HRC2016
9 – 12 October 2016
The ICC, Birmingham UK

Barts Health NHS
NHS Trust

Developing National Research Networks and Pragmatic Clinical Trials

Rui Providencia

Barts Heart Centre

Heart Rhythm Congress
HRC2016
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The Key role of High-Quality Registries and Registry-based RCTs

Rui Providencia

Barts Heart Centre

Summary

- I. Issues with RCTs
  - Main issues at the present
  - The examples of EAST, CABANA, and CASTLE-AF
- II. Can Registry-based RCTs the solution?
  - Opportunities in Nationwide registries
    - Friberg et al. 2015 Eur Heart J
  - Concept of R-RCTs
- III. SWEDEHEART
  - Concept
  - TASTE
  - Other Landmark R-RCTs in Canada
- IV. CALIBER (UK)
  - Concept

I. Issues with RCTs

Level of Evidence A Recent Guidelines

ORIGINAL CONTRIBUTION

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

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Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

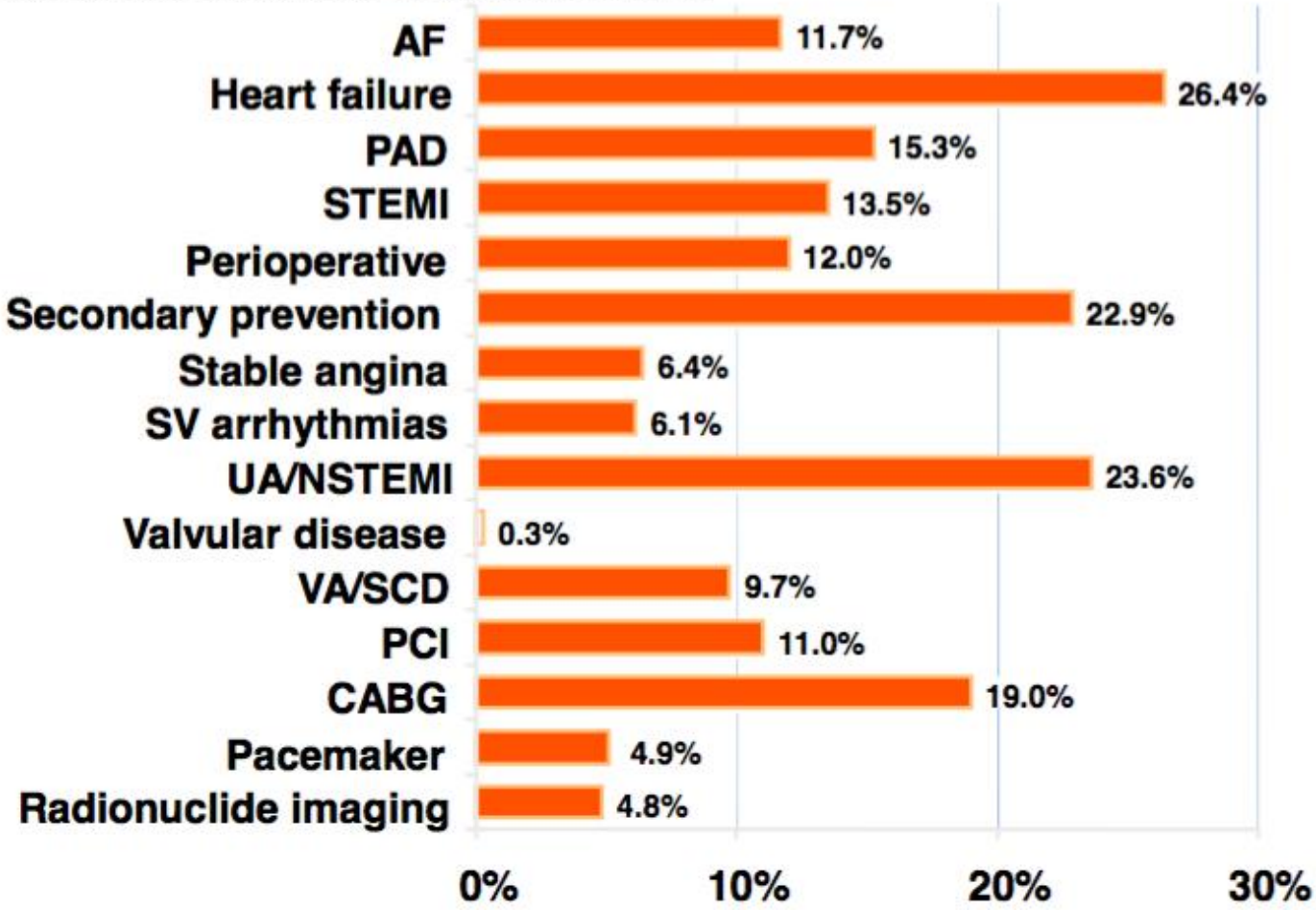
Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality

Objec cular gu dations

Data issued ence ar recomm

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

*Multiple RCTs or Meta-analyses



Background

- Post-hoc analyses of the AFFIRM study have shown that remaining in sinus rhythm is associated with a lower mortality.
  - Corley 2004 Circulation

- Also, it seems logical that eliminating AF would abolish the perturbed physiology generating atrial thrombi, and thus decrease the risk of stroke.

Knowledge Gaps

- The currently ongoing EAST, CABANA and CASTLE-AF will assess the impact of catheter ablation on hard outcomes (all-cause mortality, stroke, HF hospitalization).
  - However,
    - These RCTs have been ongoing for several years
    - Concerns exist regarding inclusion and powering for the most important endpoints.
    - Primary endpoints are thus combined
      - CABANA's 1ary endpoint changed from stroke or mortality to total mortality, disabling stroke, serious bleeding, or cardiac arrest

- Data from large registries could potentially provide an answer to this matter (looking into individual endpoints).

CABANA @ clinicaltrials.gov

Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA)

This study is ongoing, but not recruiting participants.

Sponsor:
Mayo Clinic

Collaborators:
National Heart, Lung, and Blood Institute (NHLBI)
St. Jude Medical
Biosense Webster, Inc.

Information provided by (Responsible Party):
Douglas L. Packer, Mayo Clinic

ClinicalTrials.gov Identifier:
NCT00911508

First received: May 28, 2009
Last updated: April 25, 2016
Last verified: April 2016
History of Changes

Purpose

The (Catheter Ablation Versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial) CABANA Trial has the overall goal of establishing the appropriate roles for medical and ablative intervention for atrial fibrillation (AF). The CABANA Trial is designed to test the hypothesis that the treatment strategy of left atrial catheter ablation for the purpose of eliminating atrial fibrillation (AF) will be superior to current state-of-the-art therapy with either rate control or rhythm control drugs for decreasing the incidence of the composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest in patients with untreated or incompletely treated AF.

Condition	Intervention
Atrial Fibrillation Arrhythmia	Device: Left atrial ablation Drug: Rate or Rhythm Control Therapy

CABANA @ clinicaltrials.gov

- Left atrial size, morphology and function and its relationship to morbidity and mortality [Time Frame: Baseline compared with 3-6 months post therapy initiation]
  [Designated as safety issue: No]

Enrollment: 2204
Study Start Date: August 2009
Estimated Study Completion Date: June 2018
Estimated Primary Completion Date: December 2017 (Final data collection date for primary outcome measure)

Almost 10 years!!!

Arms	Assigned Interventions
Active Comparator: Left Atrial Ablation Pulmonary vein isolation using a circumferential ablative approach in the left atrium. Ablation may be performed using circular mapping catheter-guided ablation, antral isolation using a circular guided approach, or wide area circumferential ablation.	Device: Left atrial ablation St. Jude: Livewire TC™ , Therapy™ Dual / Thermocouple, Safire,Therapy Cool Path Biosense Webster: NAVI-STAR, NAVI-STAR/NAVI-STAR DS, Celsius Braided/Long Tip, NAVI-STAR™ and Celsius™ ThermoCool, NAVI-STAR® RMT, Celsius® RMT, ThermoCool® SF Medtronic CryoCath LP: Freezor®/Freezor MAX®, Artic Front®, Cardiac Ablation System Bard: Stinger Boston Scientific: Blazer II RF/XP, Blazer RPM, Chilli II Cooled, SteeroCath
Active Comparator: Rate or Rhythm Control Therapy Current state-of-the-art drug therapy for atrial fibrillation (rate control or rhythm control). Treating physicians will be encouraged to follow the American College of Cardiology / American Heart Association / European Society of Cardiology Atrial Fibrillation Guidelines with regard to drug therapy for atrial fibrillation. The specific choice of rate control versus rhythm control drug therapy and the specific drugs to be used will ultimately be left to the discretion of the treating physician.	Drug: Rate or Rhythm Control Therapy Rate control: Metoprolol 50-100mg, Atenolol 50-100mg, Propranolol 40-80mg, Acebutolol 200-300mg, Carvedilol 6.25-25mg, Diltiazem 180-240mg, Verapamil 180-240mg, Digoxin 0.125-0.25mg Rhythm control: Propafenone 450-625mg, Flecainide 200-300mg, Sotalol 240-320mg, Dofetilide 500-1000mcg, Amiodarone 200-400mg, Quinidine 600-900mg, Dronedarone 800mg

CABANA trial - Issues

1. Slow/Long inclusion period

   Patients don't want to be randomized to drugs

2. Low event rates

   CABANA's 1^{ary} endpoint changed from stroke or mortality to total mortality, disabling stroke, serious bleeding, or cardiac arrest

3. When we finally have some results

   The ablation technology will have changed dramatically already

   Will the information be relevant?

