Changing the paradigm: registry-based randomized trials

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Scientific director Uppsala Clinical research center, Uppsala University
Senior Interventional Cardiologist Uppsala University Hospital
President Swedish Cardiac society, Sweden
Which Treatment is Best for Whom? High-Quality Evidence is Scarce
< 15% of guideline recommendations supported by high quality evidence

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

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 quality.

Data: Evidence and recommendations are based on systematic reviews, meta-analyses, and randomized controlled trials.

Clinical practice guidelines are systematically developed statements to assist practitioners with decisions about appropriate health care for specific clinical situations.

- AF
- Heart failure
- PAD
- STEMI
- Perioperative
- Secondary prevention
- Stable angina
- SV arrhythmias
- UA/NSTEMI
- Valvular disease
- VA/SCD
- PCI
- CABG
- Pacemaker
- Radionuclide imaging

We need more trials
“This randomized, double-blind trial involving over 20,000 patients was conducted over a 10 year period. Unfortunately we’ve forgotten why.”
Cost of doing trials

Key cost drivers of pharmaceutical clinical trials in the United States

We need more cost effective trials
### Pragmatic Clinical Trials

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

“Some degree of pragmatism should be included in every clinical trial”

Bob Harrington, Stanford
Usual Clinical Trial after Regulatory/FDA/Academic Interactions

Well planned and conducted pragmatic trial

Poorly planned pragmatic trial

Beautiful but expensive and cumbersome

Good enough

Simple, inexpensive but inappropriate

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

Since 1947

Population registry
By the taxation authority
For all inhabitants

540219-9750
Year/month/day-control

Used for all interaction with the society
Data bases in Sweden based on personal number with patient characteristics, treatments and outcomes

Since 1947

540219-9750

Year/month/day-control

Population registry

Hospital

admission - ICD

Board of health & welfare
### Health data registers:

<table>
<thead>
<tr>
<th>Registry</th>
<th>Contents</th>
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<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 (since 1749)</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>

### Social Services registers

- Social services to the elderly and functionally impaired (2007)
- Persons with impairments – activities according to LSS (2004)
- Social (financial) assistance (2012)
Data bases in Sweden based on personal number with patient characteristics, treatments and outcomes

Since 1947

540219-9750

Population registry

Hospital admission - ICD

Statistics Sweden

Education, salary, social status, residence etc
Data bases in Sweden based on personal number with patient characteristics, treatments and outcomes

Since 1947

540219-9750

Year/month/day-control

Population registry

Prescription registry
All dispensations from the pharmacy

Hospital admission - ICD

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

Since 1947

540219-9750

Year/month/day-control

Hospital admission - ICD

Outpatient diagnosis registry

Population registry

Prescription registry

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

Since 1947

540219-9750

Year/month/day-control

Population registry

Prescription registry

Quality registry
National health care providers and government

Hospital admission - ICD

Outpatient diagnosis registry

Statistics Sweden
Sweden’s > 100 quality registries

Figure 1. National Quality Registries by starting year. 2010 registries. Source: Applications for 2010 national quality registries.
Data bases in Sweden based on personal number with patient characteristics, treatments and outcomes

Since 1947

540219-9750

Year/month/day-control

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

Since 1947

540219-9750

Year/month/day-control

Population registry

Prescription registry

Quality registry

Quality Registry

Outpatient diagnosis registry

Hospital admission - ICD

Quality Registry

Quality Registry

Quality Registry
Number of cases annually: > 80 000

- RIKS-HIA: 73 CCU hospitals, 100%
- SCAAR: 30 PCI hospitals, 100%
- Percutaneous valves: 7 hospitals, 100%
- Heart surgery: 7 hospitals, 100%
- Secondary prevention: 67 hospitals, 90%
- Cardio genetics: 5 university hospitals
- Cardiac CT: 10 large hospitals
- Continuous bio banking: 3 university hospitals

>300 variables - baseline, procedural, outcomes

At monitoring: 95-96% agreement.
EuroHeart – The Project

EuroHeart is an ESC coordinated and sponsored programme that:

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

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

![Diagram showing the relationship between observational RWD and randomized clinical trial (R-RCT)]

**Observational RWD**
- Observational
- Hypothesis generating
- Pragmatic
- All comers
- Resource-effective

**Randomized clinical trial**
- Randomized
- Causal inference
- Efficacy
- Narrow selection
- Resource-intense
Registry-based Randomized Clinical Trial - R-RCT

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

Observational RWD
- Observational
- Hypothesis generating
- Pragmatic
- All comers
- Resource-effective

