Registry-based RCTs
What we learned from the TASTE Trial

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Potential conflicts of interest: none
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)

More than half of all clinical trials are never published ³)

R&D productivity

Level of evidence A in 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
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

Deficient data quality
Missing variables
Confounding factors
Multivariate statistics - difficult to understand
Number of cases annually: 80 000

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIKS-HIA</td>
<td>73 CCU hospitals, 100%</td>
</tr>
<tr>
<td>SCAAR</td>
<td>30 PCI hospitals, 100%</td>
</tr>
<tr>
<td>Percutaneous valves</td>
<td>7 hospitals, 100%</td>
</tr>
<tr>
<td>Heart surgery</td>
<td>7 hospitals, 100%</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>65 hospitals, 85%</td>
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</table>

>150 variables – baseline, procedural and outcome data

Monitoring: >95% agreement between patient records and registry data
Why not

• Use existing online databases for randomization, case report form and follow-up?

• And apply this "Registry-based Randomized Clinical Trial (RRCT)" concept in the largest study of a

Medical technique in ST-elevation myocardial infarction (STEMI)
Thrombus aspiration: a simple technique with little evidence
Methods

• All 29 Swedish, 1 Icelandic and 1 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 by physician / nurse

Automatic linkage with population registry

Automated data checks

<table>
<thead>
<tr>
<th>Clinical background and prior CV disease</th>
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<tbody>
<tr>
<td>Längd (cm)</td>
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<tr>
<td>Vikt (kg)</td>
</tr>
<tr>
<td>S-Kreatinin (mikromol/L)</td>
</tr>
<tr>
<td>Kreatinin clearance</td>
</tr>
<tr>
<td>Tidigare PCI</td>
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<tr>
<td>Tidigare CABG</td>
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<tr>
<td>Diabetes</td>
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Angiographic background data

Behandlad hypertoni | 1 Ja *
Two questions needed to be answered:
1. Does the patient consent orally?
2. Are inclusion and no exclusion criteria met?
Information for consent

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

TASTE

Randomisera & Spara

PCI

Operator

Spara

Segment

Segmentnummer

Groft

0 Nej

Nummer på stenos i samma segment

1 Första

Ocklusion

Stenotyp

Stenosklass

Procedurtyp

Lokal framgång

Återställ segmentformulär

Spara/Lägg till segment

Vill patient vara med i TASTE-studien

Muntligt samtycke har inhämtats efter följande information och fråga:


Vi undrar om du accepterar att delta i denna studie. Om du
**TASTE trial enrollment chart**

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

<table>
<thead>
<tr>
<th>Enrolled in Denmark</th>
<th>N=247</th>
</tr>
</thead>
</table>

| Erroneous enrollments | N=15 |

| Enrolled in TASTE | N=7259 |

| Randomized in TASTE | N=7244 |

| N=3621 assigned to thrombus aspiration |

<table>
<thead>
<tr>
<th>N=3623 were followed up</th>
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| N=222 underwent thrombus aspiration |

| N=3399 underwent thrombus aspiration |

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<tr>
<th>N=1162 were followed up</th>
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</table>

| N=178 underwent thrombus aspiration |

| N=3445 underwent conventional PCI |

<table>
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<tr>
<th>N=3621 were followed up</th>
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| N=3535 underwent conventional PCI |

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<th>N=3535 were followed up</th>
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*No patients (0) were lost to follow-up of the primary endpoint!*
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
All-cause mortality at 30 days

HR 0.94 (0.72 – 1.22), P=0.63

All-cause mortality at 1 year


HR 0.94 (0.78 – 1.15), P=0.57

Costs

• The budget for a conventional randomized clinical trial including >7000 patients at 30+ sites in three countries:

  US $2000 per patient x 7000 = US $14 000 000

• The total costs of TASTE:

  US $300 000 or US $50 per patient

  US $300 000 or US $50 per patient
  \approx 2\% \text{ of a conventional RCT}
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
# RRCT vs. RCT

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>RRCT</th>
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<tbody>
<tr>
<td>Treatment strategy</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Device – CE marked, in use</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Device, first in man</td>
<td></td>
<td>+</td>
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Challenges

• Ethics
  – Is informed consent required if randomized to treatments already in clinical use?
  – Treatment delay
  – Randomization of unconscious patients?

• Originality
  – Dare to challenge dogmas

• Protocol adherence and consecutive patient inclusion

• Is adjudication necessary?
Influenza vaccination After Myocardial Infarction (IAMT trial)

A multicenter, prospective, double-blind, randomized controlled clinical trial based on the Swedish angiography and angioplasty registry (SCAAR) platform

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Stefan K. James, MD, PhD
Bo Lagerqvist, MD, PhD
Jonas Persson, MD, PhD
Oskar Angerås, MD
Lena Jonasson, MD, PhD
Johan Nilsson, MD, PhD
John Pernow, MD, PhD

Þórarinn Gudnason, MD, PhD (Iceland)
Timo Mäkikallio, MD, PhD (Finland)
Rasmus Moer, MD, PhD (Norway)
Evald H. Christiansen, MD, PhD (Denmark)
Influenza vaccination After Myocardial Infarction (IAMT trial)

Patients with STEMI or NSTEMI referred to coronary angiography
N = 4400

PCI / coronary angiography

Online 1:1 randomization in registry

Influenza vaccination  Placebo vaccination

1 year: Composite of time to all-cause death, new AMI and stent thrombosis + secondary endpoints

2, 3 and 5 years: Secondary endpoints
An RRCT do it yourself guide

- One, simple hypothesis
- Agree! Put away all regional and (some) personal ambitions
- Get patient representatives on board early on
- 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
Conclusions

• Urgent need for randomized trials in clinical medicine

• Registries are strong networks for collaboration enrolling complete patient populations

• The Registry-based Randomized Clinical Trial (RRCT) is ideal for:

  - One clinical hypothesis, broad inclusion, hard endpoints

Keep it simple, simple, simple..