Swedish experiences:
National registries – for quality improvement and research

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Evidence based health care development

Clinical trials
Diagnostic methods
Basic research

Guidelines- Scientific evidence

Implementation
Registers – evaluation
Real world evidence

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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

<table>
<thead>
<tr>
<th>Condition</th>
<th>High-Quality Evidence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>26.4%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>15.3%</td>
</tr>
<tr>
<td>PAD</td>
<td>13.5%</td>
</tr>
<tr>
<td>Stable angina</td>
<td>22.9%</td>
</tr>
<tr>
<td>SV arrhythmias</td>
<td>23.6%</td>
</tr>
<tr>
<td>UA/NSTEMI</td>
<td>23.6%</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>19.0%</td>
</tr>
<tr>
<td>VA/SCD</td>
<td>11.0%</td>
</tr>
<tr>
<td>PCI</td>
<td>9.7%</td>
</tr>
<tr>
<td>CABG</td>
<td>4.9%</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>4.8%</td>
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<tr>
<td>Radionuclide imaging</td>
<td>4.8%</td>
</tr>
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</table>

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

Objective: To review the scientific evidence underlying the ACC/AHA guidelines.

We need more trials.
Cost of doing trials

Key cost drivers of pharmaceutical clinical trials in the United States

We need more cost effective trials
Unfortunately, too many of the decisions made today about health and healthcare are not supported by high quality evidence. Current clinical trials are too slow, too expensive, not reliable, and not designed to answer the important questions...

Rob Califf, Commissioner for medical products & tobacco FDA. “Applied clinical trials.”
Data bases for baseline characteristics and outcomes in Sweden

Since 1947

540219-9750

year month day place sex ctrl

Quality Registries

Outpatient diagnosis registry

Prescription registry

Population registry

Hospital admission registry ICD

EHRs Hospitals and primary care

Sweden statistics
Prospective randomized trial that uses a clinical registry for one or several major functions for trial conduct and outcomes reporting.

PERSPECTIVES

Registy-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
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.
SWEDEHEART: Sweden’s new online cardiac registry, the first of its kind

Covering all hospitals in Sweden, SWEDEHEART is unique because it allows long-term follow-up and immediate feedback, says Ulf Stenestrand, MD, PhD, Associate Professor of cardiology and Senior consultant interventional cardiologist, Department of Cardiology, University Hospital, Linköping, Sweden, and President of SWEDEHEART.
Randomize and store data

Did the patient consent?

Are inclusion and exclusion criteria met?
TASTE inclusion rate

Graph showing the number of patients over time, with lines for "All primary PCI:s", "Eligible", and "Randomized". The graph indicates that 7244 patients were included in the TASTE study.
The simplest and most pragmatic design

Outcomes 1 Year after Thrombus Aspiration for Myocardial Infarction

Bo Lagerqvist, M.D., Ph.D., Ole Fröbert, M.D., Ph.D., Göran K. Oliviacrona, M.D., Ph.D., Thórarinn Guðnason, 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 Göteborg, M.D., Ph.D., Peter Hårdhammar, M.D., Dan Ioanes, M.D., Anders Kalllyd, M.D., Rickard Linder, M.D., Ph.D., Anders Lundin, M.D., Jacob Odenstedt, M.D., Elmir Omerovic, M.D., Ph.D., Verner Puskár, M.D., Tim Tödt, M.D., Ph.D., Eva Zelleroth, M.D., Ollie Östlund, Ph.D., and Stefan K. James, M.D., Ph.D.