Randomized clinical trial
- Randomized
- Causal inference
- Efficacy
- Narrow selection
- Resource-intense
Prosective randomized trial that uses a clinical registry for one or several major functions for trial conduct and outcomes reporting.
R-RCT vs. classical RCT

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

<table>
<thead>
<tr>
<th>RRCT</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Evaluation of therapeutic options available/used in routine clinical care</td>
<td>Approval of new pharmaceutical agents and medical devices</td>
</tr>
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</table>
# Pre-requisites for modern R-RCTs

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CardioPulse

Sweden’s new online cardiac registry is kind

SWEDEHEART is unique because it offers immediate feedback, says Ulf Hagenhjelm, professor of cardiology and Senior Consultant, Department of Cardiology, University Hospital, Linköping, Sweden, and President of SWEDHEART.
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)
Thrombus aspiration

Thrombus aspiration

PCI alone (N=16 417)
HR (95% CI): 1.21 (1.08-1.35)

PCI + thrombus aspiration (N=3600)

RR 20%

Randomize and store data

TASTE

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

PCI

Operator

Segment

Segmentnummer
Groft
Nummer på stenos i samma segment
Oclusion
Stenotyp
Stenosklass
Procedurtyp

Återställ segmentformulär  
Spara/Lägg till segment

Vill patient vara med i Taste-studien

Munligt samtycke har inhamtats efter följande information och fråga:

Vi undrar om du accepterar att delta i denna studie. Om du
TASTE inclusion rate

All primary PCI:s
Eligible
Randomized
7244 patients
The simplest and most pragmatic design

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

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 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
Registry based Patient Follow-up

**STEMI Thrombectomy Story**

**TASTE**

### Registry-based Follow-up

1. **1\textsuperscript{st} patient:** June 2010
2. 30 centers
3. 33 months to full enrollment

### Standard site-based Follow-up

1. **1\textsuperscript{st} patient:** August 2010
2. 87 centers
3. 48 months to full enrollment


<table>
<thead>
<tr>
<th>Title</th>
<th>Citation</th>
<th>Class</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014 ESC/EACTS guidelines on myocardial revascularization</td>
<td>Eur Heart J. 2014 Oct 1;35(37):2541-619</td>
<td>IIb</td>
<td>A</td>
</tr>
<tr>
<td>2015 ACC/AHA focused update PPCI</td>
<td>JACC</td>
<td>III</td>
<td>A</td>
</tr>
<tr>
<td>2015 ACC/AHA focused update PPCI</td>
<td>JACC</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>2017 ESC Guidelines ST-segment elevation myocardial infarction</td>
<td>European Heart Journal 2017</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>
Assessing the Nationwide Impact of a Registry-Based Randomized Clinical Trial on Cardiovascular Practice:
The TASTE Trial in Perspective
Trombansugning – före, under, och efter TASTE

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

Produced more reliable and relevant evidence
2014: TASTE (n=7244)
2015: TOTAL (n=10732)
Negative results

Evidence Ecosystem reducing waste
Thrombus aspiration for MI Loop 2 2014-2017

Updated and disseminated guidance
2015: ACC/AHA guidelines
2017: ESC guidelines
Strong recommendations against

De-implemented and evaluated in Sweden, what about the rest of the world?
2014-2015: Swedish national online registry rapid de-implementation of thrombus aspirin of PCI patients), immediately following TASTE before systematic review and guidelines up
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)
Primary Endpoint up to 365 days

Oxygen treatment
Ambient air

HR 0.97
95% CI, 0.79 – 1.21
P=0.8
VALIDATE (R-RCT)

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

R
1:1

Heparin only (70-100U/kg)
Bivalirudin
(5000U Heparin pre-hospital or 3000U pre-PCI)

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

• FU: Register data, combined with phone call endpoint follow up and CEC
• Funding: Heart-lung foundation. Swedish research council, Astra Zeneca, The Medicines company.
Included NSTEMI/STEMI in relation to possible eligible patients in Sweden

- 25 PCI centers out of 29 in Sweden participated in the trial.
- 47.8% (6006 of 12,561) of all patients in Sweden presenting at enrolling hospitals with an initial diagnosis of STEMI or NSTEMI planned for PCI were randomized.
- Of all patients potentially eligible for enrollment, 70.0% (6006 of 8585) were randomized.
Primary Endpoint at 180 days

