Verwendung von routinemässig erhobenen Daten für pragmatische randomisierte Studien: Erste Erfahrungen in der Schweiz

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Overview

• Registry based randomized controlled trial
  – Advantages
  – Disadvantages
• Example of a registry based RCT in Switzerland
• The future of clinical research
  – Registry based clinical research and trials
• Summary & conclusions
Registry based randomized controlled trials

- The randomized registry trial represents a disruptive technology
- a technology that transforms existing standards, procedures, and cost structures

Real-world research and randomization are entirely compatible

• One of the most important advances in clinical trial methodology may be the broadening of the application of randomization outside more typical venues for clinical trials, such as academic research centers

• Appropriate uses of methods across disparate settings, but we must first be clear about our terminology and its application.
Concept of registry-based randomized clinical trial (RRCT)

- High quality registries contain a large and comprehensive set of variables relevant for prognosis and patient outcome

- Comprehensive coverage of patients
  - SWEDHEART registry of all hospitalized patients with heart problems (PCI, Valve replacement, ICD, etc.) in Sweden

- Patients admitted to hospital are asked to allow for randomisation rather than physician preference for treatment
Advantages of RRCTs (I)

- A large proportion of less selected patients are available

- Better identification of eligible patients by large scale screening of inclusion and exclusion criteria

- More rapid patient recruitment

- Less costly, relevant data is routinely & prospectively collected
Advantages of RRCTs (II)

• Higher external validity of RRCTs

• More ballanced research questions (investigator & industry driven)

• More appropriate benefit / harm assessment due to larger number of and less selected patients

• Collection of better health resource use data for cost-effectiveness analysis using the parallel claim data registries
Disadvantages of RRCTs (I)

• High up front costs for data system development

• Registries may contain large amount of irrelevant data

• Time intensive search strategies for identification of patients and relevant patient parameters

• For drugs or medical devices that require comprehensive safety reporting and strictly defined endpoints the methodology is not different but data collection and monitoring requirements are very high in the context of routinely collected data
Disadvantages of RRCTs (II)

- There are still walls between research and healthcare setting to enable life-span learning from real world data and shared clinical trial data

- Ethical considerations

- Unresolved issues of:
  - Patient consent
  - Ownership of data
  - Protection of personal data
  - Governance
ADAPTABLE Study Design

Patients with known ASCVD + ≥1 “Enrichment Factor”

Identified through EHR/direct patient contact in clinics and hospitals through CDRNs/PPRNs (PPRN patients would need to connect through a CDRN to participate)

Patients contacted via email, mail, and in clinic with trial information and e-Consent. Treatment assignment will be provided directly to patient

*Enrichment Factors
- Age > 65 years
- Creatinine > 1.5 mg/dL
- Diabetes mellitus (type 1 or 2)
- Known 3-vessel CAD
- Current CVD or PAD
- Known EF<50% by echo, cath, nuclear study
- Current smoker

ASA 81 mg QD

ASA 325 mg QD

Randomized Electronic Follow-Up: 3 vs 6 months Supplemented with EHR/CDM Data

Duration: Enrollment over 24 months; maximum follow up of 30 months

Primary Endpoint: Composite of all-cause mortality, hospitalization for MI, or hospitalization for stroke

Primary Safety Endpoint: Hospitalization for major bleeding
Personalized Prescription Feedback Using Routinely Collected Data to Reduce Antibiotic Use in Primary Care
A Randomized Clinical Trial

Beratungsresistente Ärzte

In einer schweizweiten Studie haben Hausärzte mit besonders hohem Antibiotikaverbrauch regelmässige Feedbacks zu ihrer Verschreibungspraxis bekommen. Die damit gemachten Erfahrungen sind ernüchternd.

Insgesamt bleibt Rosemann aber skeptisch: Die Effekte auf das ärztliche Verhalten seien mit jeder Art von Intervention relativ gering; das habe man auch bei der Frage gesehen, wie oft Hausärzte ihren Patienten dem Spezialisten überwiesen. Auch hier gebe es grosse Unterschiede. Interventionen im Februar

24.11.2017
Objective

- Can we reduce antibiotic use in primary care *nationwide* by providing personalized antibiotic prescription feedback to individual physicians?
  - Pragmatic RCT to test feasibility and effectiveness of routine feedback on antibiotic prescribing
  - Use of routinely collected health data from health insurers
  - Physicians with the highest antibiotic use in Switzerland
Methods

