Cardiovascular Round Table: Digital Health Transformation

Extracting Relevant Endpoints from Routine Clinical Data

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British Heart Foundation FIGHT FOR EVERY HEARTBEAT bhf.org.uk

efpia imi innovative medicines initiative

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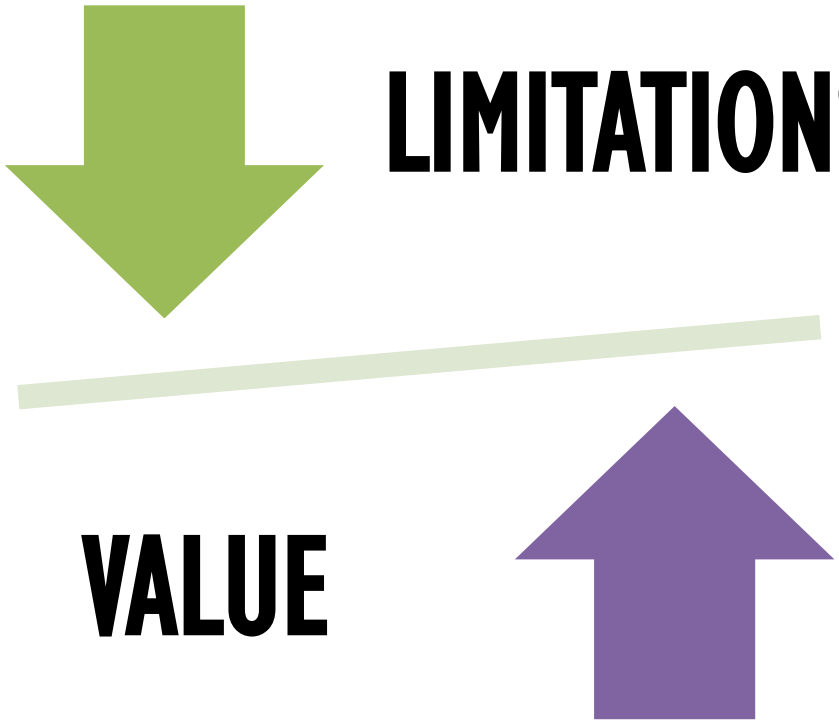
Role of real world evidence



- **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

Duplication of effort (especially follow-up visits and outcomes) with electronic health records (EHRs)

Disconnect with clinical practice:

Source	MERIT-HF RCT	PARADIGM-HF RCT	SWEDE-HF cohort
Year	1997-8	2009-12	2000-12
Mean age	64 years	64 years	72 years
Women	22%	22%	31%
AF	17%	37%	50%

Practical and logistic benefits (registry data)