HR 0.96
95% CI, 0.83 – 1.10
P=0.54
### Guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Reco</th>
<th>Guideline</th>
<th>Reco</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombus aspiration</td>
<td>IIa B</td>
<td>2017 Routine use of thrombus aspiration is not recommended</td>
<td>III A</td>
</tr>
<tr>
<td></td>
<td>2012</td>
<td>Routine thrombus aspiration should be considered</td>
<td></td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>I B</td>
<td>2018 Bivalirudin may be considered as an alternative to UFH</td>
<td>IIb A</td>
</tr>
<tr>
<td></td>
<td>2012</td>
<td>Bivalirudin (GP IIb/IIIa blocker restricted to bailout) is recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>over heparin and a GP IIb/IIIa blocker</td>
<td></td>
</tr>
<tr>
<td>Oxygen</td>
<td>I C</td>
<td>2017 Routine oxygen is not recommended if SaO2 &gt; 90%</td>
<td>III B</td>
</tr>
<tr>
<td></td>
<td>2012</td>
<td>Oxygen is indicated if hypoxia (SaO2 &lt;95%), breathlessness, or acute heart failure.</td>
<td></td>
</tr>
<tr>
<td>iFR</td>
<td>I A</td>
<td>2019 When evidence of ischaemia is not available, FFR or iFR are</td>
<td>I A</td>
</tr>
<tr>
<td></td>
<td>2014</td>
<td>recommended to assess the haemodynamic relevance of intermediate-grade stenosis.</td>
<td></td>
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## R-RCTs in Sweden

### Cardiology

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Description</th>
<th>Journal</th>
</tr>
</thead>
<tbody>
<tr>
<td>TASTE</td>
<td>7200</td>
<td>Thrombus aspiration in primary PCI</td>
<td>NEJM</td>
</tr>
<tr>
<td>iFR</td>
<td>2018</td>
<td>iFR vs FFR in stable angina or ACS</td>
<td>NEJM</td>
</tr>
<tr>
<td>VALIDATE</td>
<td>6006</td>
<td>Bivalirudin vs UFH for PCI in ACS</td>
<td>NEJM</td>
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<tr>
<td>DETO2X</td>
<td>6629</td>
<td>Oxygen therapy in myocardial infarction</td>
<td>NEJM</td>
</tr>
<tr>
<td>FULL-REVASC</td>
<td>4000</td>
<td>FFR-guidance in myocardial infarction</td>
<td>Ongoing</td>
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<tr>
<td>PROSPECT-2</td>
<td>1200</td>
<td>Near infrared spectroscopi</td>
<td>Ongoing</td>
</tr>
<tr>
<td>IAMi</td>
<td>4400</td>
<td>Influenza vaccination After Myocardial Infarction</td>
<td>Ongoing</td>
</tr>
<tr>
<td>SPIRIT HFpEF</td>
<td>3200</td>
<td>Spironolactone for HFpEF</td>
<td>Ongoing</td>
</tr>
<tr>
<td>REDUCE</td>
<td>6600</td>
<td>Betablocker post MI in patients</td>
<td>Ongoing</td>
</tr>
<tr>
<td>ABC AF</td>
<td>6500</td>
<td>Biomarker score based treatment strategies</td>
<td>Ongoing</td>
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</table>

### Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMING</td>
<td>3000</td>
<td>Treatment after ischemic stroke in atrial fibrillation</td>
<td>Ongoing</td>
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## R-RCTs in Sweden

### Cardiothoracic Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedegraft</td>
<td>(n=800)</td>
<td>Vein grafts for CABG surgery</td>
<td>Ongoing</td>
</tr>
<tr>
<td>TACSI</td>
<td>(n=2048)</td>
<td>Medication after CABG</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

### Obesity Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Description</th>
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</tr>
</thead>
<tbody>
<tr>
<td>SLITS</td>
<td>(n=2507)</td>
<td>Gastric by pass operation</td>
<td>Lancet</td>
</tr>
<tr>
<td>BEST</td>
<td>(N=4000)</td>
<td>Obesity surgery</td>
<td>Ongoing</td>
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</table>

### Vascular Surgery

<table>
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<th>Study</th>
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<tbody>
<tr>
<td>SWEDEPAD</td>
<td>(N=2400)</td>
<td>Drug Elution trial in Peripheral Arterial Disease,</td>
<td>Ongoing</td>
</tr>
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</table>

### Gynecology/Labor

<table>
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<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWEPIS</td>
<td>(n=10 000)</td>
<td>Post-term Induction of labour</td>
<td>Stopped</td>
</tr>
</tbody>
</table>
Conclusions

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

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

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