorts of ”real world” patients
- No or negligible loss to follow-up
- High impact
- Inexpensive
- Long term follow-up and follow-up of non-randomized patients

CONSORT extension coming up for trials using cohorts and routinely collected health data



Open access Protocol

BMJ Open

Protocol for a scoping review to support development of a CONSORT extension for randomised controlled trials using cohorts and routinely collected health data

Linda Kwakkenbos,[1] Mahrukh Imran,[2] Kimberly A McCord,[3] Margaret Sampson,[4] Ole Fröbert,[5] Chris Gale,[6] Lars G Hemkens,[3] Sinead M Langan,[7] David Moher,[8] Clare Relton,[9] Merrick Zwarenstein,[10,11] Eric I Benchimol,[12,13,14] Isabelle Boutron,[15,16,17] Marion K Campbell,[18] David Erlinge,[19] Sena Jawad,[6] Philippe Ravaud,[15,16,17] Danielle B Rice,[2,20] Maureen Sauve,[21,22] Tjeerd P van Staa,[23,24] Lehana Thabane,[25] Rudolf Uher,[26] Helena M Verkooijen,[27,28] Edmund Juszczak,[29] Brett D Thombs[2,20,30,31,32,33]

To cite: Kwakkenbos L, Imran M, McCord KA, *et al*. Protocol for a scoping review to support development of a CONSORT extension for randomised controlled trials using cohorts and routinely collected health data. *BMJ Open* 2018;**8**:e025266. doi:10.1136/bmjopen-2018-025266

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-025266).

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Accepted 12 July 2018

ABSTRACT

Introduction Randomised controlled trials (RCTs) conducted using cohorts and routinely collected health data, including registries, electronic health records and administrative databases, are increasingly used in healthcare intervention research. The development of an extension of the CONsolidated Standards of Reporting Trials (CONSORT) statement for RCTs using cohorts and routinely collected health data is being undertaken with the goal of improving reporting quality by setting standards early in the process of uptake of these designs. To develop this extension to the CONSORT statement, a scoping review will be conducted to identify potential modifications or clarifications of existing reporting guideline items, as well as additional items needed for reporting RCTs using cohorts and routinely collected health data.

Methods and analysis In separate searches, we will seek publications on methods or reporting or that describe protocols or results from RCTs using cohorts, registries, electronic health records and administrative databases. Data sources will include Medline and the Cochrane

Strengths and limitations of this study

- Our scoping review will be conducted using rigorous methods, with peer-reviewed searches developed by a research librarian that will comply with Institute of Medicine standards and are not limited by language.
- Due to the novelty of randomised controlled trials using cohorts and routinely collected health data, we anticipate identifying only a limited number of methods and reporting articles in our scoping review.
- To supplement articles on methods and reporting, we will review primary trial protocols and reports to identify elements that need reporting and to identify examples of good reporting.

INTRODUCTION

Randomised controlled trials (RCTs), when well designed and conducted, are widely

STUDY PROTOCOL Open Access

Protocol for the development of a CONSORT extension for RCTs using cohorts and routinely collected health data

Linda Kwakkenbos[1], Edmund Juszczak[2], Lars G Hemkens[3], Margaret Sampson[4], Ole Fröbert[5], Clare Relton[6], Chris Gale[7], Merrick Zwarenstein[8,9], Sinéad M Langan[10], David Moher[11], Isabelle Boutron[12,13,14], Philippe Ravaud[12,13,14], Marion K Campbell[15], Kimberly A Mc Cord[3], Tjeerd P van Staa[16,17], Lehana Thabane[18], Rudolf Uher[19], Helena M Verkooijen[20,21], Eric I Benchimol[22,23,24], David Erlinge[25], Maureen Sauvé[26,27], David Torgerson[28] and Brett D Thombs[29,30,31,32,33,34*]

Abstract

Background: Randomized controlled trials (RCTs) are often complex and expensive to perform. Less than one third achieve planned recruitment targets, follow-up can be labor-intensive, and many have limited real-world generalizability. Designs for RCTs conducted using cohorts and routinely collected health data, including registries, electronic health records, and administrative databases, have been proposed to address these challenges and are being rapidly adopted. These designs, however, are relatively recent innovations, and published RCT reports often do not describe important aspects of their methodology in a standardized way. Our objective is to extend the Consolidated Standards of Reporting Trials (CONSORT) statement with a consensus-driven reporting guideline for RCTs using cohorts and routinely collected health data.

Methods: The development of this CONSORT extension will consist of five phases. Phase 1 (completed) consisted of the project launch, including fundraising, the establishment of a research team, and development of a conceptual framework. In phase 2, a systematic review will be performed to identify publications (1) that describe methods or reporting considerations for RCTs conducted using cohorts and routinely collected health data or (2) that are protocols or report results from such RCTs. An initial "long list" of possible modifications to CONSORT checklist items and possible new items for the reporting guideline will be generated based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statements. Additional possible modifications and new items will be identified based on the results of the systematic review. Phase 3 will consist of a three-round Delphi exercise with methods and content experts to evaluate the "long list" and generate a "short list" of key items. In phase 4, these items will serve as the basis for an in-person consensus meeting to finalize a core set of items to be included in the reporting guideline and checklist. Phase 5 will involve drafting the checklist and elaboration-explanation documents, and dissemination and implementation of the guideline.