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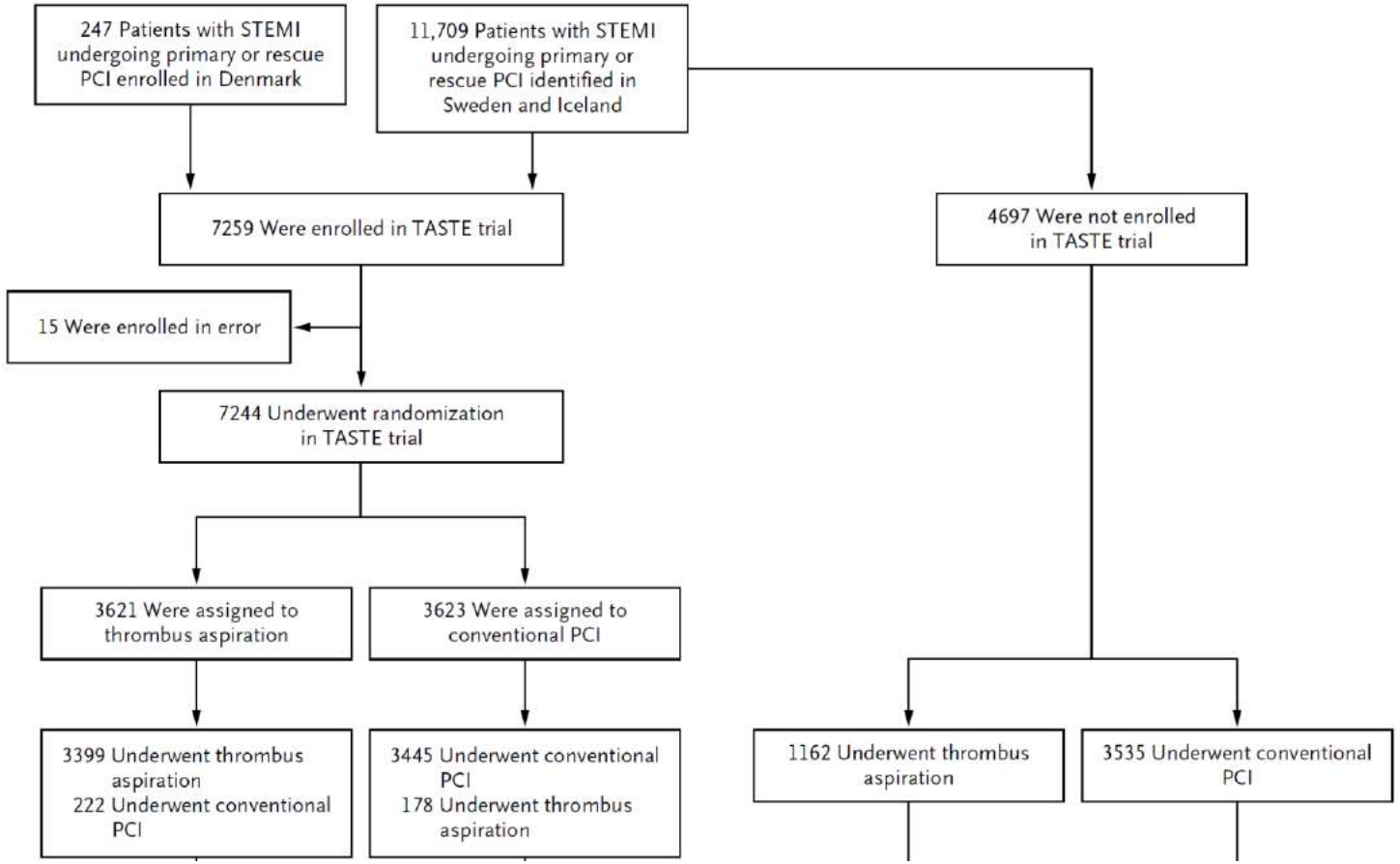
TASTE 7,244 patients with STEMI

RCT Thrombus aspiration or PCI only

Outcomes through registries



Routine practice data (primary care)

CPRD

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

NHS Digital

- 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

Courtesy: J Valentine, CPRD (MHRA UK)