EAST @ clinicaltrials.gov

Estimated Enrollment:	2745
Study Start Date:	February 2011
Estimated Study Completion Date:	November 2019
Estimated Primary Completion Date:	June 2019 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
No Intervention: Usual care Usual care closely follows the suggestions laid out in the current European Society of Cardiology (ESC) guidelines for AF treatment. In addition to antithrombotic therapy and therapy of underlying heart disease, usual care usually consists of an initial attempt to control symptoms by rate control therapy. Rhythm control interventions are recommended when symptoms can not be controlled by optimal rate control therapy in the usual care group.	
early standardised rhythm control Patients in the early therapy group will be treated following the same therapeutic recommendations of the ESC guidelines as the usual care group. In addition, rhythm control therapy will be initiated early with the aim of preventing recurrence and delaying or preventing progression of AF. Early-onset rhythm control therapy can consist of: 1. Optimal antiarrhythmic drug therapy (Dronedarone, Amiodarone, Flecainide, Propafenone), 2. Catheter ablation with the aim of pulmonary vein isolation (PVI), 3. Antiarrhythmic drug therapy and catheter ablation may be supplemented by early cardioversion in patients with persistent AF. All individual treatment decisions will be taken by the treating study physician considering the labelling of the procedures and drugs and patient preferences.	Other: early standardised rhythm control Patients in the early therapy group will be treated following the same therapeutic recommendations of the ESC guidelines as the usual care group. In addition, rhythm control therapy will be initiated early with the aim of preventing recurrence and delaying or preventing progression of AF. Early-onset rhythm control therapy can consist of: 1. Optimal antiarrhythmic drug therapy 2. Catheter ablation with the aim of pulmonary vein isolation (PVI), 3. Antiarrhythmic drug therapy and catheter ablation may be combined and supplemented by early cardioversion in patients with persistent AF. All individual treatment decisions will be taken by the treating study physician considering the labelling of the procedures and drugs and patient preferences.

CASTLE-AF @ clinicaltrials.gov

- All-cause mortality Cardiovascular mortality Unplanned hospitalization due to cardiovascular reason Worsening heart failure requiring unplanned hospitalization Cerebrovascular accidents Left ventricular function Exercise tolerance Quality of life [Time Frame: 7 years] [Designated as safety issue: No]

Enrollment:	398
Study Start Date:	January 2008
Estimated Study Completion Date:	September 2019
Estimated Primary Completion Date:	April 2019 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: 1 Radiofrequency ablation of atrial fibrillation: Subjects assigned to the catheter AF ablation strategy will undergo ablation within 48 hours after baseline evaluation. The aim of the procedure is to achieve isolation of all Pulmonary Veins (PVs) and to restore sinus rhythm. Only radiofrequency catheter based AF ablation is permitted; other methods, like cryoablation, ultrasound and laser, are not permitted in this study. Before ablation, a transesophageal echocardiogram must be performed in order to rule out presence of atrial thrombi. Anticoagulation should be initiated, or continued, for at least six months post ablation. Six months after successful ablation and in absence of any recurrence of AF, antiarrhythmic drugs should be discontinued.	Procedure: Radiofrequency ablation Radiofrequency ablation of atrial fibrillation
Active Comparator: 2 Conventional treatment: Subjects assigned to the conventional treatment strategy will be treated according to current guidelines for the management of patients with chronic heart failure and/or atrial fibrillation. Efforts to maintain sinus rhythm in this study arm are recommended. Anticoagulation will be initiated, if not already started, and maintained throughout the study according to current guidelines.	Other: Conventional treatment The best medical treatment according to the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult and the ACC/AHA/ESC 2006 Guidelines for Management of Patients with Atrial Fibrillation.

Detailed Description:

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice; its incidence and prevalence increase exponentially with increasing age and it is associated with increased mortality, more frequent hospitalization, and decreased quality of life.

Randomized Controlled Trials

Strengths

- Correctly designed studies with adequate power are gold standard
- Randomization Extinguishes confounding variables/factors

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 with economic interest will be performed

Cost of Doing Trials

How Much They Cost: R&D Spending Per New Drug

	Company	Number of new drugs	10 year R&D spending ($MIL)	R&D per drug ($MIL)
1				3
2				8
3				1
4				6
5				9
6				7
7				8
8	Bayer	5	33118	6624
9	Schering-Plough	3	18845	6282
10	Novartis	10	60727	6073
11	Takeda	4	24132	6033
12	Merck&Co	9	49133	5459
13	GlaxoSmithKline	11	57595	5236
14	J&J	13	67624	5202
15	Novo Nordisk	2	9251	4625

"Current clinical trials are too slow, too expensive, not reliable and not designed to answer the important questions…"

Rob Califf, Duke University

II. R-RCTs

Observational Registries

Strengths

- Ideal for description of standards
- Unselected patient populations – generalizable
- Large number of events – possible to identify rare events
- Inexpensive

Weaknesses

- Data quality variable and questionable
- Cannot be used for comparable outcomes research
- Confounding factors can not be adjustable despite advanced statistical models

Swedish Registry Data

- Retrospective and Registry data has shown that catheter ablation of AF may be associated with a lower risk of stroke [1-3] and mortality [3] in the long-term
  - [1] Bunch 2013 Heart Rhythm
  - [2] Hunter 20012 Heart
  - [3] Friberg 2016 Eur Heart J

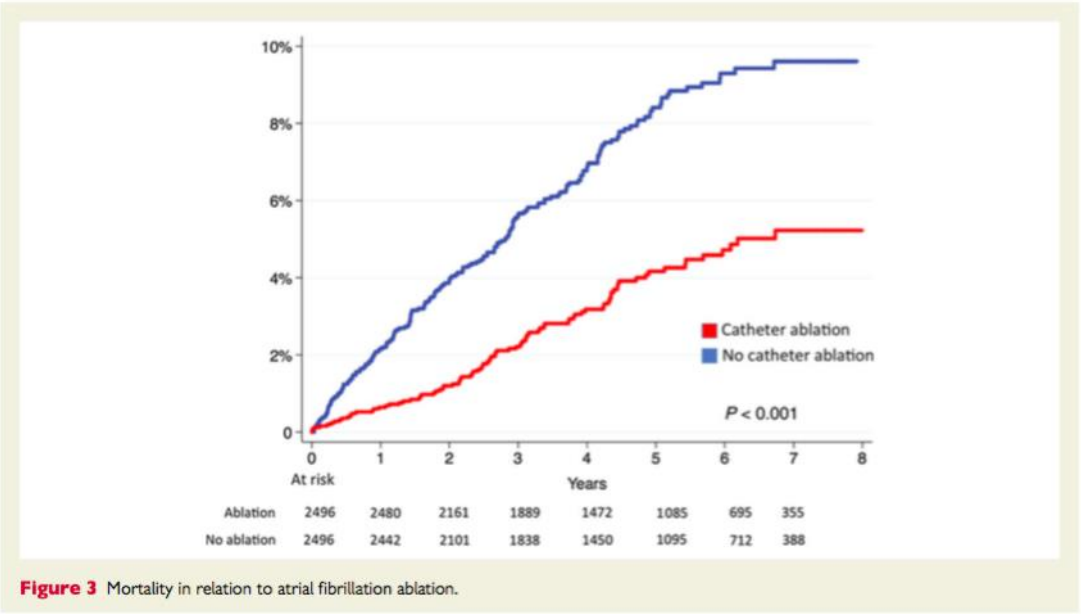


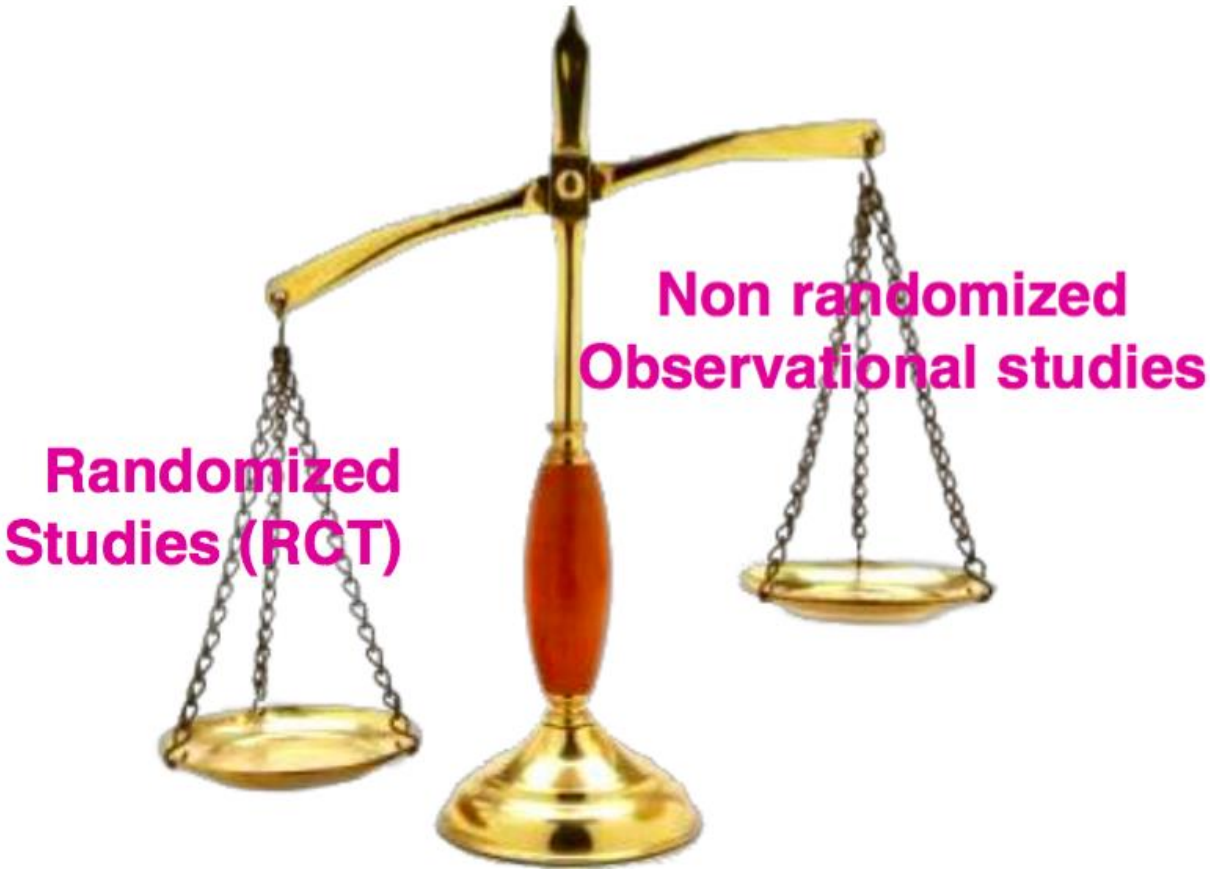
Figure 3 Mortality in relation to atrial fibrillation ablation.