Discussion: Development of this CONSORT extension will contribute to more transparent reporting of RCTs conducted using cohorts and routinely collected health data.

Keywords: Administrative data, Cohort, CONSORT, Electronic health records, Electronic medical records, Electronic patient records, Randomized controlled trials, RCTs, Registries, Reporting guideline, Routinely collected health data

1) Kwakkenbos L. BMJ Open 2018;8:e025266
2) Kwakkenbos L. Research Integrity and Peer Review (2018) 3:9

Conclusions

- Urgent need for randomized trials in clinical medicine
- Registries are strong networks for collaboration enrolling complete patient populations
- Registry-based Randomized Clinical Trials are ideal for:
  One clinical hypothesis, broad inclusion, hard endpoints
- Baseline and outcome variables from registries
- Initiated by clinicians, not Big Pharma
- Fast enrollment, low cost
- Keep it simple

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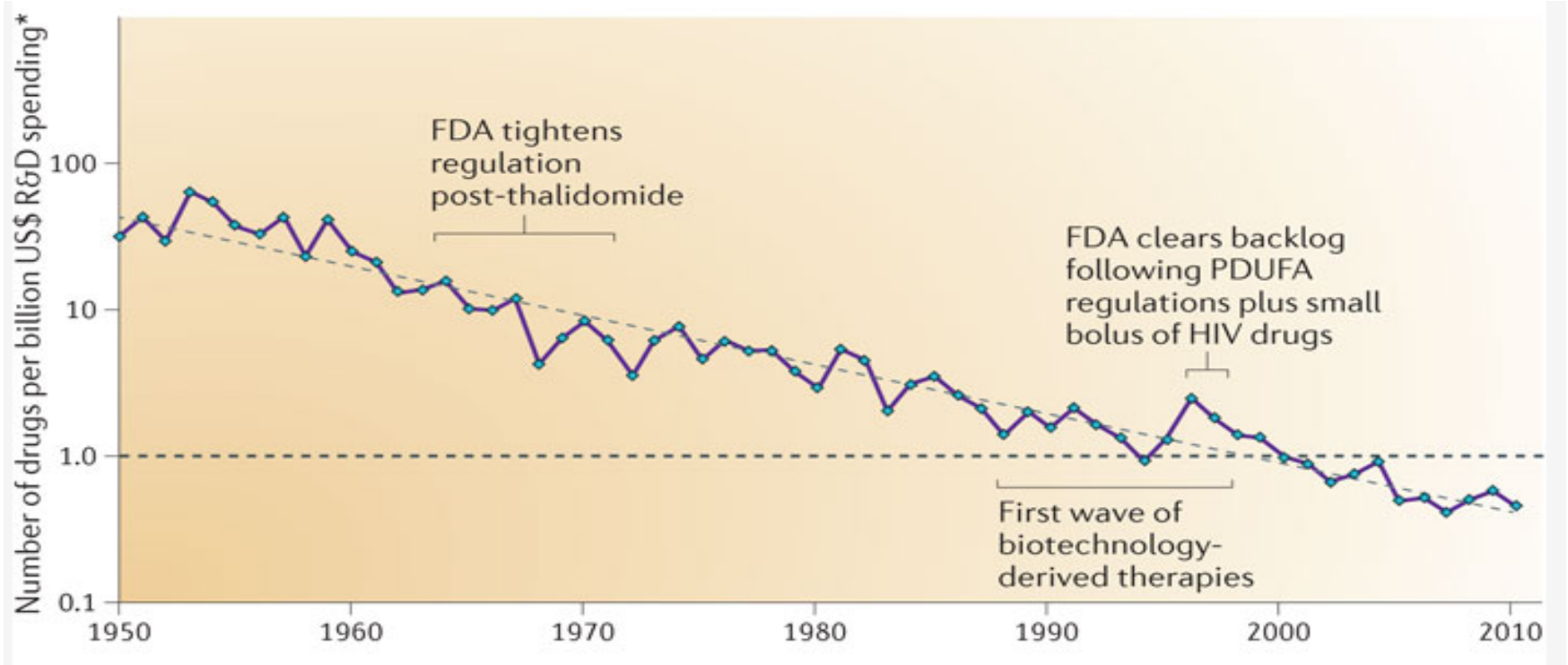
Back-up slides

An RRCT do-it-yourself guide

- One, simple hypothesis
- Patient representatives on board if possible
- Well-defined baseline and primary outcome variables
- All centers and colleagues
- Limit additional workload, simple randomization
- Reduce monitoring
- Adjudicate selected variables only
- Online inclusion status
- Broad representation in publications

