Lessons from the TASTE trial:
Prospective registry-based randomized clinical trials
– a new concept for clinical research

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Professor of Cardiology
Uppsala Clinical Research Centre
Uppsala University Uppsala, Sweden
Clinical research: time for sensible global guidelines

Clinical research is being slowly strangled by bureaucracy because guidelines that were developed for product-registration trials are being applied rigidly to all types of clinical research. Complex, often confusing, and readily misinterpreted regulations, and their consequent spiralling costs, are a dangerous disincentive to medical progress. The problem is already serious and is now being exported to the developing world—which can least afford it. Populations in developing countries are under-represented in all areas of clinical research, yet those regions of the world that carry the highest disease burdens obviously

Evidence based medicine: a movement in crisis?
## Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

**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 care. These guidelines are systematically developed statements to assist practitioners with decisions about appropriate health care for specific conditions.

### Evidence Levels

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>A</td>
</tr>
<tr>
<td>Heart failure</td>
<td>A</td>
</tr>
<tr>
<td>PAD</td>
<td>A</td>
</tr>
<tr>
<td>STEMI</td>
<td>A</td>
</tr>
<tr>
<td>Perioperative</td>
<td>A</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>A</td>
</tr>
<tr>
<td>Stable angina</td>
<td>A</td>
</tr>
<tr>
<td>SV arrhythmias</td>
<td>A</td>
</tr>
<tr>
<td>UA/NSTEMI</td>
<td>A</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>A</td>
</tr>
<tr>
<td>VA/SCD</td>
<td>A</td>
</tr>
<tr>
<td>PCI</td>
<td>A</td>
</tr>
<tr>
<td>CABG</td>
<td>A</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>A</td>
</tr>
<tr>
<td>Radionuclide imaging</td>
<td>A</td>
</tr>
</tbody>
</table>

- **AF**: Atrial Fibrillation
- **PAD**: Peripheral Arterial Disease
- **STEMI**: ST-segment Elevation Myocardial Infarction
- **PCI**: Percutaneous Coronary Intervention
- **CABG**: Coronary Artery Bypass Graft surgery
- **VA/SCD**: Ventricular Arrhythmia/Supraventricular Tachycardia

### Evidence Distribution

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
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<tbody>
<tr>
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<td>PAD</td>
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<tr>
<td>STEMI</td>
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<tr>
<td>Perioperative</td>
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<td>Secondary prevention</td>
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<tr>
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<td>6.4%</td>
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<tr>
<td>SV arrhythmias</td>
<td>6.1%</td>
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<tr>
<td>UA/NSTEMI</td>
<td>23.6%</td>
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<tr>
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<td>0.3%</td>
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<td>VA/SCD</td>
<td>9.7%</td>
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<tr>
<td>PCI</td>
<td>11.0%</td>
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<td>CABG</td>
<td>19.0%</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>4.9%</td>
</tr>
<tr>
<td>Radionuclide imaging</td>
<td>4.8%</td>
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**Authors**: Pierluigi Tricoci, MD, MHS, PhD
Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD
Randomized Clinical Trials- RCT

**Strengths**
- Correctly designed studies with adequate power are gold standard
- 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 with economic interest will be performed
## Cost of doing trials

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

<table>
<thead>
<tr>
<th>Company</th>
<th>Number of new drugs</th>
<th>10 year R&amp;D spending ($MIL)</th>
<th>R&amp;D per drug ($MIL)</th>
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<td>1. Abbott</td>
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<td>2. Sanofi</td>
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<td>10128</td>
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<td>3. AstraZeneca</td>
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<td>4. Hoffmann-La Roche</td>
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<td>5. Pfizer</td>
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<td>6. Wyeth</td>
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<td>7. Eli Lilly</td>
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<td>8. Bayer</td>
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<td>9. Schering-Plough</td>
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<td>10. Novartis</td>
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<td>11. Takeda</td>
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<td>12. Merck&amp;Co</td>
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<td>15. Novo Nordisk</td>
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Current clinical trials are too slow, too expensive, not reliable, and not designed to answer the important questions…

Rob Califf, Duke University

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Cost of doing trials

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

Rob Califf, Duke University

‘There is a peculiar paradox that exists in trial execution - we perform clinical trials to generate evidence to improve patient outcomes; however, we conduct clinical trials like anecdotal medicine’