Friberg 2016 Eur Heart J

Swedish registry data

2496 in each treatment arm

Propensity-matched comparison


Non randomized
Observational studies
Randomized
Studies (RCT)

Register-based Randomized Controlled Trials

- Prospective randomized trial that uses a clinical registry for one or several major functions for trial conduction and outcomes reporting

What can a Registry do?

- Some or all parts of the trial
  - Identify Patients
  - Randomize
  - Collect Baselines and Procedural characteristics
  - Collect consent forms
  - Endpoint detection
  - Control clinical endpoint events (adjudication)

Registry-based RCTs

Strengths

- Correctly designed studies with adequate power are gold standard
- Extinguishes confounding factors
- Unselected patient population – generalizable
- Large number of events – makes possible to identify rare events
- Inexpensive

Weaknesses

- Data quality
- Variable definition

R-RCT vs. Classical RCT

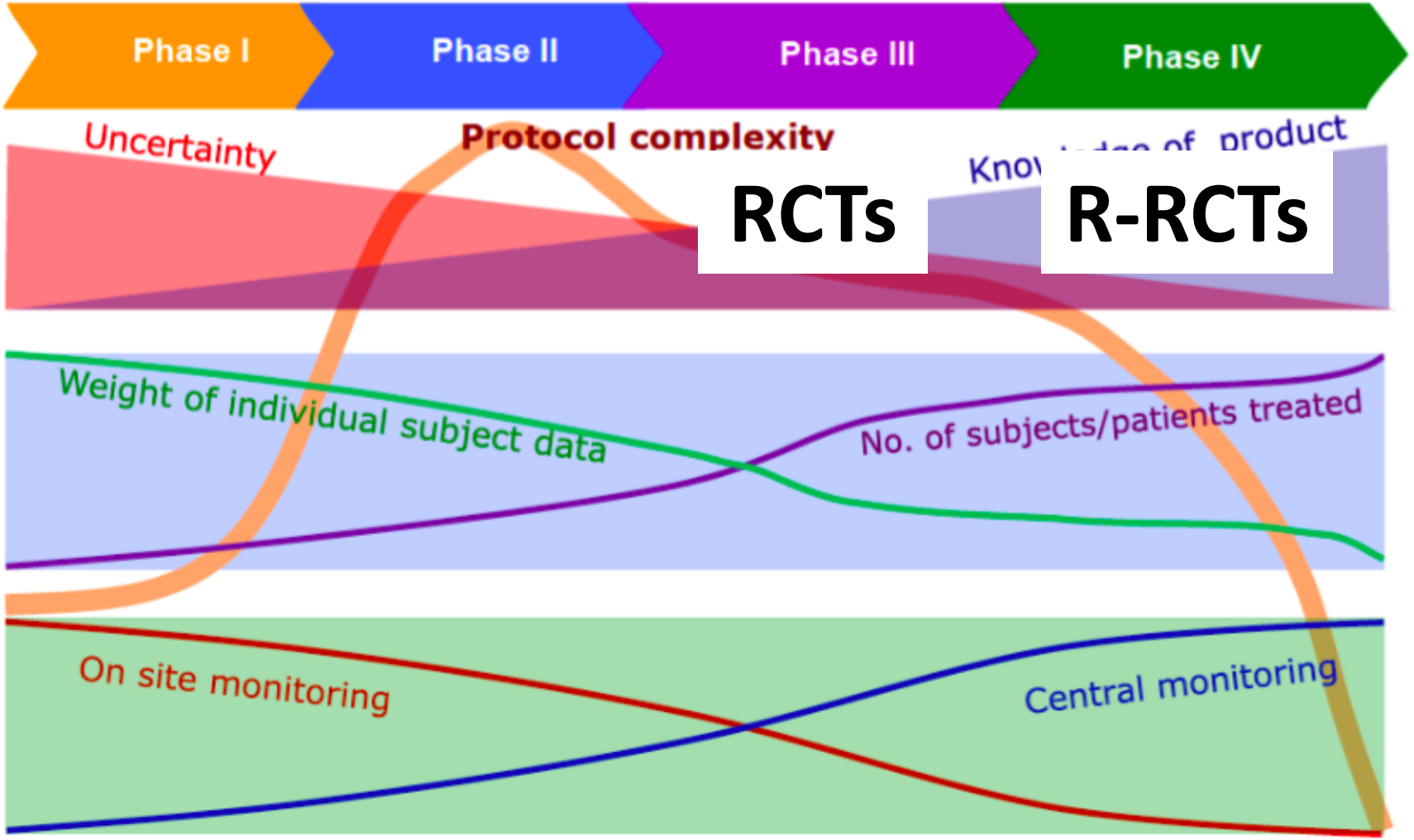
- Combines the advantages of a clinical registry and randomized study
- Complement to classical RCT –No substitute
- No formal definition

•RRCT •Evaluation of therapeutic options available/used in routine clinical care	⟺	RCT Approval of new pharmaceutical agents and medical devices

Clinical trial – product lifecycle

EUROPEAN MEDICINES AGENCY

Clinical trial conduct including monitoring and data collection need to be proportionate to the knowledge of the product, protocol complexity and the risks involved to study participants and robustness of data



This representation is conceptual. The actual situation will vary for different medicines, population and trials.

Study Design

	RCT	R-RCT
Strategy		+
Device – CE mark, used		+
Drugs approved/ used in clinical practise		+
Drugs for new indication	+	+
Device, first in man	+	
New drugs	+	

III. SWEDEHEART

TASTE and other Landmark r-RCTs

Swedish Personal ID Number

Mandatory Swedish National Registries (selection)

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	Causes of death, including conributing factors
Swedish Out-Patient Registries (since 2005)	Hospital-based -> mandatory; primary care -> voluntary

SWEDE HEART

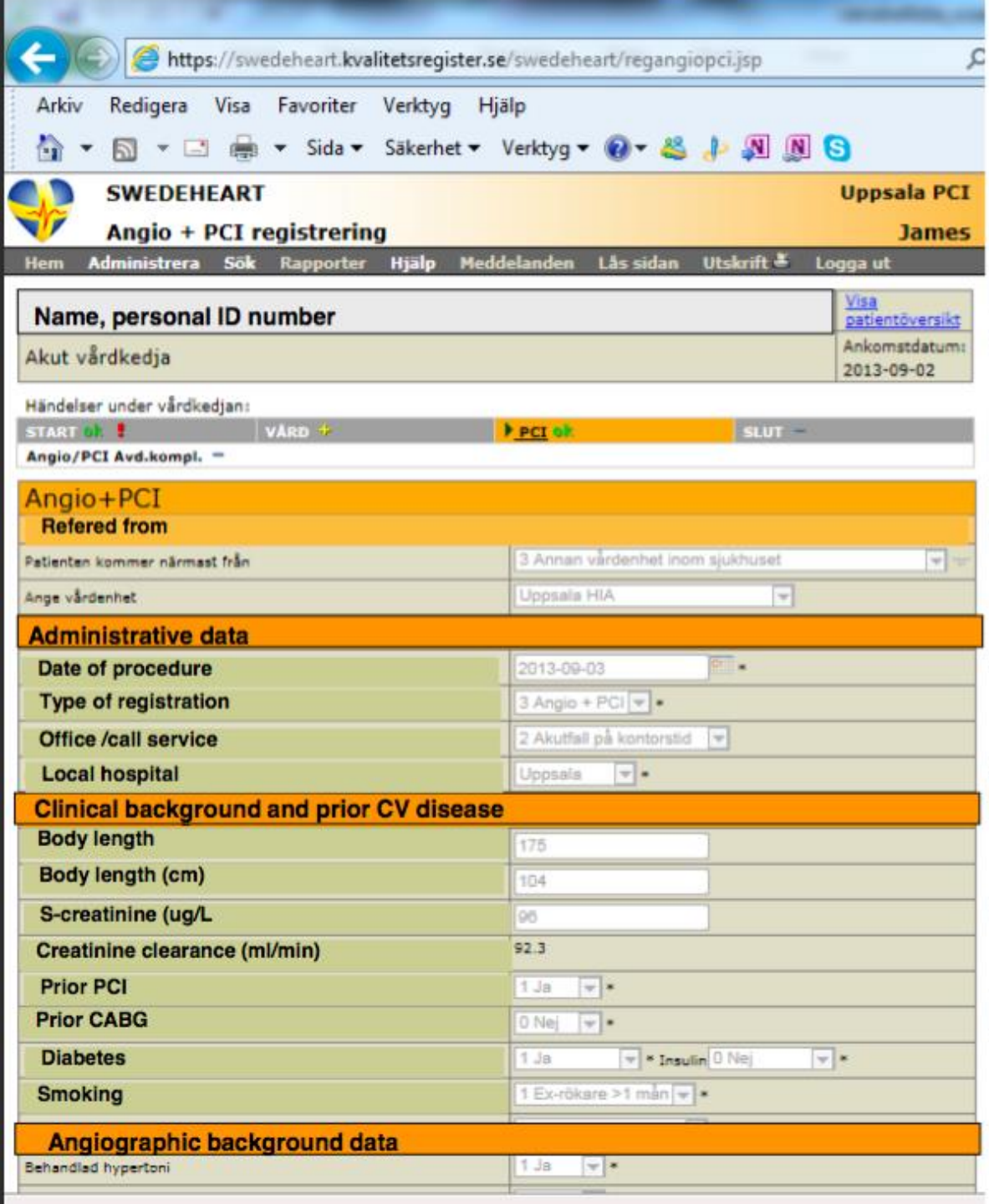
Number of cases annually: 80 000

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%

>200 variables

(Baseline data, procedural and outcome measures)