HR up to 30 days 0.94 (0.72–1.22), P=0.63

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 from other conditions.
Registry based Patient Follow-up

**STEMI Thrombectomy Story**

**Registry-based Follow-up**

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

**Standard site-based Follow-up**

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

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500,000 €

15,000,000 €
<table>
<thead>
<tr>
<th>Title</th>
<th>Citation</th>
<th>Class</th>
<th>LOE</th>
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<tr>
<td>2014 ESC/EACTS guidelines on myocardial revascularization</td>
<td>Eur Heart J. 2014 Oct 1;35(37):2541-619</td>
<td>Ilb</td>
<td>A</td>
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<tr>
<td>2015 ACC/AHA focused update PPCI</td>
<td>JACC</td>
<td>III</td>
<td>A</td>
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<tr>
<td>2015 ACC/AHA focused update PPCI</td>
<td>JACC</td>
<td>Ilb</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>

- **2012 ESC Guidelines ST-segment elevation myocardial infarction**
  - Routine aspiration should be considered

- **2014 ESC/EACTS guidelines on myocardial revascularization**
  - May be considered in selected patients

- **2015 ACC/AHA focused update PPCI**
  - Routine thrombectomy not useful

- **2015 ACC/AHA focused update PPCI**
  - Selective and bailout thrombectomy not well established

- **2017 ESC Guidelines ST-segment elevation myocardial infarction**
  - Routine use of thrombus aspiration is not recommended.
Thrombus aspiration post Taste

Mean use during trial

Mean use immediately after trial

Län (folkbokföring)
- Stockholms län
- Uppsala län
- Södermanlands län
- Östergötlands län
- Jönköpings län
- Kronobergs län
- Kalmar län
- Gotlands län
- Blekinge län
- Skåne län
- Hallands län
- Västra Götalands län
- Värmlands län
- Örebro län
- Västmanlands län
- Dalarnas län
- Gävleborgs län
- Västernorrlands län
- Jämtlands län
- Västerbottens län
- Norrbottens län
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 documented rapid de-implementation of thrombus aspiration (to <20% of PCI patients), immediately following TASTE trial results, before systematic review and guidelines updated
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
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

Oxygen
6l/min for (6-)12h via Oxymask

Air

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 5.0 %

Ambient air 5.1 %

HR 0.97
95% CI, 0.79 – 1.21
P=0.8

The New England Journal of Medicine

Oxygen Therapy in Suspected Acute Myocardial Infarction

Robin Hofmann, M.D., Stefan K. James, M.D., Ph.D.,
Tomas Jernberg, M.D., Ph.D., Bertil Lindahl, M.D., Ph.D.,
David Erlinge, M.D., Ph.D., Nils Witt, M.D., Ph.D., Gabriel Arefalk, M.D.,
Mats Frick, M.D., Ph.D., Joakim Alfredsson, M.D., Ph.D.,
Lennart Nilsson, M.D., Ph.D., Annica Ravn-Fischer, M.D., Ph.D.,
Elmir Omerovic, M.D., Ph.D., Thomas Kellerth, M.D., David Sparv, B.Sc.,
Ulf Ekelund, M.D., Ph.D., Rickard Linder, M.D., Ph.D.,
Mattias Ekström, M.D., Ph.D., Jörg Lauermann, M.D., Urban Haaga, B.Sc.,
John Pernow, M.D., Ph.D., Ollie Östlund, Ph.D., Johan Herlitz, M.D., Ph.D.,
and Leif Svensson, M.D., Ph.D., for the DETO2X-SWEDEHEART Investigators*
Relief of hypoxaemia and symptoms

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen is indicated in patients with hypoxaemia (SaO2 &lt;90% or PaO2 &lt;60 mmHg).</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Routine oxygen is not recommended in patients with SaO2 ≥90%.</td>
<td>III</td>
<td>B</td>
</tr>
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</table>
VALIDATE (R-RCT)

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

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.
Primary Endpoint at 180 days

HR 0.96
95% CI, 0.83 – 1.10
P=0.54
SPIRRIT- HFPEF

Patients enrolled from ~11,018 eligible patients in registry
N=3,200

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

Primary Endpoint: Cardiovascular death,
Secondary efficacy endpoints: HF hospitalization and other cardiovascular outcomes
Safety endpoints related to renal function and potassium
R-RCTs in Sweden (known to us)

**TASTE (n=7200)** Thrombus aspiration in primary PCI  
Completed  
Clinical registry: Swedeheart  
Funding: Swedish Heart-Lung foundation, Sw Research council, Medtronic, Vascular Solutions, Terumo.  
Study sponsor and ARO:

**iFR Swedeheart (n=2018)** iFR vs FFR in stable angina or ACS  
Completed  
Clinical registry: Swedeheart  
Funding: Volcano. Study sponsor and ARO: UCR.