Monica Shah NHI, quoted in Gheorghiade et al 2014
Register studies
Observational studies (Non-inverventional)

**Strengths**

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

**Weaknesses**

- Data quality variable and questionable
- Cannot be used for comparative outcomes research
- Confounding factors can not be adjusted for despite advanced statistical models
The anatomy of the Swedish personal identification number

640429-6730
The anatomy of the Swedish personal identification number

640429-6730

year
The anatomy of the Swedish personal identification number

640429-6730

year  month
The anatomy of the Swedish personal identification number

640429-6730

year  month  day
The anatomy of the Swedish personal identification number

640429-6730

year month day place
The anatomy of the Swedish personal identification number

640429-6730

year  month  day  place  sex
The anatomy of the Swedish personal identification number

640429-6730

year   month   day   place   sex   ctrl
A selection of mandatory Swedish national registries

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

79 Clinical Quality registries
Clinical Quality registries
Performance is the basis for certification level which in turn directs funding

- **NQR level 1** – 7 registers
- **NQR level 2** – 22 registers
- **NQR level 3** – 52 registers
- **NQR candidate** – 24 registers
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.
**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**
Thrombus aspiration in Sweden
TAPAS

TAPAS / Swedish registry data

**HR (95% CI): 1.21 (1.08-1.35)**

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>Conventional PCI</th>
<th>Thrombus aspiration</th>
<th>Total</th>
</tr>
</thead>
<tbody>
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<td>0</td>
<td>536</td>
<td>535</td>
<td>1071</td>
</tr>
<tr>
<td>60</td>
<td>506</td>
<td>519</td>
<td>1025</td>
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<td>120</td>
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<td>180</td>
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<td>300</td>
<td>494</td>
<td>506</td>
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</tr>
<tr>
<td>360</td>
<td>489</td>
<td>505</td>
<td>994</td>
</tr>
</tbody>
</table>
Randomized Controlled/Clinical Trials - RCT

Randomized Studies (RCT)

Non randomized Observational studies
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.
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)
Registry based Randomized Clinical trials - R-RCT

**Strengths**

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

**Challenges**

- 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 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

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>R-RCT</th>
</tr>
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<tbody>
<tr>
<td>Strategy</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Device – CE mark, used</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Drugs approved/ used in clinical practise</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Drugs for new indication</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Device, first in man</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>New drugs</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
Data base

Clinical registry
(variables incl. personal ID)

Extra study specific Variables/ EDC

Informed consent
Randomisation code
Incl-/exclusion critera

Study database
All variables

Other national registries
(hospital discharge, pharmacy, other clinical registries etc)

Analyse database
Personal ID replaced with study code

Open database
Available for investigators
Possibility to remove patients from registry

Available for registry staff/ for registry staff/trialists
Not possible to remove patients from a trial
Audit trail

Only relevant registry variables

Available for trialists, sponsor
Data checks
All patients
Two questions need to be answered:

Did the patient consent orally?
Are inclusion and no exclusion criteria met?
Information for consent

Did the patient consent?
Are inclusion and exclusion criteria met?

Randomisera & Spara

PCI
Operator

Segment
Segmentnummer
Graft
Nummer på stenos i samma segment
Ocklusion
Stenotyp
Stenosklasse
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:
Vi undrar om du accepterar att delta i denna studie. Om du
Randomize and store data

Did the patient consent?
Are inclusion and exclusion criteria met?

TASTE

PCI

Segment

Stresskardiomyopathy
Primärt beslut
Avböj från operation

9 PCI ad hoc

Vill patient vara med i Taste-studien

Munligt samtycke har inhämpts efter följande information och fråga:


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

Återställ segmentformular
Spara/Lägg till segment
TASTE inclusion rate

All primary PCI:s

Randomized

7244 patients
All patients with STEMI in Sweden and Iceland undergoing primary or rescue PCI. N=11 709 *)