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



SWEDE HEART

Data entry on line by the operator

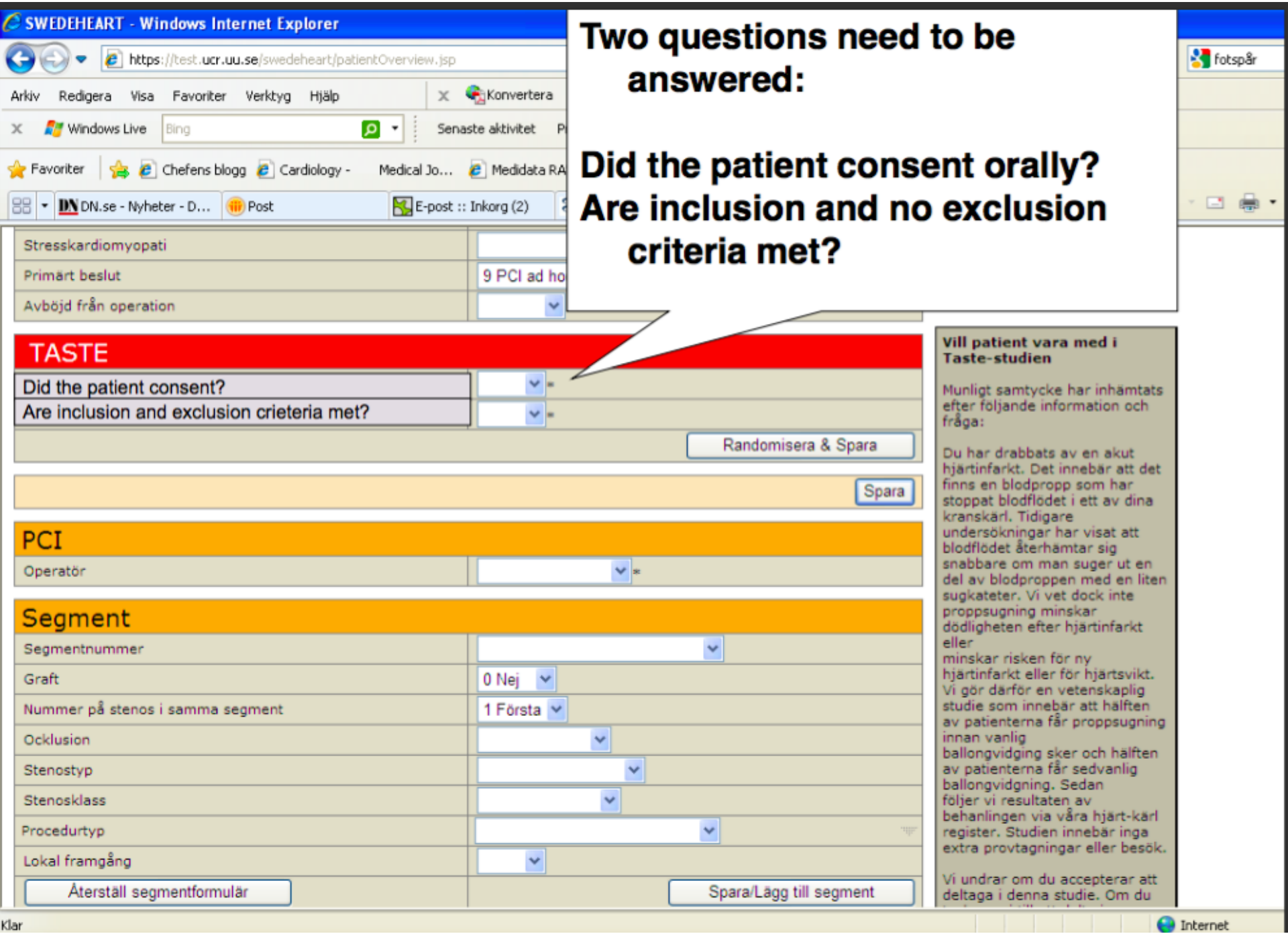
Automatic linkage with population registry to provide name, sex