UK primary care research

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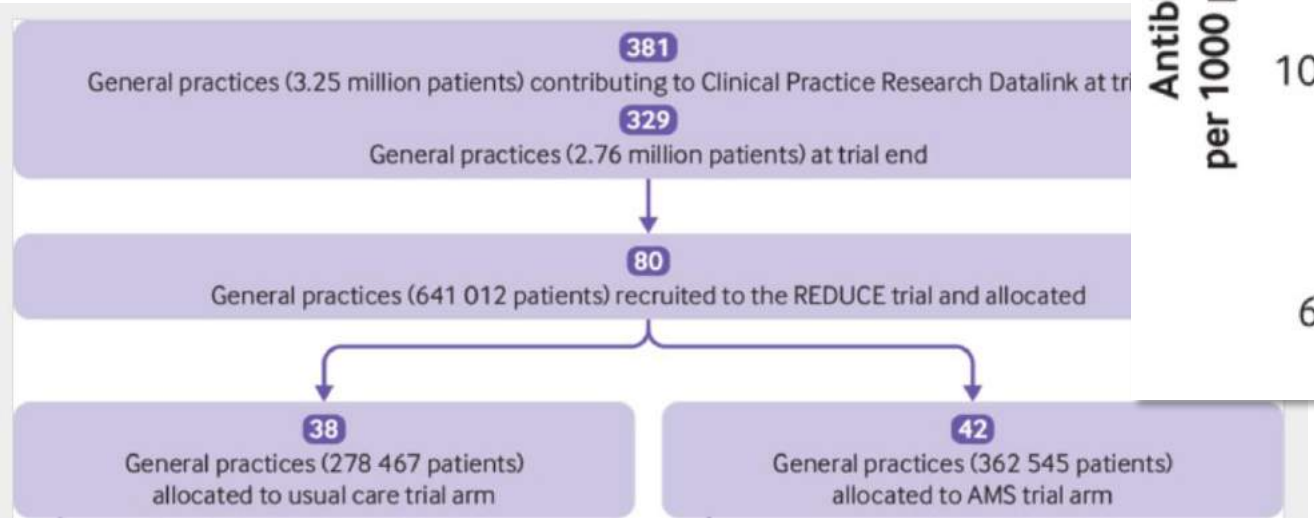
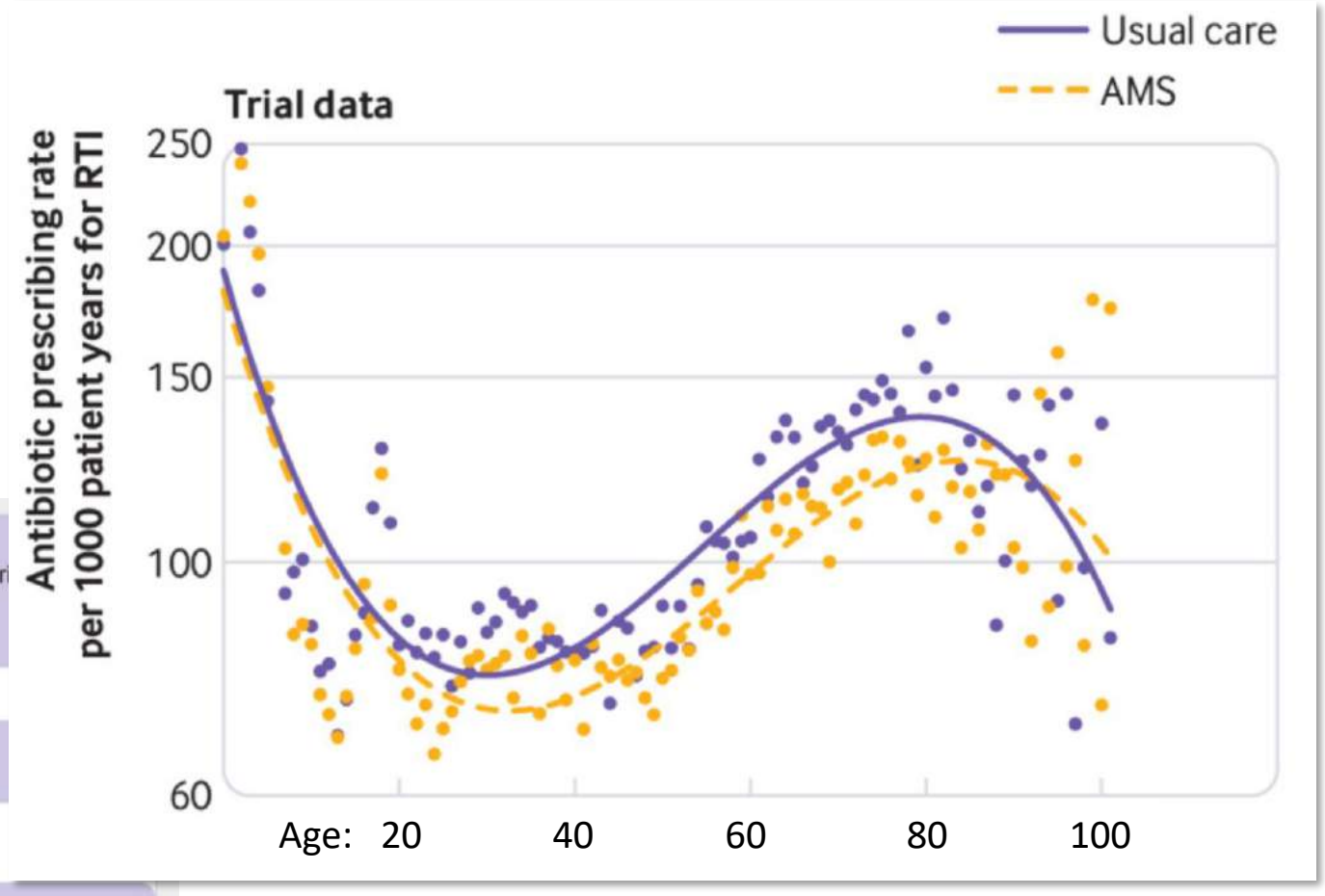
REDUCE	79 general practices
cluster	582,675 patient years
RCT	Education & support tools for antibiotic use
	Standard care outcomes





