Cardiovascular Round Table: Digital Health Transformation

Extracting Relevant Endpoints from Routine Clinical Data
Disclosures

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EU Innovative Medicines Initiative – BigData@Heart Consortium.
Role of real world evidence

- **Observational research**
  - Clinical phenotypes
  - Outcome prediction
  - Epidemiology

- **Controlled trials**
  - Treatment outcomes
  - (Patient selection)
  - Real world comparisons

- **Health resource planning, health economics, etc.**
Need for new trial approaches

Expense of conventional RCTs...

Prolonged design phase
Over 50% fail to recruit
Most require amendment
80% delayed

Disconnect with clinical practice:

<table>
<thead>
<tr>
<th>Source</th>
<th>MERIT-HF RCT</th>
<th>PARADIGM-HF RCT</th>
<th>SWED-E-HF cohort</th>
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</thead>
<tbody>
<tr>
<td>Year</td>
<td>1997-8</td>
<td>2009-12</td>
<td>2000-12</td>
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<tr>
<td>Mean age</td>
<td>64 years</td>
<td>64 years</td>
<td>72 years</td>
</tr>
<tr>
<td>Women</td>
<td>22%</td>
<td>22%</td>
<td>31%</td>
</tr>
<tr>
<td>AF</td>
<td>17%</td>
<td>37%</td>
<td>50%</td>
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</tbody>
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Duplication of effort (especially follow-up visits and outcomes) with electronic health records (EHRs)
Practical and logistic benefits (registry data)

**TASTE** 7,244 patients with STEMI
**RCT** Thrombus aspiration or PCI only

Outcomes through registries

- 247 Patients with STEMI undergoing primary or rescue PCI enrolled in Denmark
- 11,709 Patients with STEMI undergoing primary or rescue PCI identified in Sweden and Iceland
- 7259 Were enrolled in TASTE trial
- 15 Were enrolled in error
- 7244 Underwent randomization in TASTE trial
- 3622 Were assigned to thrombus aspiration
- 3623 Were assigned to conventional PCI
- 3399 Underwent thrombus aspiration
- 222 Underwent conventional PCI
- 3445 Underwent conventional PCI
- 176 Underwent thrombus aspiration
- 1162 Underwent thrombus aspiration
- 3535 Underwent conventional PCI
Routine practice data (primary care)

- UK primary care
- Linked to national hospital and mortality data

CPRD

- Coded data on >3.4 billion consultations
- 35 million total patient lives on CPRD database
- 10 million currently registered patients
- Data representative of UK population
- Median follow up time of 10 years – some life long follow up
- In-house quality checks to ensure a high quality research-ready data

NHS Digital

ESC Digital Summit 2019

Courtesy: J Valentine, CPRD (MHRA UK)
UK primary care research

REDUCE 79 general practices
cluster 582,675 patient years
RCT Education & support tools for antibiotic use
Standard care outcomes
Cardiovascular ‘real-world’ data sources

Heart failure (2010-2018)

- Europe: 46.9%
- USA: 21.4%
- APMA: 19.6%
- LaCan: 8.1%
- Multi-regional: 4.0%

Publications

<table>
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<th>Registry</th>
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</tr>
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<tr>
<td>Gulf Acute Heart Failure Registry</td>
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<tr>
<td>Swedish Heart Failure Registry</td>
<td>27</td>
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<tr>
<td>Get With The Guidelines-Heart Failure Registry</td>
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</tr>
<tr>
<td>Nationwide Inpatient Sample database</td>
<td>34</td>
</tr>
<tr>
<td>Korean Acute Heart Failure Registry</td>
<td>37</td>
</tr>
</tbody>
</table>

Access

- Unknown
- Yes
- Unknown
- Unknown
- No

Linkage

- Unknown
- Yes
- Unknown
- Unknown
- Yes

Pre-publication: BigData@Heart IMI: Novartis (Studer), Bayer (Sartini), UoB (Kotecha), UCL (Dobson)
Opportunities with machine learning for ‘big data’

Neighbour regression
Naive Bayes
Decision trees
Ordinary least squares regression
Logistic regression
Support vector machines
Convolutional neural network
Recurrent neural network
Long short-term memory
Autoencoder
Random forests
Boosting ensemble
Evolutionary algorithms
Genetic algorithm
Differential evolution

Metaheuristic and swarm intelligence
Ant colony optimization
Particle swarm optimization
Centroid-based clustering
Density-based clustering
Association rule mining
Variational autoencoders
Mincut semi-supervised learning
Harmonic graph-based algorithms
Local and global consistency
Manifold regularization
Generative adversarial networks
Q-learning reinforcement
Temporal difference
Deep adversarial networks
SwedeHF registry: 44,886 HF patients

Unsupervised machine learning approach

4 clusters of factors associated with 1-yr mortality

Cluster 1: 23%
Cluster 2: 7%
Cluster 3: 31%
Cluster 4: 8%

By LVEF category:
Machine learning & prediction in EHR data

Sutter PAMF California: 3884 incident HF, 28903 controls

e-health records: neural network deep learning, including temporal relationships

12 to 18 month observation window for incident HF
Birmingham routine hospital healthcare data: 35,710 ECGs in 24,013 patients with a ‘normal’ ECG.

Raw 10s ECG data from 8 leads. Split into training and validation datasets. 1997-2018 with subsequent heart failure hospitalisation (ICD-10).