Enrolled in Denmark
N=247

Enrolled in TASTE
N=7259

Erroneous enrollments
N=15

Randomized in TASTE
N=7244

N=3621 assigned to thrombus aspiration
N=3623 assigned to conventional PCI

N=3399 underwent thrombus aspiration
N=222 underwent conventional PCI

N=3445 underwent conventional PCI
N=178 underwent thrombus aspiration

N=3621 were followed up
N=3623 were followed up

Not enrolled
N=4697

N=1162 underwent thrombus aspiration
N=1162 were followed up

N=3535 underwent conventional PCI
N=3535 were followed up
All patients with STEMI in Sweden and Iceland undergoing primary or rescue PCI. N=11,709 (*)

Enrolled in TASTE N=7259

N=3621 assigned to thrombus aspiration
N=3399 underwent thrombus aspiration
N=222 underwent conventional PCI
N=3445 underwent conventional PCI
N=1162 underwent thrombus aspiration
N=3535 underwent conventional PCI
N=3445 were followed up
N=3621 were followed up
N=3399 were followed up
N=1162 were followed up
N=3535 were followed up

Erroneous enrollments N=15
N=7244 Randomized in TASTE
N=3621 were followed up
N=3623 were followed up
N=1162 were followed up
N=3535 were followed up

No patients (0) were lost to follow-up of the primary outcome!

Not enrolled N=4697

Enrolled in Denmark N=247
All-cause mortality up to 1 year

HR up to 30 days 0.94 (0.72–1.22), P=0.63
All-cause mortality up to 1 year

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

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., Thörarinn 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
RRCT and RCT

TOTAL, N=10,732
Cost 15,000,000 €

Jolly et al NEJM 2015
Thrombus aspiration
RRCT and RCT

TOTAL, N=10,732
Cost 15,000,000 €

TASTE, N=7,244
Cost 500,000 €

Jolly et al NEJM 2015
<table>
<thead>
<tr>
<th>Title</th>
<th>Citation</th>
<th>Routine aspiration should be considered</th>
<th>Class</th>
<th>LOE</th>
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<tbody>
<tr>
<td>2014 ESC/EACTS guidelines on myocardial revascularization</td>
<td>Eur Heart J. 2014 Oct 1;35(37):2541-619</td>
<td>May be considered in selected patients</td>
<td>IIB</td>
<td>A</td>
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<tr>
<td>2015 ACC/AHA focused update PPCI</td>
<td>JACC on line</td>
<td>Routine thrombectomy not useful</td>
<td>III</td>
<td>A</td>
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<td>2015 ACC/AHA focused update PPCI</td>
<td>JACC on line</td>
<td>Selective and bailout Thrombectomy not well established</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>
Oxygen therapy for acute myocardial infarction (Review)

Cabello JB, Burls A, Emparanza JJ, Bayliss S, Quinn T

AUTHORS' CONCLUSIONS

Implications for practice

The evidence in this area is sparse, of poor quality, and predates the advances in reperfusion techniques and trial methods of recent years. The evidence available is suggestive of harm but lacks power, so this could be due to chance. Current evidence neither supports nor clearly refutes the routine use of oxygen in people with AMI.
Primary Endpoint Infarct Size on Cardiac Enzymes

Area under curve p = 0.04

Secondary Endpoint
ST segment resolution / CMR Infarct Size at 6 months

<table>
<thead>
<tr>
<th>CMR Infarct Size</th>
<th>Oxygen Arm N=65</th>
<th>No Oxygen Arm N=74</th>
<th>Ratio of means (Oxygen/No Oxygen)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR), grams</td>
<td>20.3 (9.6, 29.6)</td>
<td>13.1 (5.2, 23.6)</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Geometric Mean (95% CI), grams</td>
<td>14.6 (11.3 – 18.8)</td>
<td>10.2 (7.7 – 13.4)</td>
<td>1.43 (0.99 – 2.07)</td>
<td>0.06</td>
</tr>
<tr>
<td>Median (IQR) proportion of LV mass</td>
<td>12.6 (6.7, 19.2)</td>
<td>9.0 (4.1, 16.3)</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Geometric Mean (95% CI) proportion of LV mass</td>
<td>10.0 (8.1 – 12.5)</td>
<td>7.3 (5.7 – 9.3)</td>
<td>1.38 (0.99 – 1.92)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Eligible patient*:
in ambulance, ED or cath lab
N=6600

*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 SWEDHEART registry and national mortality registry