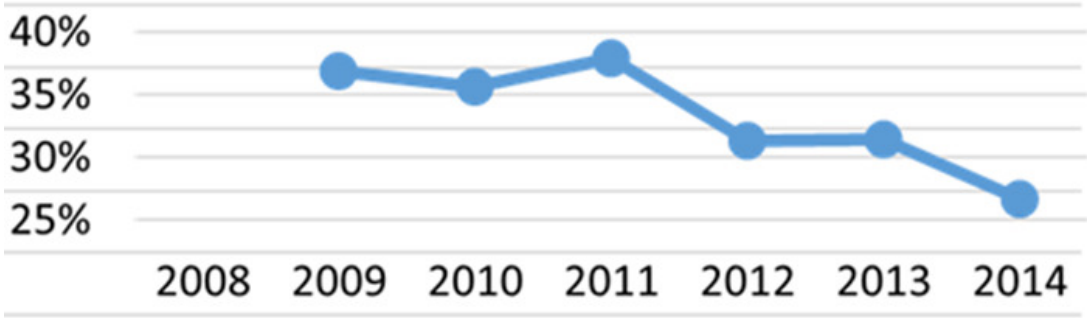
R&D productivity



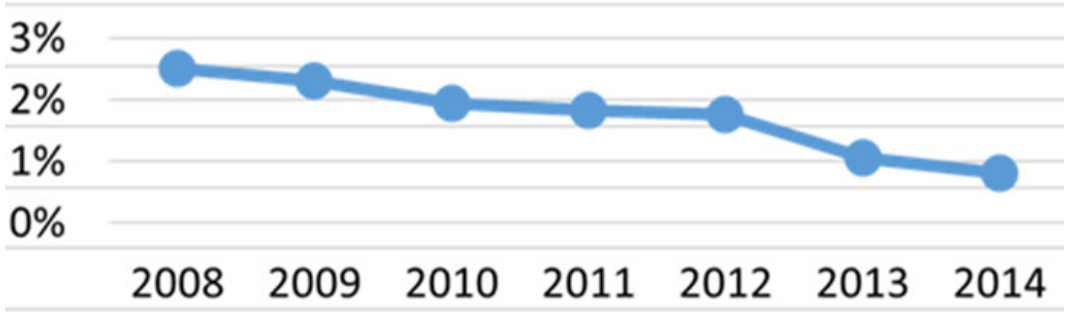
Scanell, JW, Nature Reviews Drug Discovery 2012: 11; 191