• Pragmatic randomized parallel group trial

• Data source: Routinely collected claims data
  - SASIS, covering 64% of Swiss population
  - Aggregated per month and physician

• Population: 2900 primary care physicians
  - top antibiotic prescribers
  - with more than 100 patients/year
Methods

Intervention:
- Every 3 months an updated personalized prescription feedback
- Provided as letter and online
- 2 years of intervention
- Once evidence-based guidelines
- No information about RCT nature
- Continuously collecting routine prescribing data

Control:
- No information
- Continuously collecting routine prescribing data
Selection of physicians and intervention

Benchmark Trial

Intervention: Personalized prescription feedback

RÜCKMELDUNG ZU IHRER ANTIBIOTIKA-VERSCHREIBUNG

Auf dieser Seite werden verschiedene Informationen zu Ihren Antibiotika-Verschreibungen während der vergangenen Monate präsentiert. Quelle der Daten ist der Tarifpool der SASS AG.

Aufgrund einer Latenz bei der Datenerhebung können keine Informationen zu den letzten sechs Monaten präsentiert werden.

Rate der Antibiotika-Verschreibungen als DDD (=defined daily dose)
(Details dazu auf der Studienwebsite)

Anzahl Patienten, welche für den jeweiligen Monat im Datensatz vorhanden sind

Anzahl Konsultationen, die für den jeweiligen Monat gezählt wurden
(Tarbed Position 00|0010: Konsultation, erste 5 Min.)

Altersverteilung der Patienten
Kinder 0 - 15 Jahre
Erwachsene 16 - 65 Jahre
Senioren 66+ Jahre

Verteilung der Geschlechter
Frauen     Männer

Details zur Berechnung der Verschreibungsrate, weiterführende Informationen und detaillierte Statistiken zu jedem Monat finden Sie auf der unten angegebenen Studienwebsite.

www.quality.evibox.ch

PERSÖNLICHE ID ***************
PASSWORT ***************
Results

We analyzed

- 10,660,124 consultations
- 1,175,780 packages of antibiotics
- 10,290,182 defined daily doses (DDD)

over 2 years in 2814 physicians
Results

Between group differences (ITT):  

1st year: 0.81% (95% CI -2.56 to 4.30)  
2nd year: -1.73% (-5.07 to 1.72)  

The future of clinical research: the Swedeheart registry

SWEDEHEART

Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

Tomas Jernberg
Chairman, SWEDEHEART
Karolinska University Hospital, Stockholm

Source: medicalonline.hu/download.php?id=11786
Why SWEDHEART?

- National registry of coronary artery disease care and valvular interventions

- Effects
  - Improves quality of care
  - Improves outcome
  - Powerful tool for research
  - Improves cost-effectiveness and saves money

Source: medicalonline.hu/download.php?id=11786
SWEDHEART

- Annual enrolment: 80,000 cases
  - 20,000 myocardial infarctions
  - 10,000 unstable angina
  - 25,000 with other causes to their symptoms
  - 40,000 coronary angiography or angioplasty
  - 7,000 Heart surgery
  - 6,000 secondary prevention

- >500 variables

- 2,737 users (mainly doctors and nurses)

- At a given time: ~60 simultaneous users

Source: medicalonline.hu/download.php?id=11786
Quality Register
RIKS-HIA Quality index (0-9) in treatment of MI 2008
in hospital or at discharge in target patients

Factors in index
(% adherence to guidelines)

STEMI
• Reperfusion
• Time to reperfusion

NSTEMI
• Coronary angio at high risk
• LMWH
• Clopidogrel or Prasugrel

All MI
• ASA
• Statin at LDL > 2.5mm/L
• Beta-blockade
• ACEI/ARB at LV dysf

Source: medicalonline.hu/download.php?id=11786
Register research

- Every hospital owns its own data – participation in National reports and scientific databases voluntary
- Research projects based on the National database must be approved by SWEDHEART-steering group
- All projects must be approved by an Ethical Committee
- Any database is de-identified before reaching the scientist
- Statistical analyses are often done in collaboration with epidemiologist/biostatistician from National Competence Center

Source: medicalonline.hu/download.php?id=11786
Future developments

- Randomisation module for prospective randomised registry based trial
- Integration with Patient Electronic Health Records
- Patients will be able to report directly into the system
- Integration with modules for blood sampling for biobanking for genetic and proteomic research
- International collaborations: MINAP (UK), Infarctus Regiszter (Hungary), ACTION (USA)
Reasons for success