Automated data checks

Auto populated fields from previous registrations

Calculated variables

Interactive stent report


SWEDEHEART - Windows Internet Explorer
https://test.ucr.uu.se/swedeheart/patientOverview.jsp
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Post
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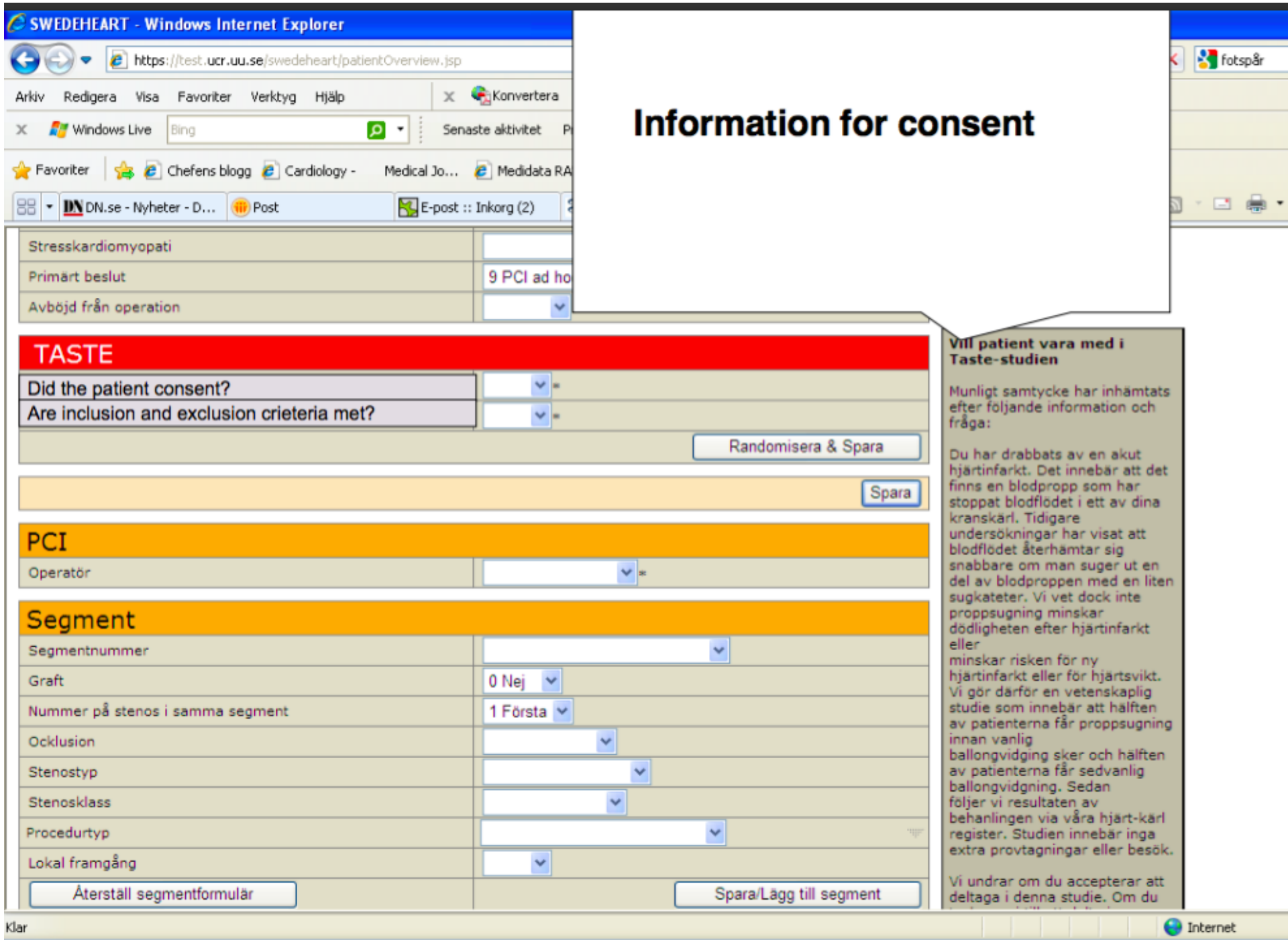
fotspår
Two questions need to be answered:
Did the patient consent orally?
Are inclusion and no exclusion criteria met?
Stresskardiomyopati
Primärt beslut
9 PCI ad ho
Avböjd från operation
TASTE
Did the patient consent?
Are inclusion and exclusion crieteria met?
Randomisera & Spara
Spara
PCI
Operatör
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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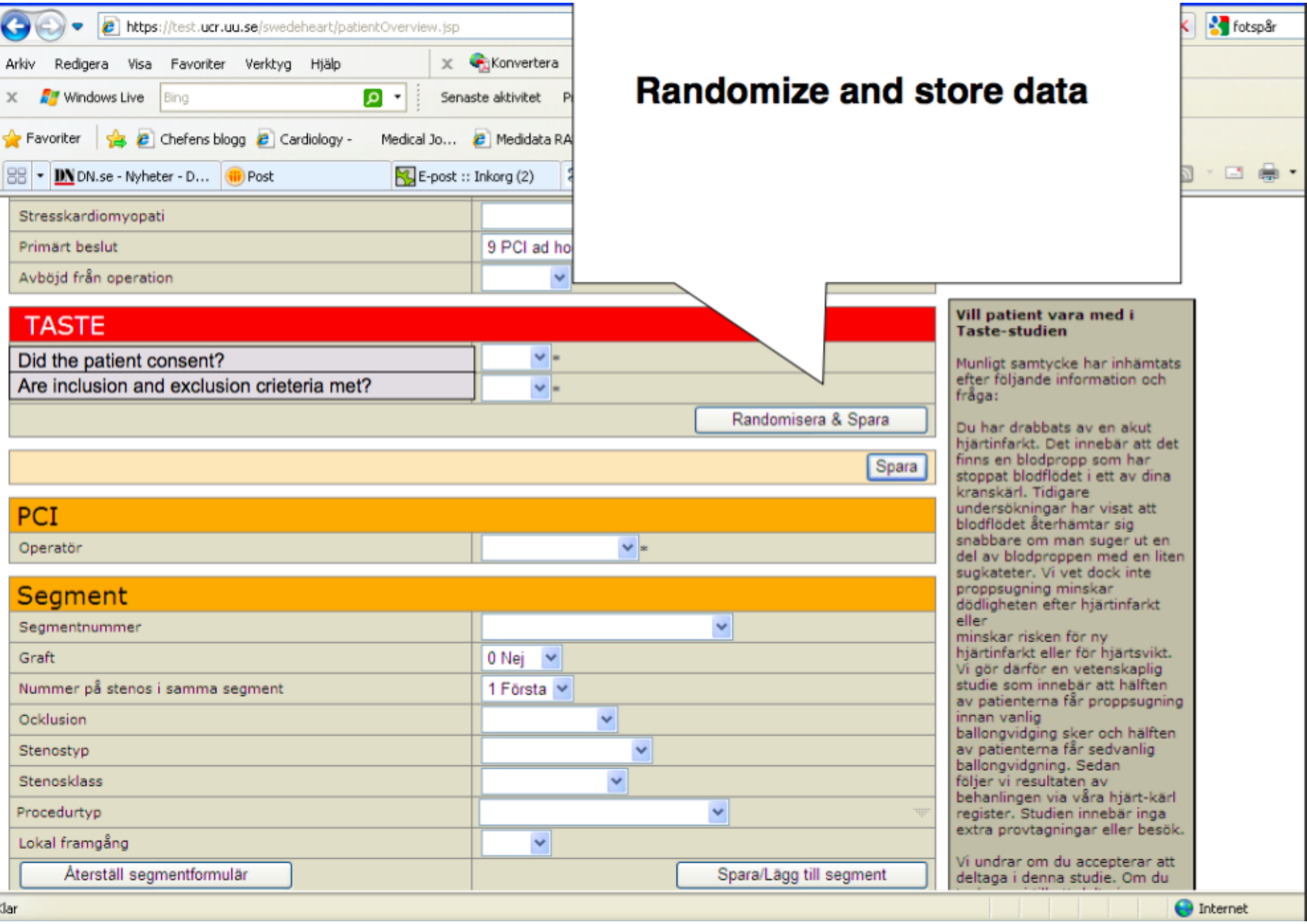
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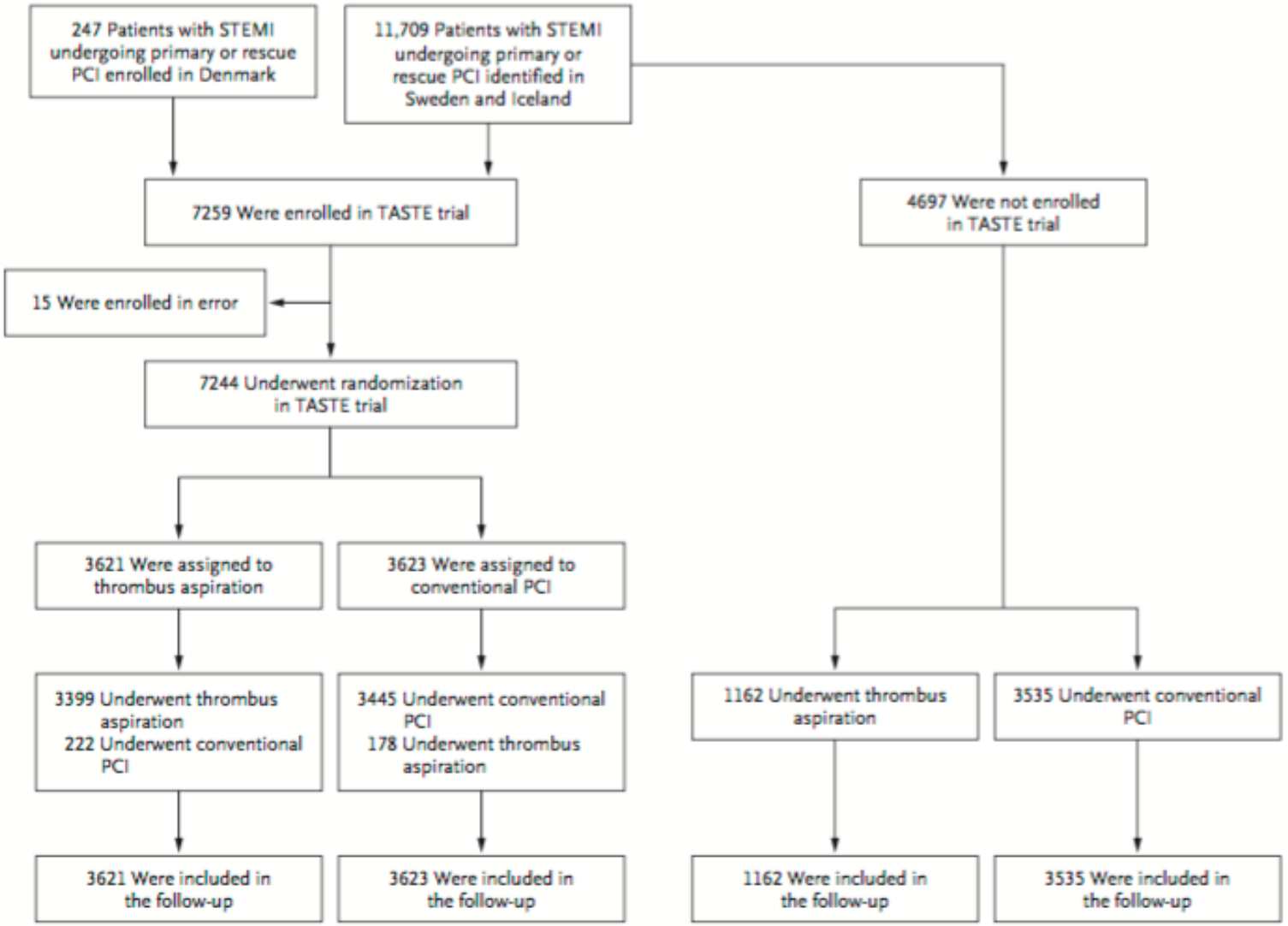
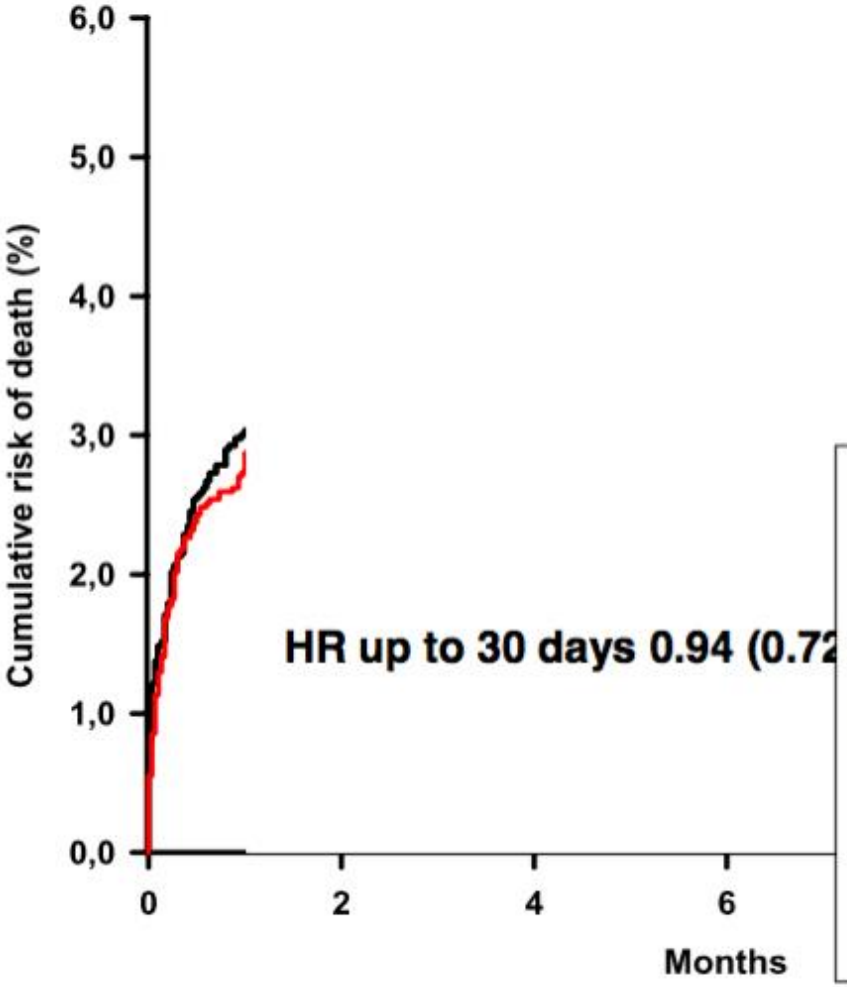


Figure 1. Enrollment, Randomization, and Follow-up.

