Registry-based randomised clinical trials
- An innovative trial paradigm

Ole Fröbert, MD, PhD, FESC
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)

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

- AF: 11.7%
- Heart failure: 26.4%
- PAD: 15.3%
- STEMI: 13.5%
- Perioperative: 12.0%
- Secondary prevention: 22.9%
- Stable angina: 6.4%
- SV arrhythmias: 6.1%
- UA/NSTEMI: 23.6%
- Valvular disease: 0.3%
- VA/SCD: 9.7%
- PCI: 11.0%
- CABG: 19.0%
- Pacemaker: 4.9%
- Radionuclide imaging: 4.8%

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

- Quality Registries
- Outpatient diagnosis registry
- Prescription registry
- Hospital admission registry
- ICD
- EHRs
- Hospitals and primary care
- Population registry

Sweden statistics
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

• 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 SWEDHEART Registry

Data entry online

Automatic linkage with population registry

Automated data checks

### Name, personal ID number

<table>
<thead>
<tr>
<th>Name, personal ID number</th>
<th>Uppsala PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Administrative data

<table>
<thead>
<tr>
<th>Datum för procedur</th>
<th>2013-08-03</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typ av registrering</td>
<td>3 Angio + PCI</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Clinical background and prior CV disease

<table>
<thead>
<tr>
<th>Längd (cm)</th>
<th>175</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vikt (kg)</td>
<td>104</td>
</tr>
<tr>
<td>S-Kreatinin (mikromol/L)</td>
<td>90</td>
</tr>
</tbody>
</table>

### Angiographic background data

<table>
<thead>
<tr>
<th>Behandlad Hypertonii</th>
<th>1 Ja</th>
</tr>
</thead>
</table>
Two questions needed to be answered:
1. Does the patient consent orally?
2. Are inclusion and no exclusion criteria met?
Does the patient consent?

Are inclusion and no exclusion criteria met?

Information for consent


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

Vill patient vara med i Taste-studien

Muntligt semtycke hör inhämtats efter följande information och fråga:


Vi undrar om du accepterar att delta i denna studie. Om du
Does the patient consent?

Are inclusion and no exclusion criteria met?

Randomize and save data
No patients (0) were lost to follow-up of the primary endpoint.
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

Registry-based Patient Follow-up

**STEMI Thrombectomy Story**

**TASTE**

Registry-based Follow-up

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

Standard site-based Follow-up

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

Thrombus aspiration
downgraded in ACC/AHA and ESC guidelines from:
Ila (reasonable to consider)
to: IIIa (not recommended)

TASTE – clinical impact

## RRCT vs. RCT

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>RCT</th>
<th>RRCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device – CE marked, in use</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Device, first in man</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
Four finalized RRCTs – all guideline changing

**TASTE**
Thrombus aspiration in ST-elevation myocardial infarction, N=7244

**iFR-SWEDEHEART**
Comparison of two invasive diagnostic methodologies, N=2037

**DETO2X-AMI**
Determination of the role of oxygen in acute myocardial infarction, N=6629

**VALIDATE-SWEDEHEART**
### Impact on Swedish health economy

<table>
<thead>
<tr>
<th>Study</th>
<th>Cost of study</th>
<th>Cost reduction for health care system</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TASTE</strong></td>
<td>350,000 €</td>
<td>220,000 €/year</td>
</tr>
<tr>
<td><strong>DETO2X-AMI</strong></td>
<td>950,000 €</td>
<td>3,800,000 €/year</td>
</tr>
<tr>
<td><strong>VALIDATE-SWEDEHEART</strong></td>
<td>1,600,000 €</td>
<td>4,700,000 €/year</td>
</tr>
</tbody>
</table>
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

Limitations

• Data quality (?)

• Need for personal ID to track patients

• Best suited for simple questions

• Not for new drugs or devices

• Event adjudication if outcome variables not clearly defined
CONSORT extension coming up for trials using cohorts and 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
THANK YOU!

ole.frobert@regionorebrolan.se
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

Number of patients

TOTAL
TASTE
TAPAS
JETSTENT
AIMI
INFUSE-AMI
VAMPIRE
PREPARE
Chevalier
Kaltoft
MUSTELA
X AMINE ST
PIHRATE
EXPIRA
DEAR-MI
Liistro
A disruptive technology?

- The New England Journal of Medicine suggested it:
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
Patients with **myocardial infarction**, undergoing angiography and if appropriate revascularization and **LV-EF ≥ 50%**, included in SWEDHEART

**Informed consent**

**Randomization**

n = 7000

**Oral Beta-blockade**

(Metoprolol Succinate or Bisoprolol)

n = 3500

**No Beta-blockade**

N = 3500

**Primary endpoint**: Death or non-fatal MI

(Event driven ITT, expected median follow-up of 2 years)

**Secondary endpoints**: Death, cardiovascular death, MI, HF, atrial fibrillation

(Safety data, PROM)
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

Josefin Sundh, MD, PhD
Gustaf Rindler, MD
Naja Hulvej Rod, MD, PhD
Ole Fröbert, MD, PhD, FESC (Sponsor)

1) Örebro University, School of Medical Sciences, Department of Respiratory Medicine, Örebro, Sweden
2) Primary care, Capio Lekeberg Health Centre Lekeberg, Fjugesta, Sweden
3) Department of Public Health, Section of Social Medicine, University of Copenhagen, Denmark
4) Örebro University Hospital, Faculty of Health, Department of Cardiology, Örebro, Sweden