Gulliford: BMJ. 2019;364:1236

Cardiovascular 'real-world' data sources

BigData@Heart

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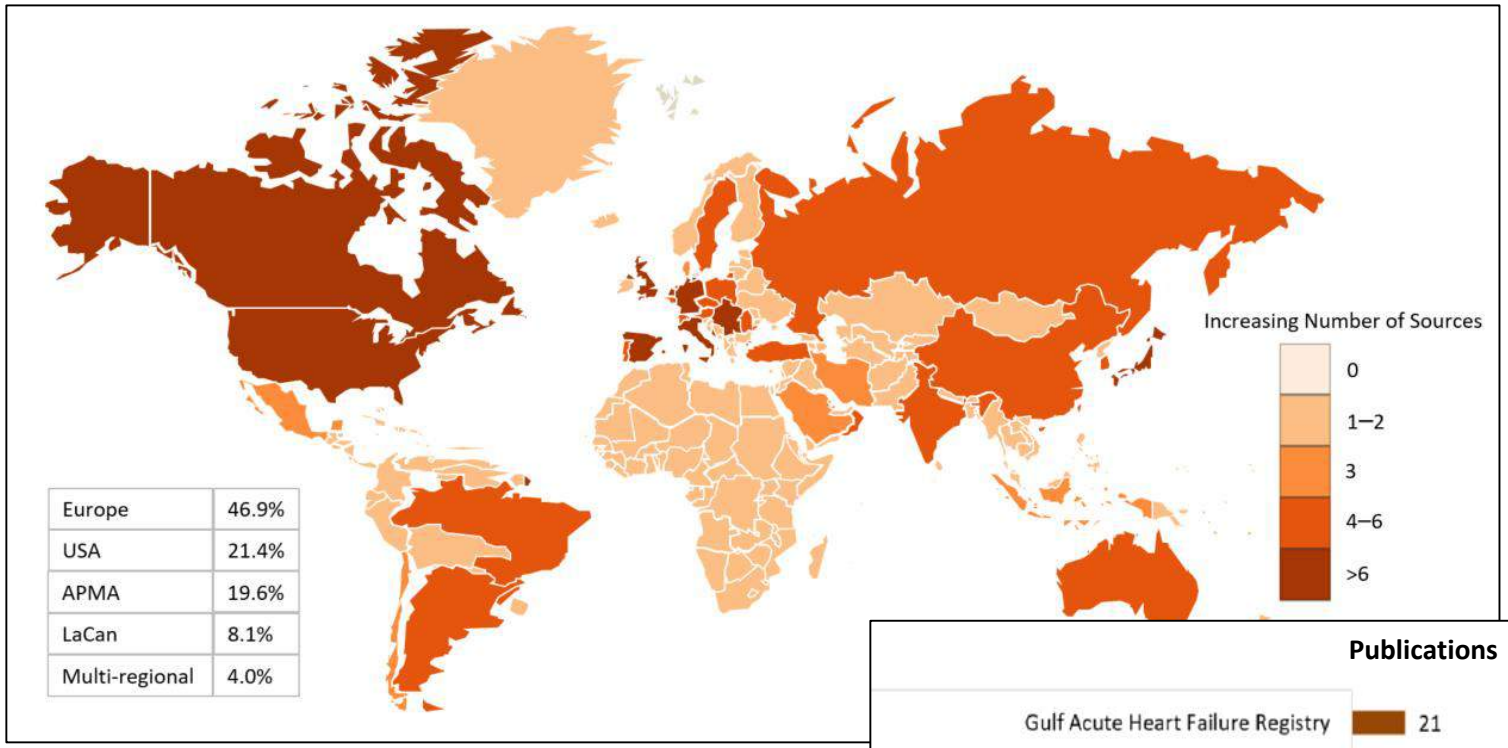
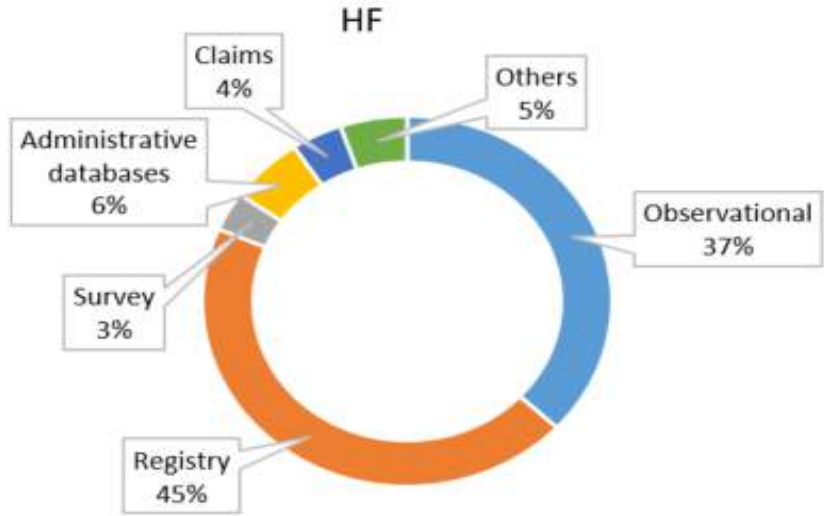
Heart failure (2010-2018)