**VALIDATE (n=6006)** Bivalirudin vs UFH for PCI in ACS  
Completed  
Clinical registry: Swedeheart  
Funding: Swedish Heart-Lung foundation, Sw Research council, The MedCo, AZ  
Study sponsor and ARO: UCR

**DETO2X (n=6629)** Oxygen therapy in suspected myocardial infarction  
Completed  
Clinical registry: Swedeheart  
Funding: Swedish Heart-Lung foundation, Sw Research council.  
Study sponsor: Karolinska Institute. ARO: UCR

**SLITS (n=2507)** Closure of the meso-defect at gastric by pass operation  
Completed  
Clinical registry: SOREG  
Funding: Örebro County Council, Stockholm City Council, and the Erling-Persson Family Foundation  
Sponsor: Örebro University

**SWEDEPAD (N=2400)** Drug Elution trial in Peripheral Arterial Disease,  
Ongoing  
Clinical registry: SwedVasc - Swedish vascular surgery registry  
Funding: Sw Research council. Study sponsor: Göteborg University. ARO: UCR

**TIMING (n=3000)** Time point for NOAC treatment after ischemic stroke in atrial fibrillation  
Ongoing  
Clinical registry: Swedish Stroke Registry  
Funding: Swedish Research council (VR), Study sponsor: UCR. ARO: UCR
R-RCTs in Sweden (cont’d)

PROSPECT-2 (n=1200, hybrid trial) near infrared spectroscopy
Clinical registry: Swedeheart
Funding: The Medicines Company/ Abbot vascular. Study sponsor: UCR

FULL-REVASC (n=4000) FFR-guidance for ST elevation myocardial infarction revascularization
Clinical registry: Swedeheart
Funding: Swedish Research council (VR), Study sponsor: Karolinska Institute. ARO: KTC

SWEPIS (n=10 000) Post-term Induction of labour
Clinical registry: Pregnancy Register and Swedish Neonatal Q registry
Study sponsor: Göteborg University

IAMi (n=4400) Influenza vaccination After Myocardial Infarction
Clinical registry: Swedeheart
Funding: Sanofi, Study sponsor: Örebro University hospital. ARO: KTC

BEST (N=4000) Gastric by pass vs sleeve operation in obesity surgery
Clinical registry: SOREG
Study sponsor: Göteborg University

SPIRRIT HFpEF (n=3200) Spironolactone for HFpEF
Clinical registry: SwedeHF
Funding: Swedish Heart and lung foundation. NIH, Erling Persson
Study sponsor: UCR. ARO: UCR
R-RCTs in Sweden (cont’d)

**REDUCE (n=6600)** Betablocker post MI in patients with normal left ventricular function.  
Funding: Swedish Research council (VR),  
Study sponsor: Karolinska Institute. ARO: UCR  
*Ongoing*

**Swedegraft (n=800)** Patency of vein grafts for CABG surgery evaluated by coronary CT  
Clinical registry: Swedeheart  
Funding: Swedish Heart and lung foundation.  
Study sponsor: Uppsala Univ hospital. ARO: UCR  
*Ongoing*

**MINOCA BAT (n=2048)** ACE/ARBi after MI with non-obstructive coronary arteries  
Clinical registry: Swedeheart  
Funding: Swedish Research council (VR).  
Study sponsor: UCR. ARO: UCR  
*Soon to start*

**TACSI (n=2048)** Ticagrelor and ASA vs. ASA alone after CABG in patients with ACS  
Clinical registry: Heart surgery/ Swedeheart  
Funding: Swedish Research council (VR).  
Study sponsor: Göteborg University. ARO: UCR  
*Soon to start*

**ABC AF (n=6500)** ABC-risk score based treatment strategies in patients with AF  
Clinical registry: AURICULA  
Funding: Swedish Foundation for Strategic Research, Sw Heart-Lung Foundation, Roche Diagnostics.  
Study sponsor: UCR  
*Soon to start*
R-RCTs in Oncology?