Hospital participation in MI trials

Proportion of hospitals enrolling at least 1 MI patient/year

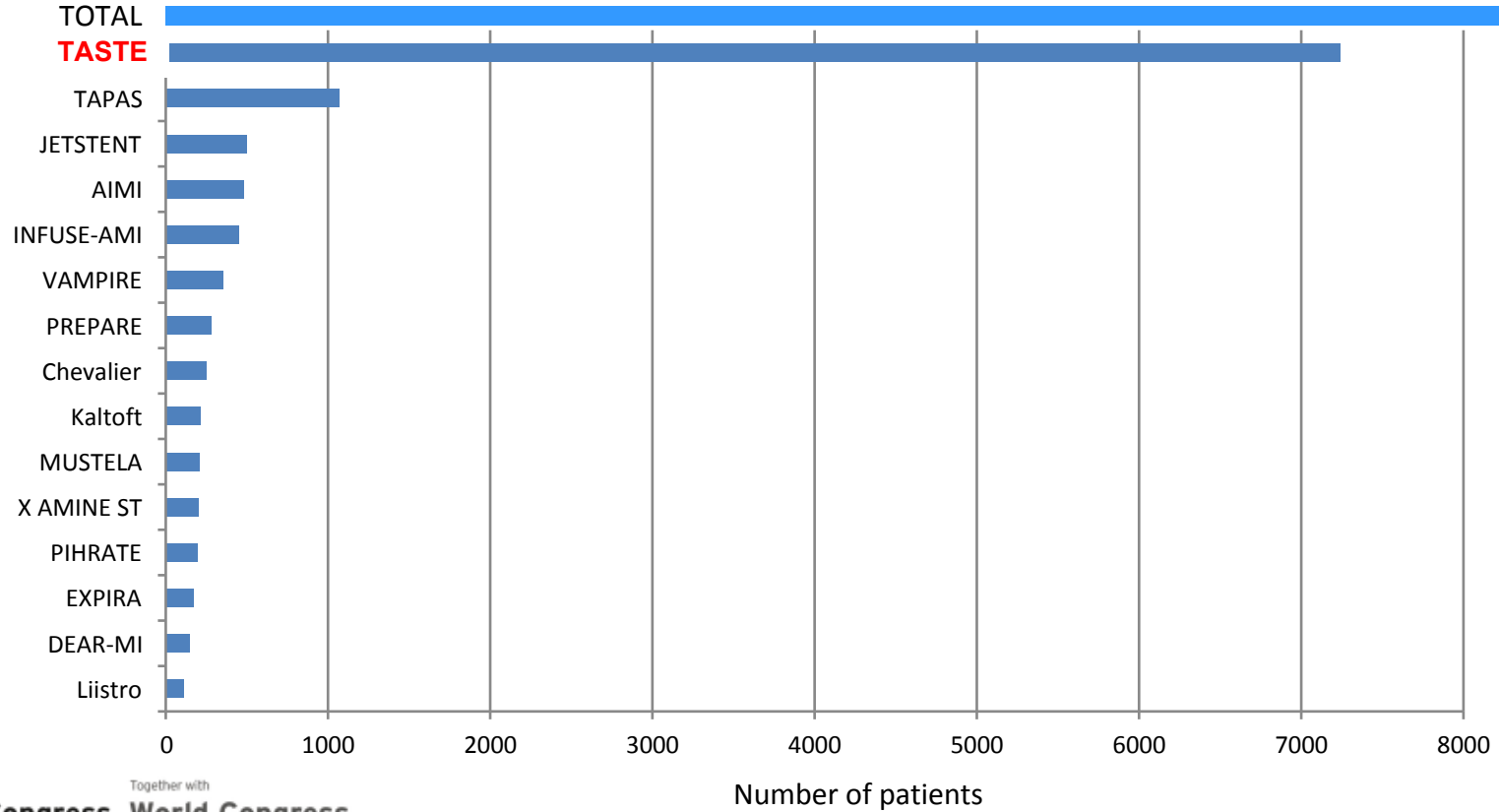


Proportion of patients with MI enrolled in a clinical trial



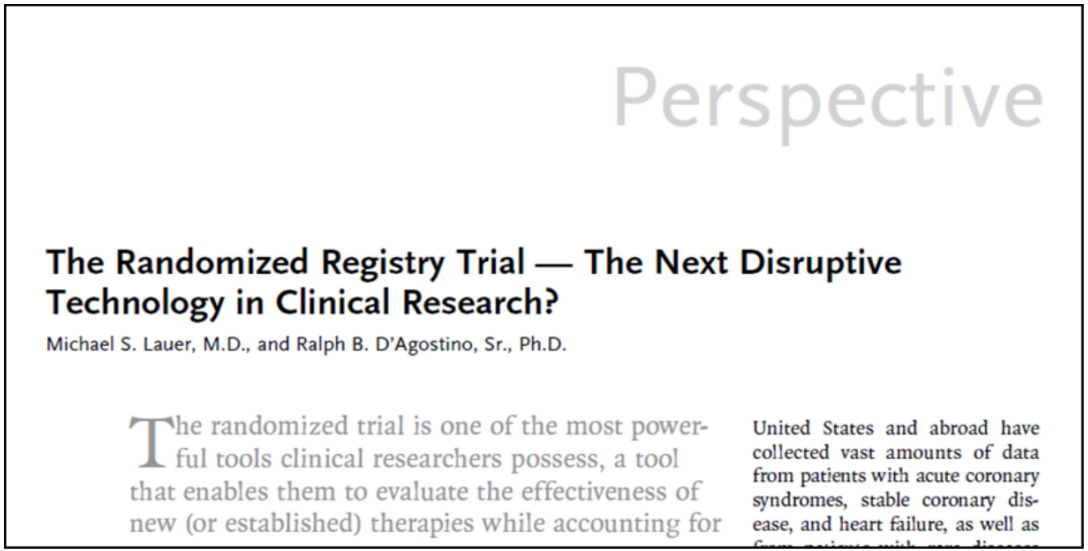
Fanaroff, AC. Am. Heart J 2019; 214: 184

TASTE and previous trials



A disruptive technology?

- The New England Journal of Medicine suggested it:



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.

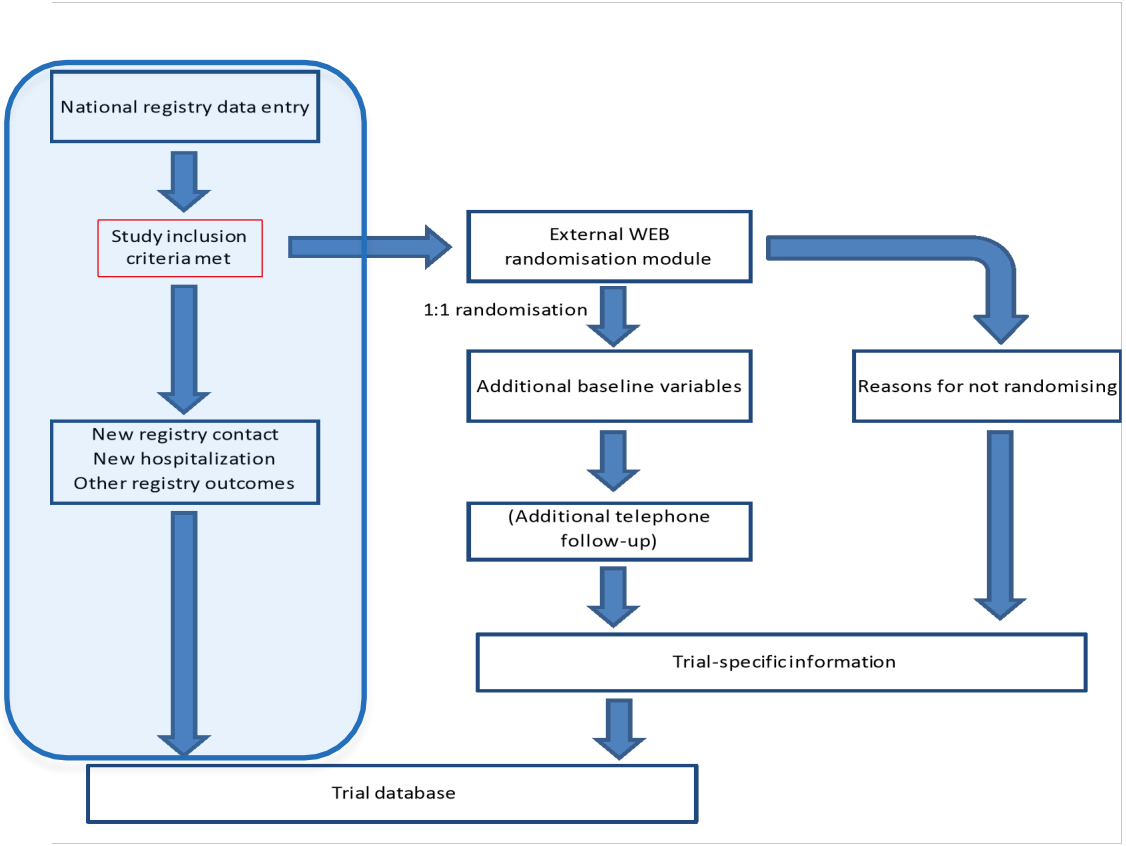
The randomized trial is one of the most powerful tools clinical researchers possess, a tool that enables them to evaluate the effectiveness of new (or established) therapies while accounting for