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



	Publications	Access	Linkage
Gulf Acute Heart Failure Registry	21	Unknown	Unknown
Swedish Heart Failure Registry	27	Yes	Yes
Get With The Guidelines-Heart Failure Registry	34	Unknown	Unknown
Nationwide Inpatient Sample database	34	Unknown	Unknown
Korean Acute Heart Failure Registry	37	No	Yes

Pre-publication: BigData@Heart IMI: Novartis (Studer), Bayer (Sartini), UoB (Kotecha), UCL (Dobson)

Opportunities with machine learning for ‘big data’

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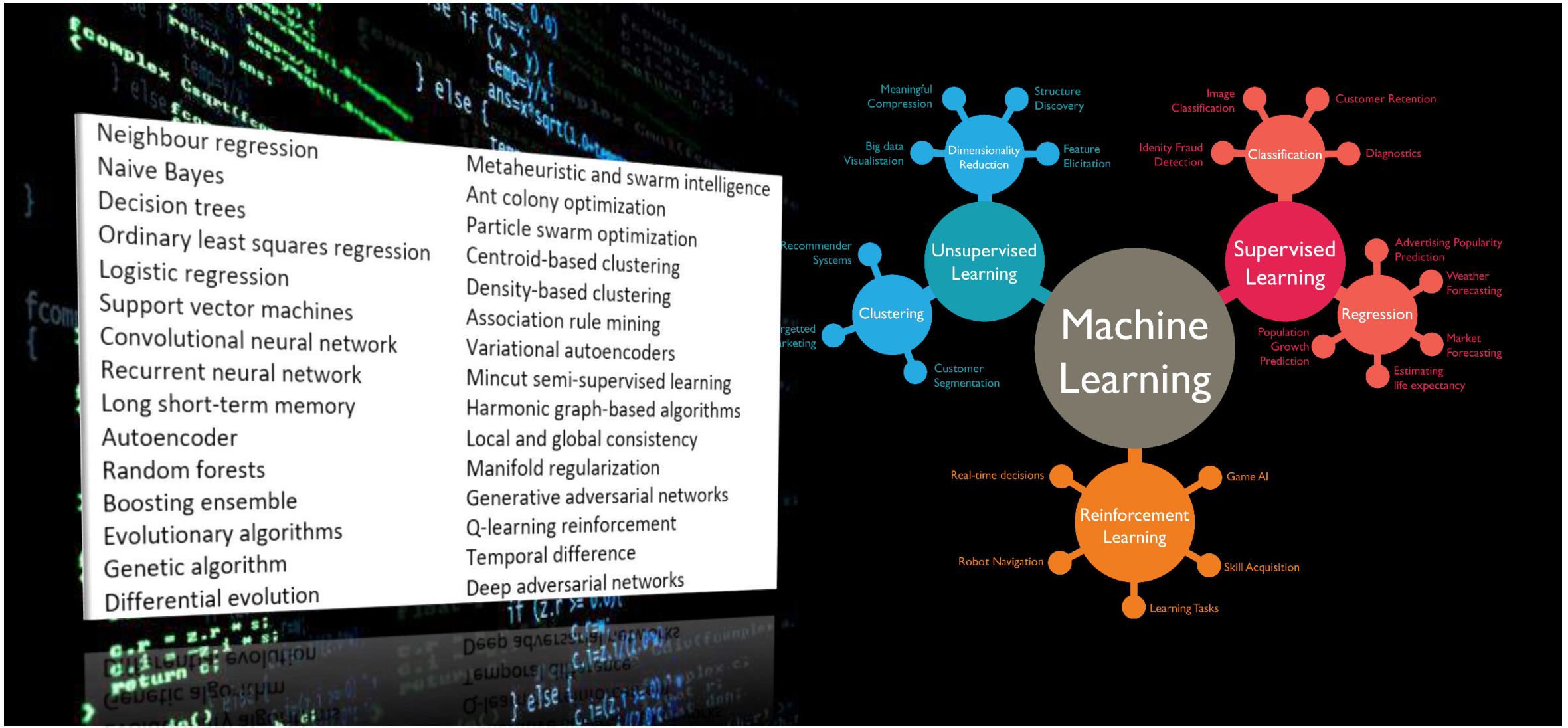