Patients with ST-segment elevation myocardial infarction (STEMI) who were undergoing percutaneous coronary intervention (PCI) were considered for inclusion in the study. Shown are the numbers of patients who were enrolled in the study, randomly assigned to a study group, and followed up during the study period, as well as the number of patients who were not enrolled in the study (most of whom did not meet the inclusion criteria) but who were followed up during the study period. TASTE denotes Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia.

TASTE

WEDE 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?

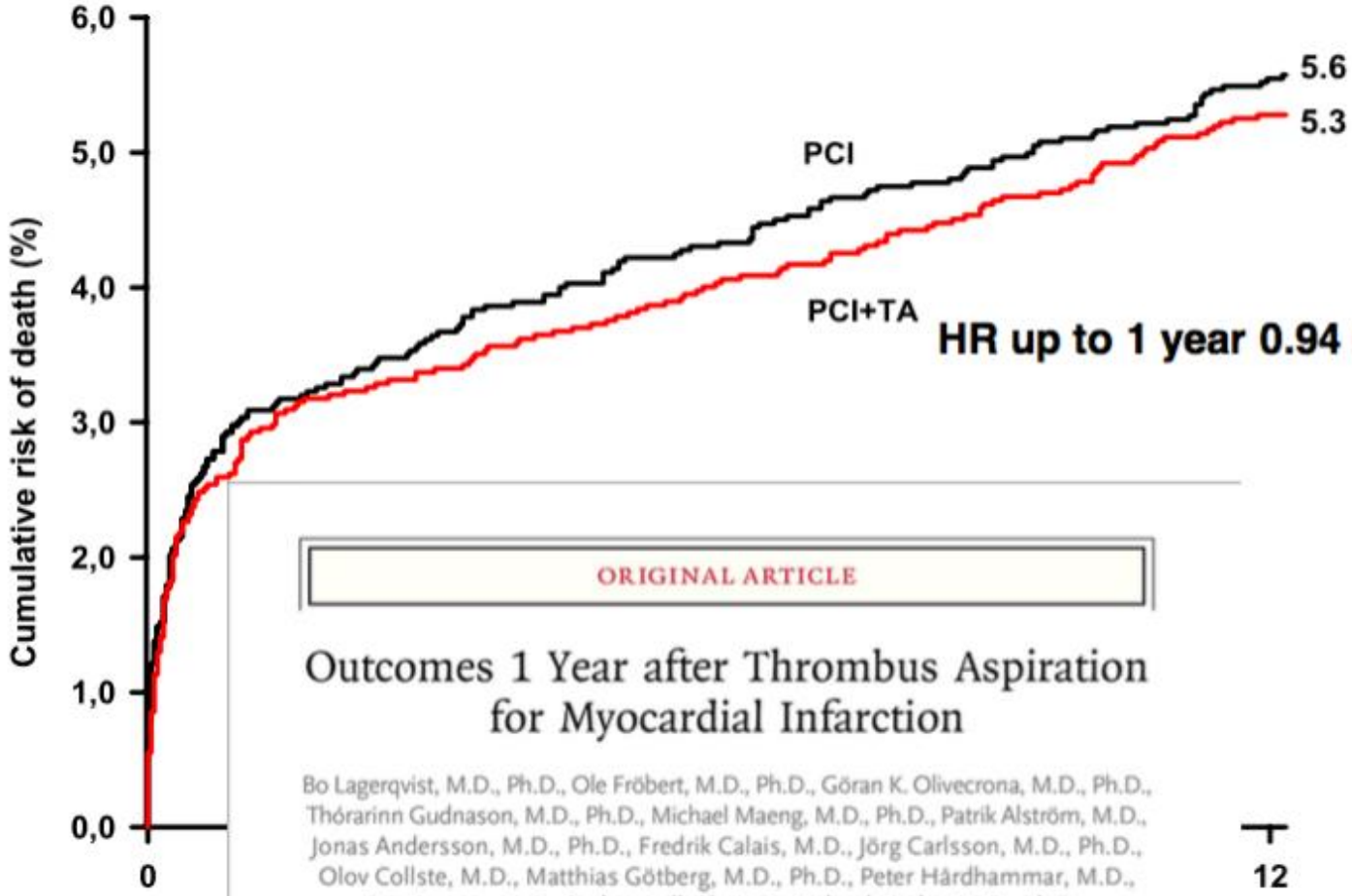
Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

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

TASTE

All-cause mortality up to 1 year



ORIGINAL ARTICLE

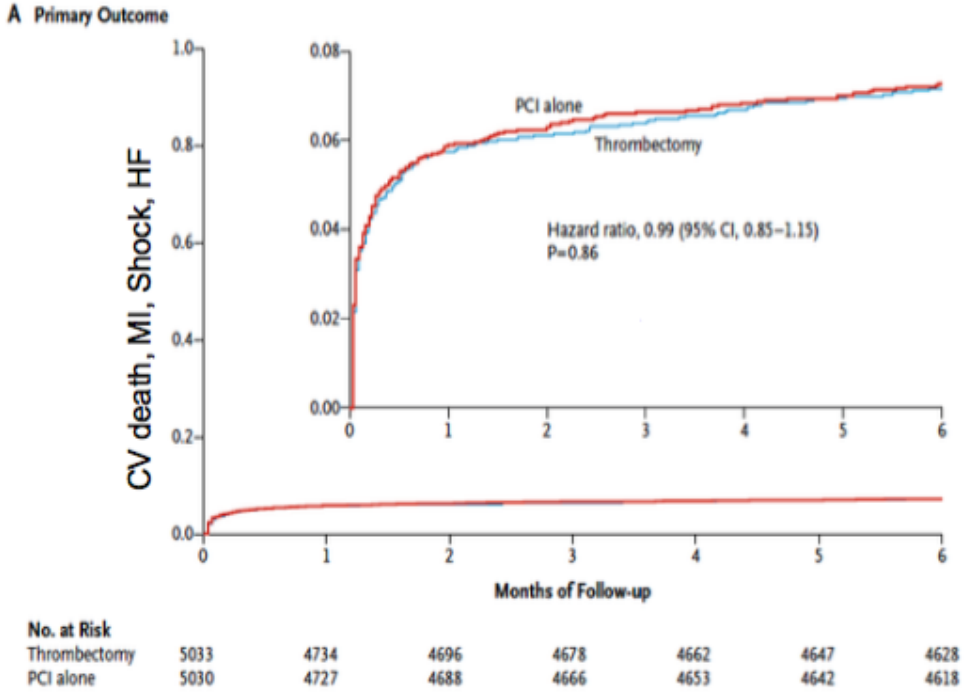
Outcomes 1 Year after Thrombus Aspiration for Myocardial Infarction

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.

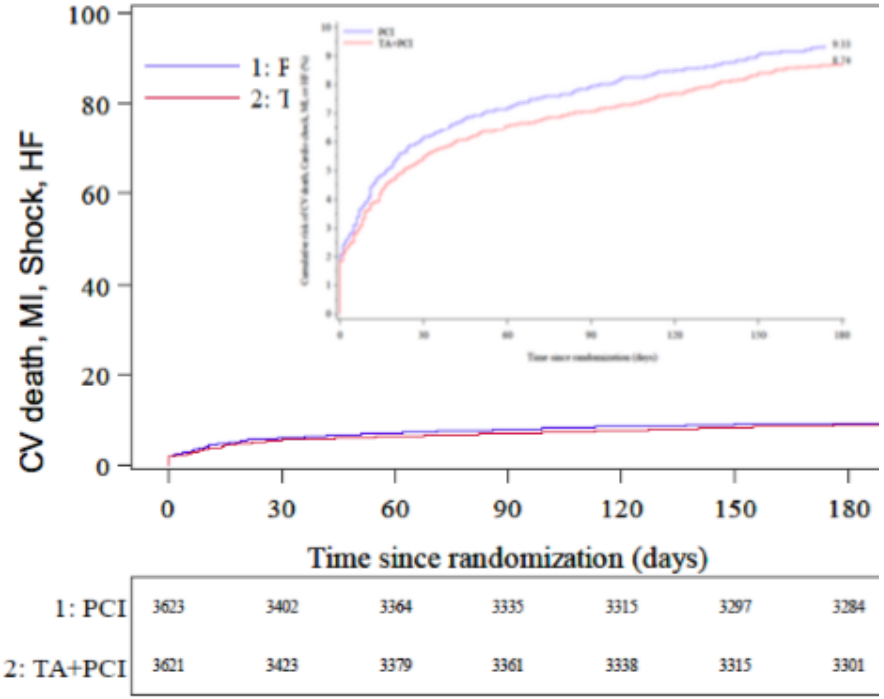
Thrombus Aspiration
RCT vs. R-RCT

TOTAL, N=10.732
Cost 15,000.000 €

TASTE, N= 7.244
Cost 500.000 €



Jolly et al NEJM 2015



Other Landmark R-RCTs

- **Cardiovascular Health Awareness Program (CHAP)**
  - 39 mid-sized communities Canada
  - 15,889 community dwellers aged ≥ 65
  - 10 administrative database sources for data collection, follow-up and outcome measures
- Randomized Comparison
  - volunteer run cardiovascular risk assessment and education sessions held in community based pharmacies (20 communities) vs. usual care (19 communities)
  - over a 10-week period
- Aim
  - Assess the effectiveness of cardiovascular risk assessment and education sessions
- Endpoint
  - hospital admissions for acute myocardial infarction, stroke, and congestive heart failure
- Intervention was significantly related to 9% ↓ risk of the composite endpoint, 13% AMI, 10% CHF