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

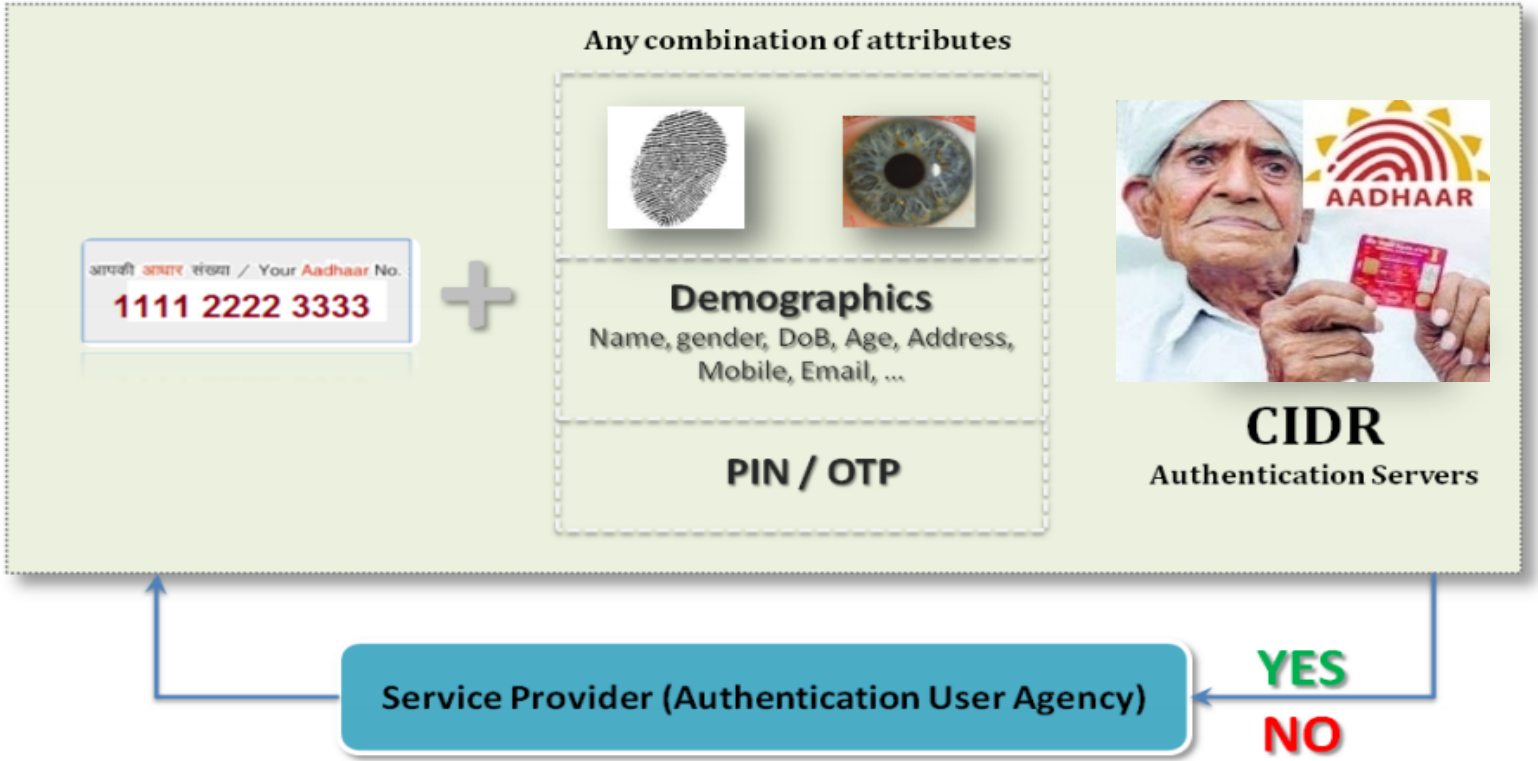
A disruptive technology?