Machine learning & outcomes in EHR data

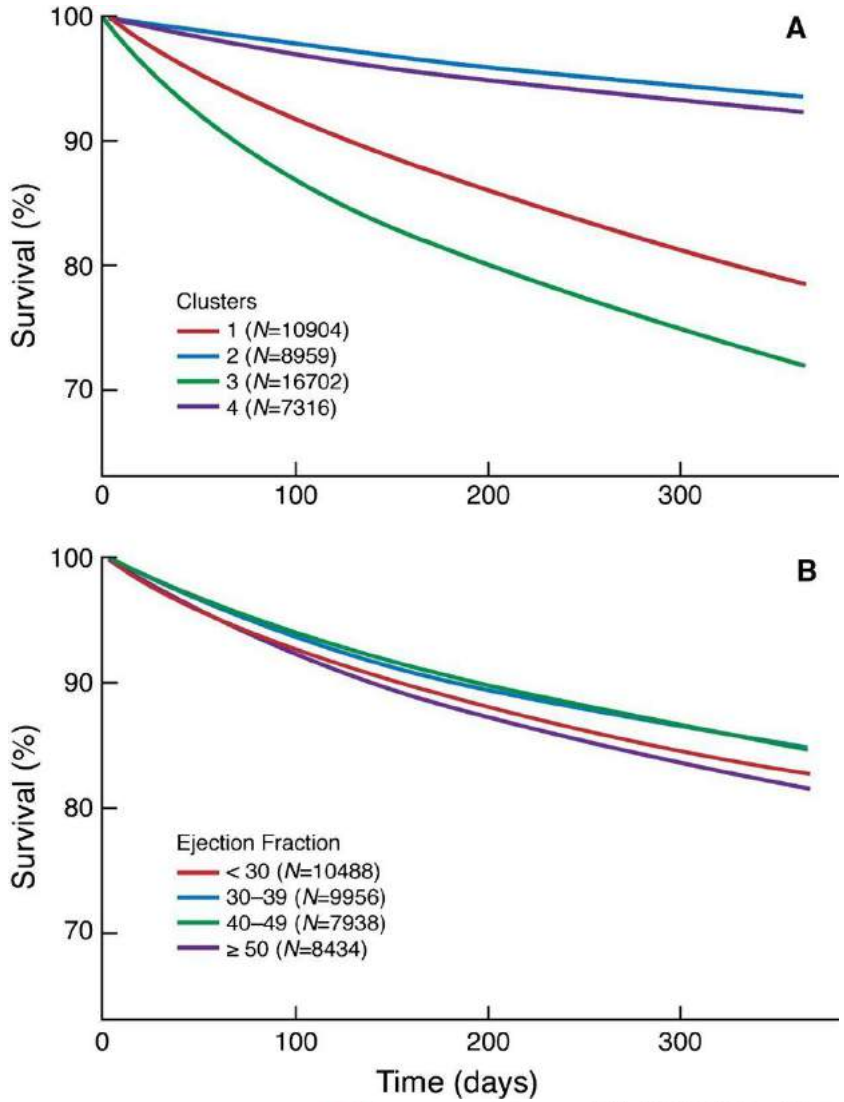
SwedeHF registry:
44,886 HF patients

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:



Ahmad: J Am Heart Assoc. 2018;7:e008081