Kaczorowsky et al. BMJ 2011

REDUCE-MRSA

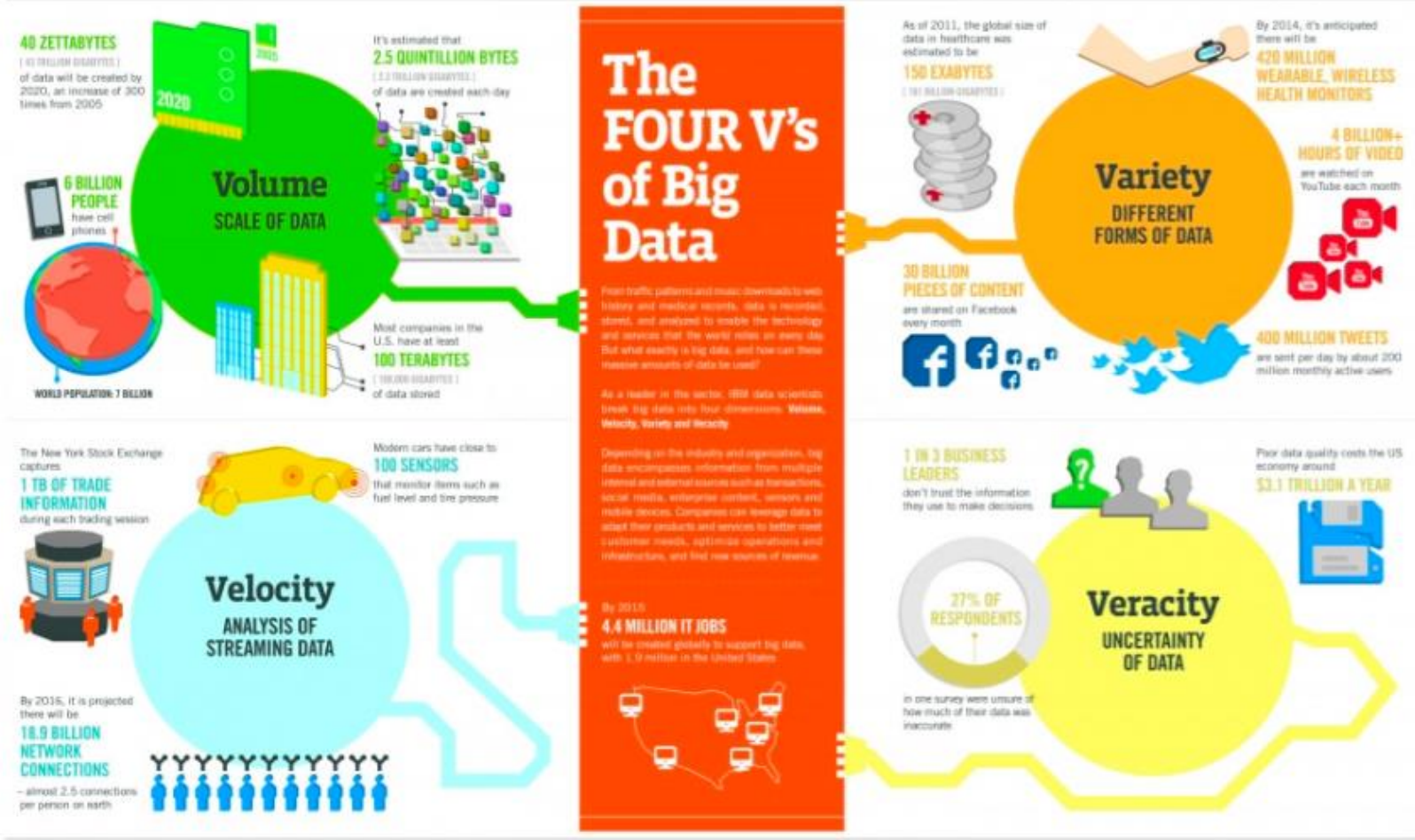
Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate MRSA

- ICUs at high risk of health-related infections by MRSA
- Screening + Isolation vs. Targeted isolation vs. Universal decontamination vs.
- 74,256 patients in 43 hospitals (74 ICUs)
  - Hospitals were randomized
- Universal decolonization was more effective (30 to 45%↓ in culture/infection)

Huang et al. 2013 NEJM

IV. CALIBER

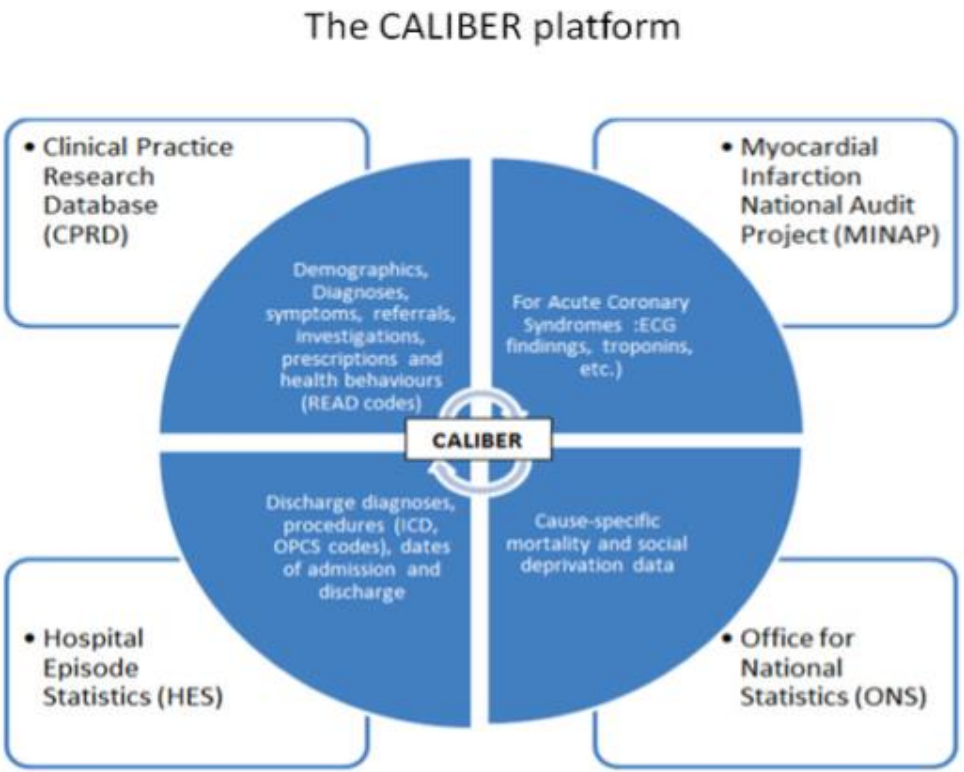
What is big data?



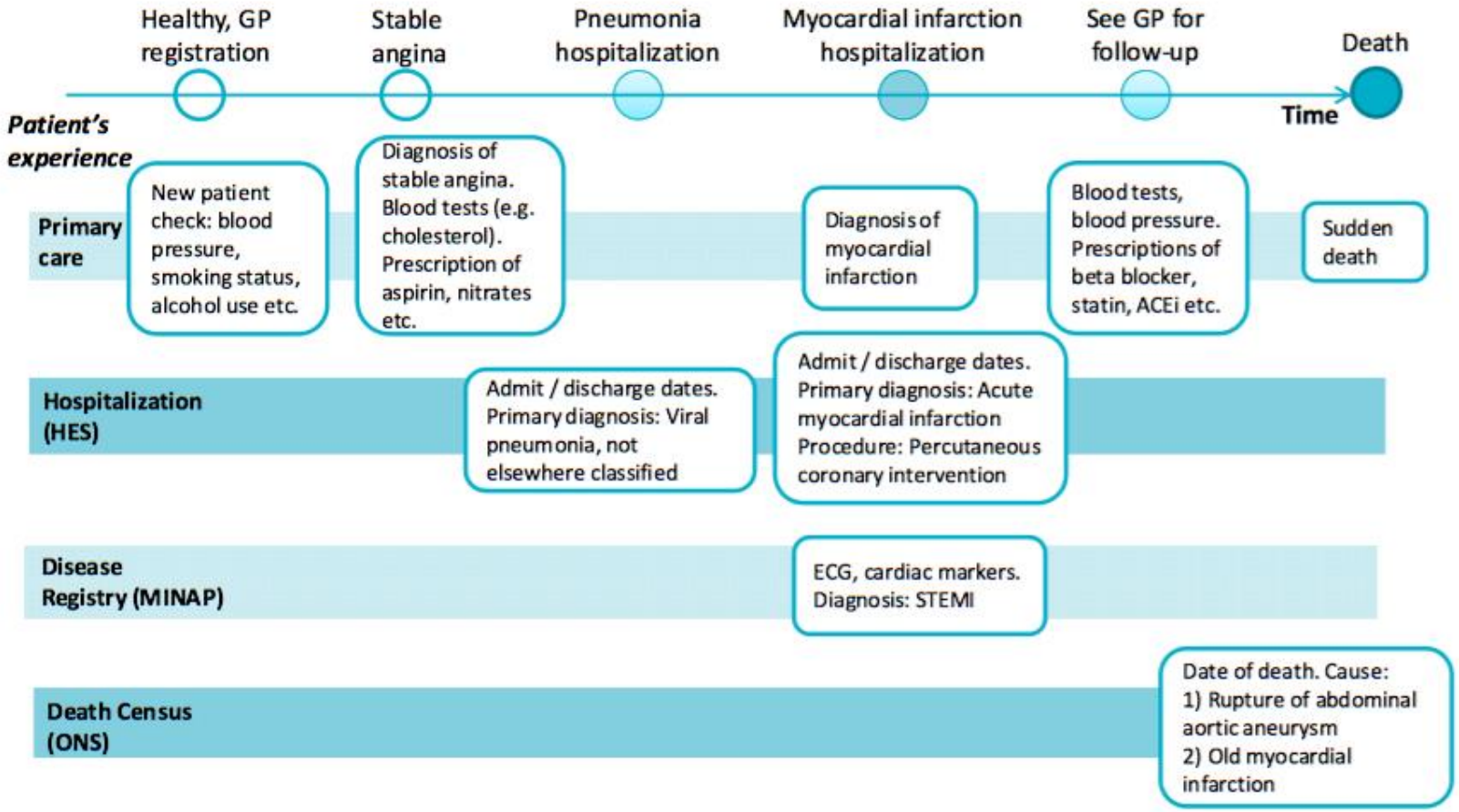
Sources: McKinsey Global Institute, Twitter, Cisco, Gartner, EMC, SAS, IBM, MEPTEC, QAS