- .. is one that displaces an established technology and shakes up the industry or a ground-breaking product that creates a completely new industry

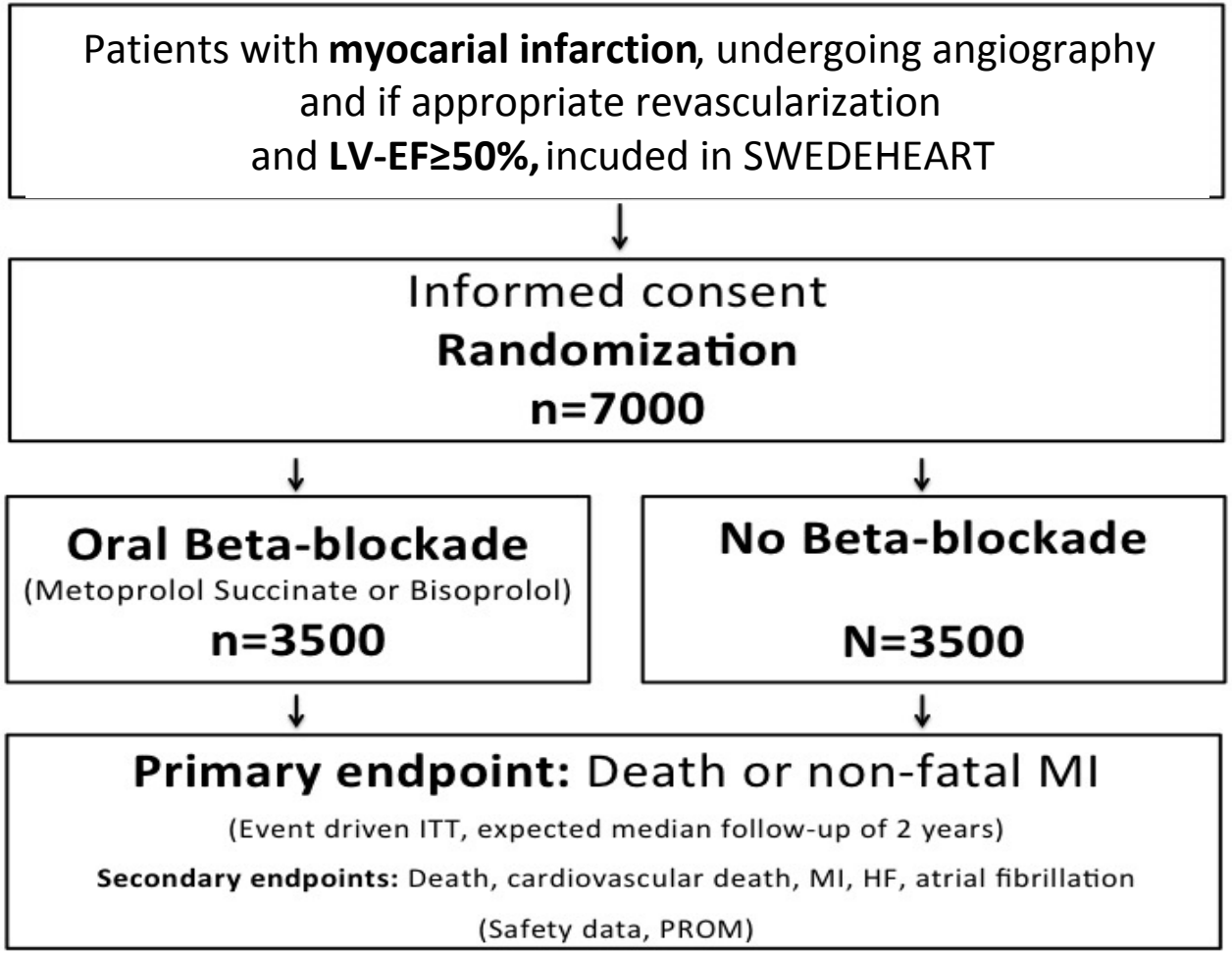
Several countries with different registries