♦ Initiated by cardiologists, driven by National and local enthusiasts
♦ Highly motivated users
♦ Immediate benefit at the local unit – on-line-reports.
♦ Open comparison of hospital performances
♦ We have demonstrated that we can improve quality of care
♦ High degree of transparency

Source: medicalonline.hu/download.php?id=11786
Thrombus aspiration during ST-segment elevation myocardial infarction: TASTE a registry based RCT


**BACKGROUND:** The clinical effect of routine intracoronary thrombus aspiration before primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) is uncertain. We aimed to evaluate whether thrombus aspiration reduces mortality.

**METHODS:** We conducted a multicenter, prospective, randomized, controlled, open-label clinical trial, with enrollment of patients from the national comprehensive Swedish Coronary Angiography and Angioplasty Registry (SCAAR) and end points evaluated through national registries. A total of 7244 patients with STEMI undergoing PCI were randomly assigned to manual thrombus aspiration followed by PCI or to PCI only. The primary end point was all-cause mortality at 30 days.

**RESULTS:** No patients were lost to follow-up. Death from any cause occurred in 2.8% of the patients in the thrombus-aspiration group (103 of 3621), as compared with 3.0% in the PCI-only group (110 of 3623) (hazard ratio, 0.94; 95% confidence interval [CI], 0.72 to 1.22; P=0.63). The rates of hospitalization for recurrent myocardial infarction at 30 days were 0.5% and 0.9% in the two groups, respectively (hazard ratio, 0.61; 95% CI, 0.34 to 1.07; P=0.09), and the rates of stent thrombosis were 0.2% and 0.5%, respectively (hazard ratio, 0.47; 95% CI, 0.20 to 1.02; P=0.06). There were no significant differences between the groups with respect to the rate of stroke or neurologic complications at the time of discharge (P=0.87). The results were consistent across all major prespecified subgroups, including subgroups defined according to thrombus burden and coronary flow before PCI.

**CONCLUSIONS:** Routine thrombus aspiration before PCI as compared with PCI alone did not reduce 30-day mortality among patients with STEMI. (Funded by the Swedish Research Council and others; ClinicalTrials.gov number, NCT01093404).
## Cost per patient recruited in RCD-RCTs: Some Examples

<table>
<thead>
<tr>
<th>Trial</th>
<th>Country Design</th>
<th>Topic</th>
<th>Outcome</th>
<th>Duration Size</th>
<th>Total Costs ($)</th>
<th>Costs/Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fröbert et al. NEJM 2013 (TASTE)</td>
<td>USA RCT</td>
<td>Thrombus aspiration plus PCI in MI</td>
<td>All-cause mortality (30-day)</td>
<td>2.75 yrs 7244 pts</td>
<td>300,000</td>
<td>50$</td>
</tr>
<tr>
<td>Kaczorowski et al. BMJ 2011 (CHAP)</td>
<td>Canada Clust.RCT</td>
<td>Cardiovascular risk assessment and education in elderly</td>
<td>Hospital admissions for MI, stroke, heart failure</td>
<td>1 yr 15,889 pts</td>
<td>250,000(?)</td>
<td>16$</td>
</tr>
<tr>
<td>Huang et al. NEJM 2013 (REDUCE MRSA)</td>
<td>USA Clust.RCT</td>
<td>MRSA-Decolonization/Screening/Isolation in ICU pts</td>
<td>MRSA infection rates</td>
<td>2.5 yrs 74,246 pts</td>
<td>&lt;3,000,000</td>
<td>40$</td>
</tr>
<tr>
<td>Hemkens et al. JAMA IM 2017</td>
<td>Switzerland RCT</td>
<td>Prescription feedback in high antibiotic prescribers</td>
<td>Antibiotic prescriptions</td>
<td>2 yrs 2900 physicians 10,000,000 consult.</td>
<td>300,000</td>
<td>&lt;0.1$ (physician)</td>
</tr>
</tbody>
</table>
Summary & Conclusions

• Real world evidence and routinely collected data will play a massive role in clinical research, quality of care research and for benchmarking
• Technology and know-how to nest RCTs into RCD is growing
• Standardization of routinely collected clinical data from registry / medical records and new algorithm based technology to extract relevant patient data from RCD (drug safety, detection of early signals) is rapidly evolving
• Technology to guarantee privacy of patients must be developed (e informed consent)