Funding: Swedish Research council (VR)
Inkludera patienter

Datum

2013-01-01
2013-07-01
2014-01-01
2014-07-01
2015-01-01
2015-07-01
2016-01-01

Alla vårdenheter
Enköping Detox-AMI
Gävle Detox-AMI
Göteborg SU Mölndal Detox-AMI
Göteborg SU Sahlg Detox-AMI
Göteborg SU Östra Detox-AMI
Halmstad Detox-AMI
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Inkluderade patienter


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35 hospitals
Inkluderade patienter

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Total: 6092 enrolled (92%)
Inkluderade patienter

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Totalt: 60922 patienter (92%) erhölls

72% AMI

Of these 55% STEMI

35 hospitals
VALIDATE (R-RCT)

STEMI (n=3000) or NSTEMI (n=3000) Pre-treatment with Ticagrelor, Prasugrel or Cangrelor
Angiography: PCI intended

Primary Endpoint:
NACE: Death, Myocardial Infarction or Bleeding complication (BARC 2, 3 or 5) at 6 months

- Hybrid R-RCT: Register data, register randomisation combined with phone call endpoint follow up and CEC
- Total cost: <2 million dollar
Some sites include 90% of eligible patients.
Included NSTEMI/STEMI in relation to possible eligible patients in Sweden

>60% of all eligible patients in a whole country is enrolled
A substudy to prove the validity of pharmaceutical R-RCT, by comparing a Hybrid R-RCT (phone follow up, CEC) with a pure R-RCT

- Inclusion CRF
- 7 days CRF

Background data from SCAAR

1500 and 3000 patients
DSMB

Comparison of 6 months endpoint data

Randomised in VALIDATE

Study data base
Phone Call 6 months CRF
Hypothesis

Drug eluting devices (DEB/DES) are superior to conventional endovascular therapy:
Lower amputation incidence for critical ischemia (SWEDEPAD 1)
Improved health related QoL with claudication (SWEDEPAD 2)

Funding: Heart-lung foundation. Swedish Research council (VR) and several stent manufacturers (Bard norden AB, Biosensors Europe, Boston Scientific, Cook Sweden AB, Eps Vascular AB, Meliora Medtech)
Hypotheses

Closure of the meso-defect occurring at gastric by pass operation will reduce proprooperative ileus

Without increase in early severe complications (def : >= Clavien-Dindo grade 3B)

Procedure

From May 2010 – Nov 2011, 2500 patients randomized at 12 surgical sites randomized
SPIRIT- HFPEF

N=3583

Patients enrolled from ~11.018 eligible patients in registry

R 1:1

Spirinolactone

Standard of care

Event driven 1073 events

Primary Endpoint: All cause death,
Secondary efficacy endpoints: HF hospitalization and other cardiovascular outcomes
Safety endpoints related to renal function and potassium

• Stable chronic HF
• Age ≥ 50 years
• EF ≥ 40%
• NT-proBNP
  > 300 (sinus rhythm);
  > 750 (AF)
Other ongoing R-RCT Sweden

IFR SWEDEHEART (n=2000)
*Instantaneous Wave-Free Ratio versus Fractional Flow Reserve in ACS*
Funding: Volcano. Study sponsor: UCR
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PROSPECT-2 (n=1200, hybrid trial)
*Providing Regional Observations to Study Predictors of Events in the Coronary Tree.* Evaluate future events from cholesterol plaques detected by near infrared spectroscopy
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Funding: Swedish Research council (VR). Study sponsor: UCR

**U-CARE** (n=500)
Evaluation of internet based cognitive behavioural therapy (iCBT) versus usual care in patients with depression/anxiety post MI.
Funding: Swedish Research council (VR). Study sponsor: UCR
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
Conclusions

- Large need for randomized trials (RCT) particularly for the evaluation of strategies, devices, pharmacological therapies

- Classical RCTs are often not performed in broad representative patient populations

- The national clinical registries are strong networks for collaboration and enroll complete patient populations

- Prospective Registry based Randomized Clinical Trials (RRCT) is a new opportunity for clinical research

- RRCT is ideal for one clinically important hypothesis with reliable hard endpoints
Uppsala Clinical Research Center

Part of Uppsala University and Uppsala University Hospital.