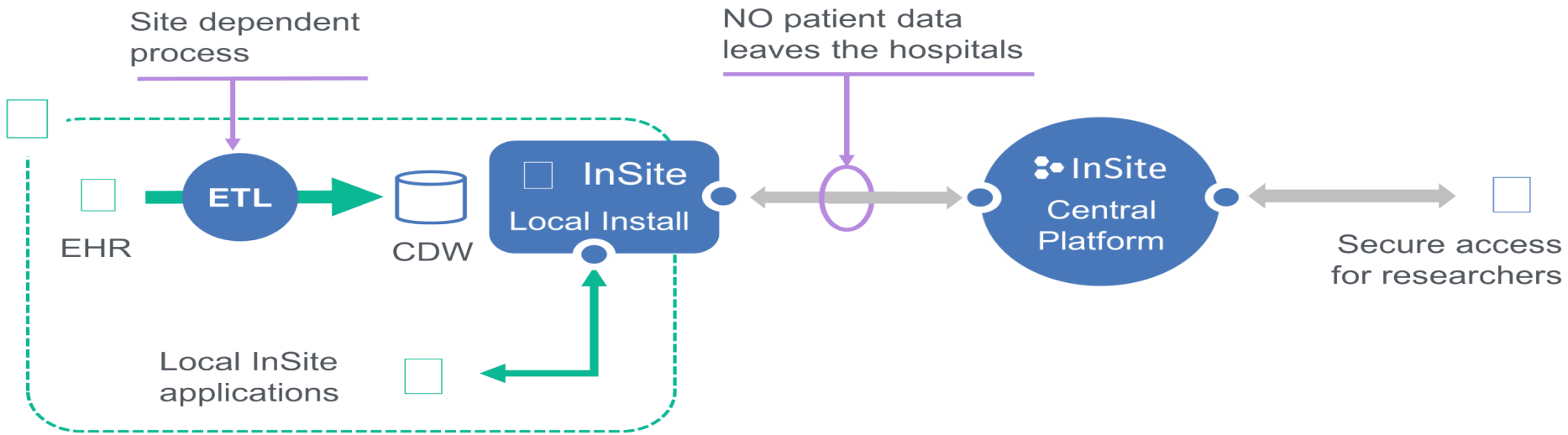
RRCTs – not only possible in Scandinavia