IBM

Multiple Record Linkages…needs expansion across NICOR registries



Four nationwide EHR sources linked



Denaxas et al, Data Resource Profile: CALIBER, *Intl Journal Epidemiology*, 2012

CALIBER Data Portal

- Online data discovery tool **caliberresearch.org**
- Access to *all* CALIBER phenotypes, algorithms and implementation details and scripts (SQL,R, Stata)
  - 45 users, 4 institutions, 538 phenotypes, >15,000 clinical diagnostic codes curated
- Standardization
  - Frontend is ICD10, backend becoming SNOMED-CT, LOINC
- A community rather than a static resource
  - Researchers contribute phenotypes and algorithms
  - Other researchers validate/enhance/correct them

Farr
The Farr Institute of Health Informatics Research

CALIBER Home Projects Data Portal Tracker Software About Logout (logged in)

Definition | Sources | Implementation | Files | Publications | Genomics | Trials

Atrial Fibrillation

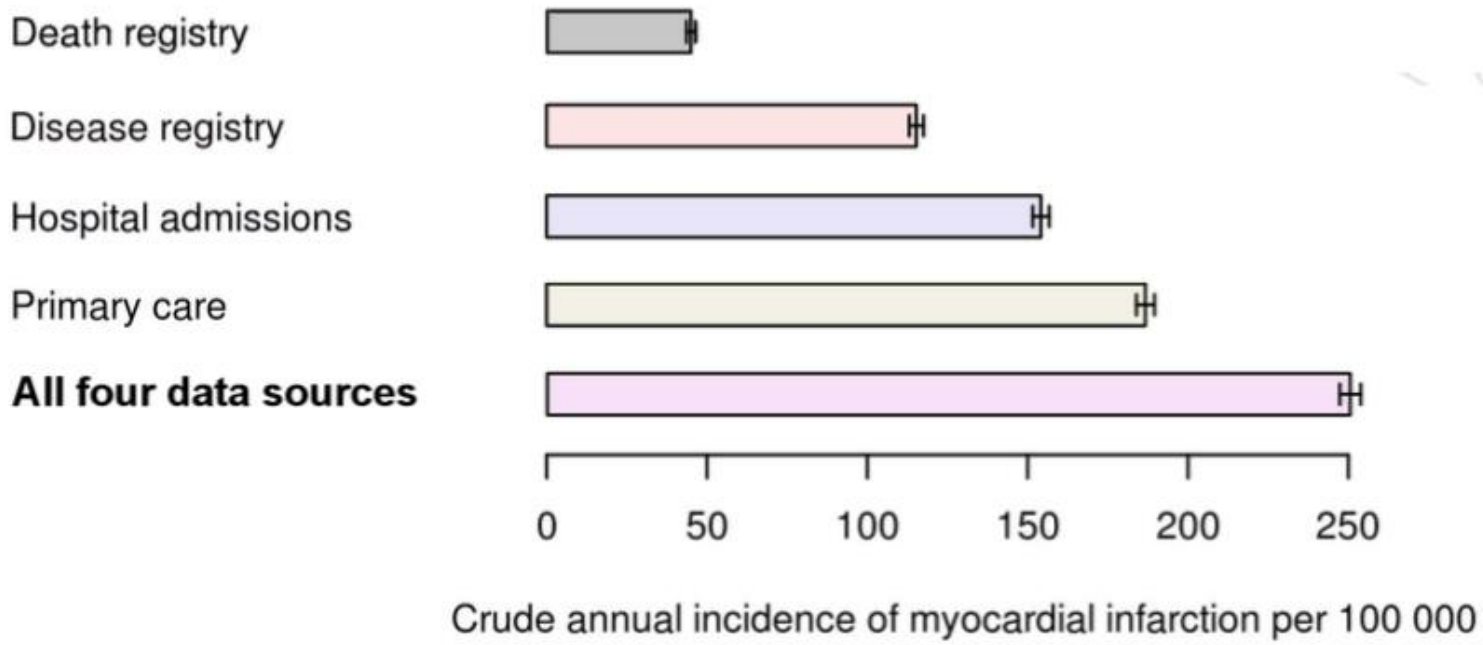
Name	af
Chapter	Circulatory disease/Atrial fibrillation
Definition	Diagnosis of atrial fibrillation.
Data Type	Categorical
Data sources	GPRD, HES
Dictionaries	Read, ICD10, BNF, Free text
Authors	K. Morley (UCL), Shah A. (UCL), Patel R. (UCL), Liam Smeeth (LSHTM), R. Schilling (St Bartholomews & The Royal London Hospital), R. Hunter (St Bartholomews & The Royal London Hospital)
Agreed	01/02/2013 (Revision 1)

Category	**Definition**
1	Historic AF diagnosis
2	AF diagnosis inferred
3	AF diagnosis confirmed

Source variables

Description	**Source**	**Variable**
Atrial fibrillation diagnosis	Primary care	af_gprd
Atrial fibrillation diagnosis	Secondary care	af_hes
Atrial fibrillation procedures	Primary care	af_proc_gprd
Atrial fibrillation procedures	Secondary care	af_proc_opcs
AF medication	Primary care	af_drugs_gprd
warfarin or digoxin prescription	Primary care	af_warfarin_digoxin
Deep vein thrombosis	Primary care	dvt_gprd
Deep vein thrombosis	Secondary care	dvt_hes
Pulmonary embolism	Primary care	pe_gprd
Pulmonary embolism	Secondary care	pe_hes
ECG Text/Notes text mining	Secondary care	Algorithm

Outcomes assessment: importance of linking multiple record sources



Herrett, Shah et al CALIBER BMJ 2013

Genomics

biobank uk

500k participants, 47 baseline biomarkers and custom gene array data available in 2014, cardiac and brain imaging in 100k underway

Open access

Scalable approaches to disease phenotypes (startpoints or endpoints) based on linked electronic health record resources

- cardiac
- diabetes
- stroke
- cancer

Example of Farr Institute working across Wales, Scotland and England

Developing informatics platforms for stratified trials

Rapid feasibility

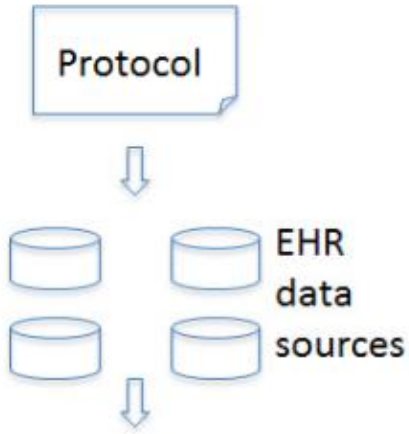
Recruiting

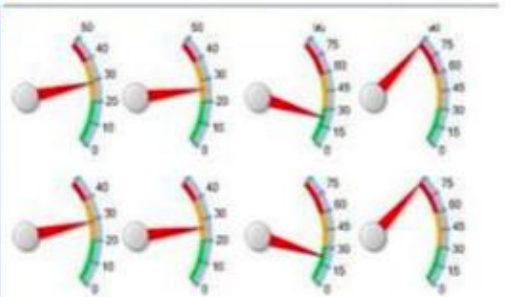
Following up & safety

EHR-based eligibility counts

EHR randomisation

Real-time outcome dashboards





UCLP eConsent

Embedded eCRF

Final Remarks

Conclusion

- Large need for RCTs
  - + evaluation of strategies, devices, drugs
- Classical RCTs are often not performed in broad representative patient populations
- National clinical registries are strong networks for collaboration and enroll complete patient populations
- Prospective R-RCTs are a new opportunity for clinical research
- R-RCTs are ideal for clinical important hypotheses with reliable hard endpoints

Registry-based RCTs

Advantadges

- Remarkably low cost
- Enhanced generalizability of findings
- Rapid consecutive enrolment
- Potential completeness of patient FUP

Challenges

- Registry data quality
  - i.e. accuracy, missing data, missing variables, outcome definition
- Ethical issues
  - i.e. consenting, privacy, withdrawal
- Methodological challenges
  - i.e. research question, study design and outcomes are limited by quality and features of the registry used

Li et al. 2016 J Clin Epidemiol