Machine learning & prediction in EHR data

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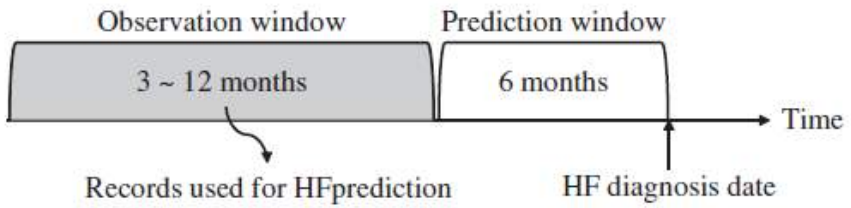
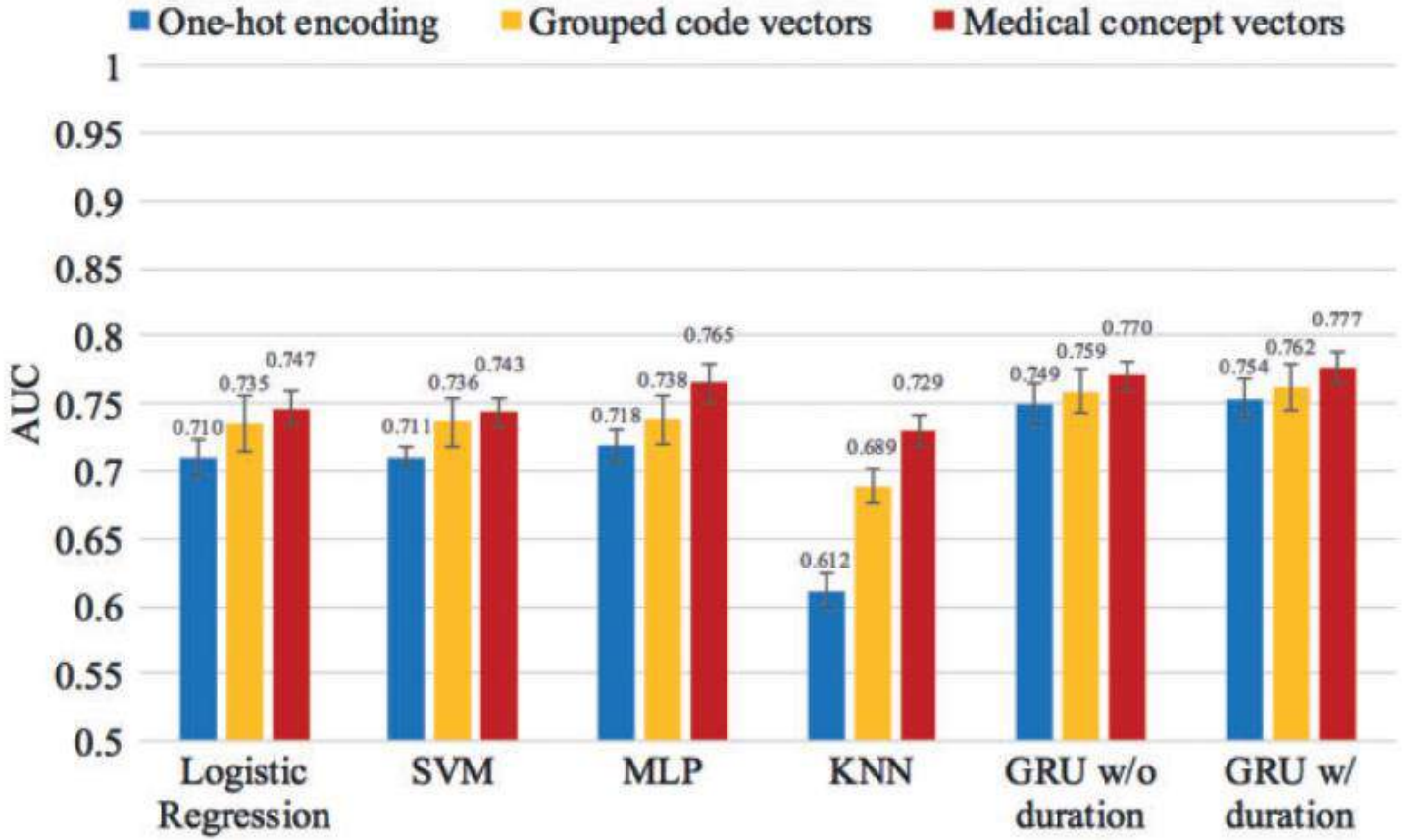
Sutter PAMF California: 3884 incident HF, 28903 controls