“not a black-box” methodology
Deep neural network architecture

ROC area (c-statistic) for incident HF:
0.78 in the validation cohort
0.83 ECG plus clinical factors

Pre-publication: Cardoso, Gkoutos, Kotecha (cardAIc group)
Limitations of routine data capture

1. Coding: Variable quality across and within nations, and by disease

**Diagnosis:**
- ICD-11 (coming)
- ICD-10 (68,000 codes)
- ICD-10 -CM (USA) -CA (Canada) -AM (Aust/NZ)
- ICD-9 -CM (clinical modification)
- ICD-9 (17,000 codes)
- DSM (mental health)
- READ (298,102 concepts)
- SNOMED-CT (311,000 concepts)

**Procedures:**
- CPT (10,000 codes)
- ICD-10-PCS
- HCPCS
- ICPM (now defunct) leading to OPS
- OPCS-4
- ICHI (coming)

+ Drugs.... +Devices... +Labs, Therapeutics, etc.
Limitations of routine data capture

1. Coding: Variable quality across and within nations, and by disease

Systematic review of UK coding accuracy (EHR data vs. case note review or registry data in 32 studies):

Accuracy of the primary diagnosis
pre-2004: 74% (IQR 59-92%)
post-2004: 96% (IQR 89-96%)

Overall coding accuracy after ‘Payment by Results’
86% (IQR 73-96)
Limitations of routine data capture

1. Coding: Variable quality across and within nations, and by disease

2. Financial: Implications on primary and secondary coding

UK system:

- Clinical notes: eg ward round entries, discharge summary, investigation reports
- Primary and secondary codes using ICD-10 and OPCS-4
- Single HRG code
- Resultant tariff and financial reimbursement

Audit / Clinician-involvement

HRG = Healthcare Resource Group

In 8888 discharges in London, clinician auditing led to £816,977 extra income (+5.0%) – Nouraei: J Pub Health 2016:38;352-362

Adapted from Mahbubani: Fut Healthc J. 2018:5;47-51
Limitations of routine data capture

1. **Coding**: Variable quality across and within nations, and by disease

2. **Financial**: Implications on primary and secondary coding

3. **Regulatory**: FDA/EMA/MHRA interpretation of evidence quality

Clinical endpoint adjudication (CEA):
Limitations of routine data capture

1. **Coding:** Variable quality across and within nations, and by disease

2. **Financial:** Implications on primary and secondary coding

3. **Regulatory:** FDA/EMA/MHRA interpretation of evidence quality

**CLARICOR trial:** n=4,372 patients with stable CAD
RCT clarithromycin versus placebo; 2.6 year follow-up.
(Copenhagen)

**RCT adjudication committee** vs. **ICD coding public registers**

- Overall agreement
  - 74% for hospital discharges
  - 60% for cause of death

- Primary outcome (all-cause mortality, MI or unstable angina)
  - Hazard ratio **1.15 (0.99-1.34)** vs. **1.13 (0.98-1.30)**

- Tertiary outcome (CV mortality, MI, USA, cerebro+periph vasc)
  - Hazard ratio **1.20 (1.02-1.39)** vs. **1.15 (1.01-1.32)**
Limitations of routine data capture

1. **Coding:** Variable quality across and within nations, and by disease

2. **Financial:** Implications on primary and secondary coding

3. **Regulatory:** FDA/EMA/MHRA interpretation of evidence quality

4. **Results:** Effect of interventions on ‘less-selected’ populations

**Intervention heterogeneity:**

Confidence intervals vs. sample size

Not always a bad thing!

Intracranial haemorrhage with apixaban:

- Apixaban vs. warfarin ARISTOTLE RCT  n=18,201
  HR 0.51 (0.35-0.75)
- Observational *real-world* studies  n=41,299
  HR 0.45 (0.31-0.63)

**FDA adverse event reporting**

137,026 HF patients

Warfarin inferior to NOACs for all efficacy outcomes
Flexible and robust pipeline for the development of pragmatic, efficient research for patient benefit

- Local healthcare priorities
- Educational & lifestyle interventions
- New diagnostic & management devices
- Novel compounds from industry
- Address (inter)national health priorities

At scale, minimised cost for follow-up, integrated tech, generalisable results
Data-driven EHR trials.... pipe dream?

Automated screening of electronic health record:
- a
- b
- c

Inclusion criteria:
- a

Exclusion criteria:
- x
- y
- z

Minimal additional criteria by investigator:
- a

Inclusion criteria:
- a

Exclusion criteria:
- y

Daily automated screening

Patient invited and attends trial baseline visit

Patient consent

Randomisation

Intervention

Control

Tech

Patient outcome events through e-Health records

No visits
Data-driven EHR trials.... reality ! (proposed; not yet funded)

Confidential content
Summary

• Controlled trials will remain the foundation of evidence-based clinical practice.

• Escalating cost and the need to provide evidence for older, more comorbid and less selected patients will mean redirecting some effort to gain community-based evidence of the same quality.

• Key benefits will be generalizable results (to the community of patients), utilisation and repurposing of data already collected as part of standard care (hence reducing cost), and the ability to test interventions or clinical pathways at a scale not previously possible.

• The limitations and obstructions are considerable, but can be overcome or incorporated into evidence interpretation.

Doug Altman, 1948-2018

We need less research, better research, and research done for the right reasons