REDUCe SWEDEHEART

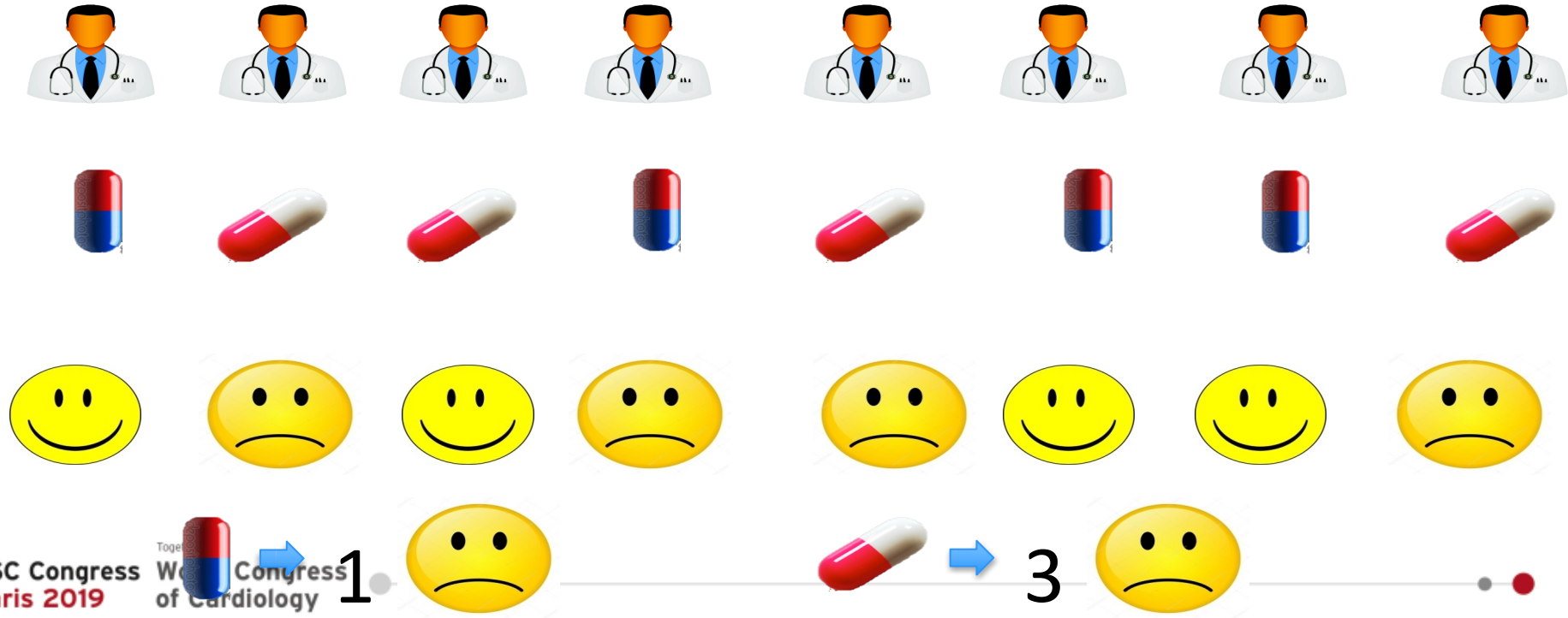


A new tool – The InSite platform for identifying eligible patients



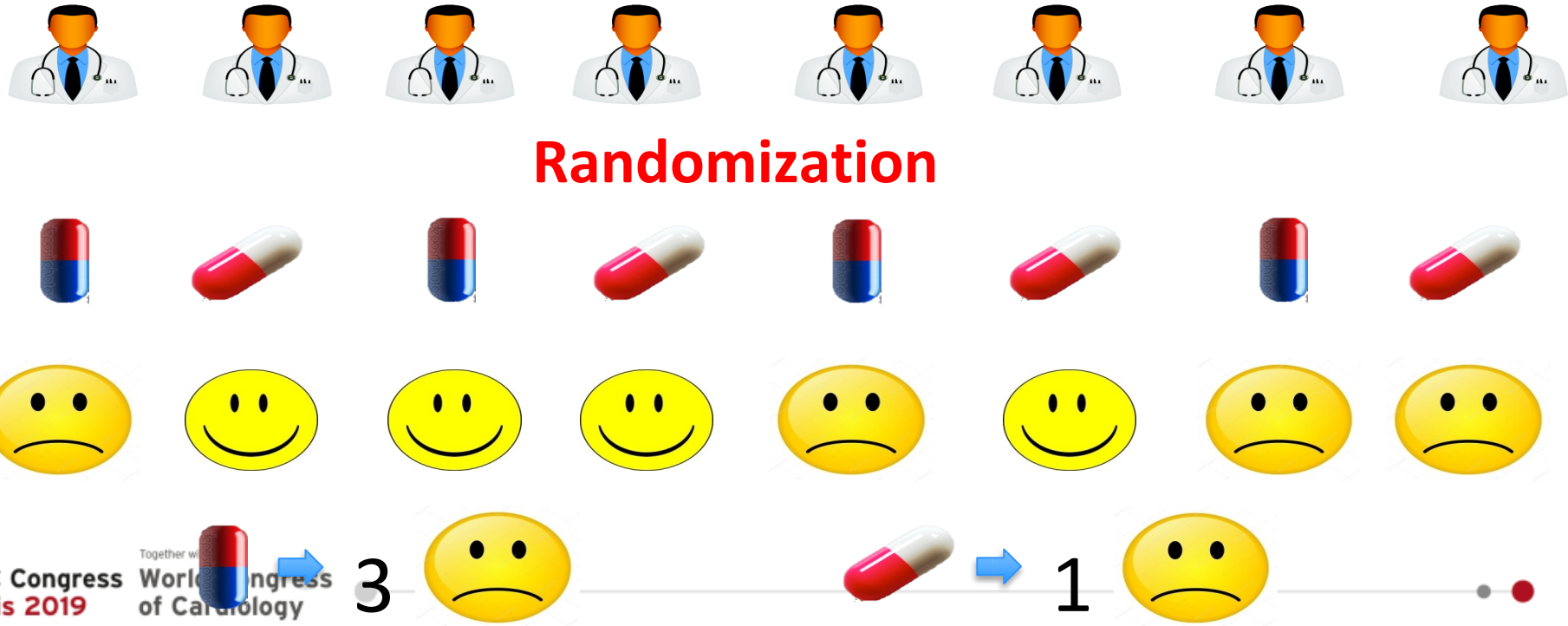
Retrospective observational study

- Different doctors and hospitals choose different treatments for no obvious reason



Prospective randomization in a registry (RRCT)

- Instead of different treatment dependent on local preferences one could randomize



Beta-blockeRs tO patieNts with CHronIc Obstructive puLmonary diseasE (BRONCHIOLE)

A pragmatic clinical trial with partial registry-based follow-up

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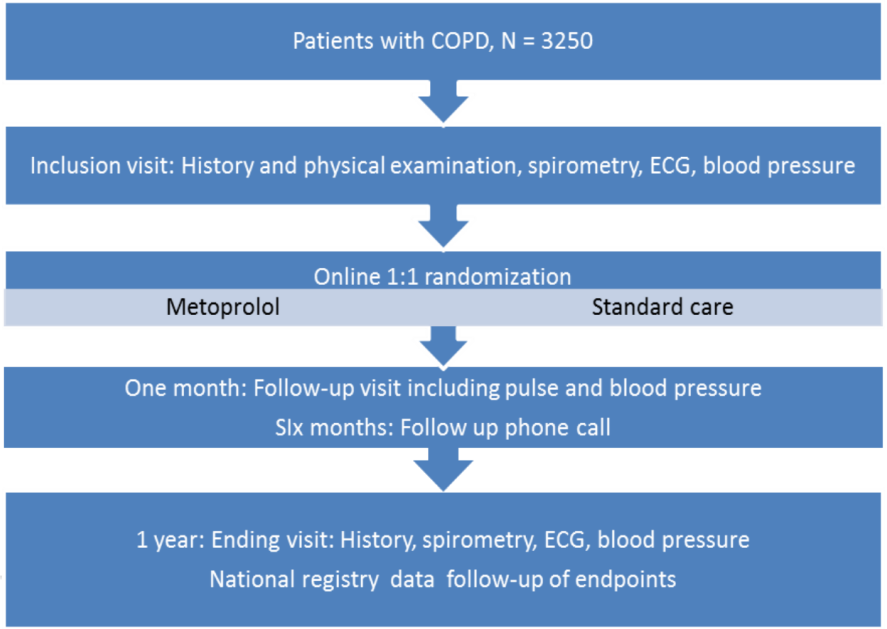

ESC Congress Paris 2019
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