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

12 to 18 month observation window for incident HF





Choi: JAMIA 2017;24:361-70

Machine learning & prediction in EHR data

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Birmingham routine hospital healthcare data:
35,710 ECGs in 24,013 patients with a 'normal' ECG

→ "**not** a black-box" methodology

Deep neural network architecture

↓

Raw 10s ECG data from 8 leads.

Split into training and validation datasets.

1997-2018 with subsequent heart failure hospitalisation (ICD-10).

ROC area (c-statistic) for incident HF:

0.78 in the validation cohort
0.83 ECG plus clinical factors

Pre-publication: Cardoso, Gkoutos, Kotecha (**card*AI*c** 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

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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)

Burns: J Pub Health. 2012:34;138-148

Limitations of routine data capture

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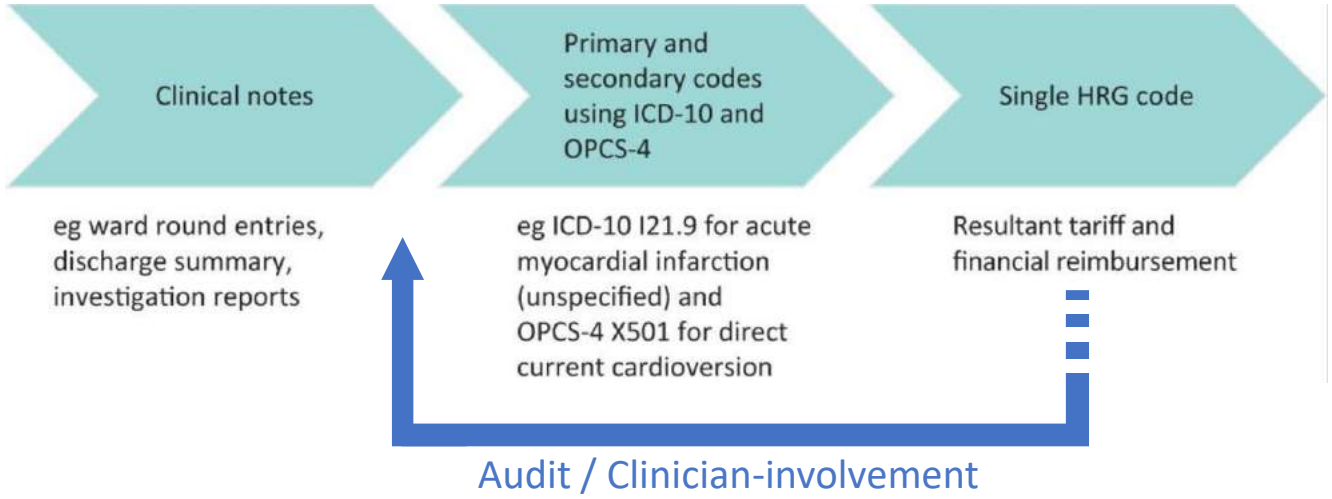
1. Coding: Variable quality across and within nations, and by disease

2. Financial: Implications on primary and secondary coding

UK system:



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

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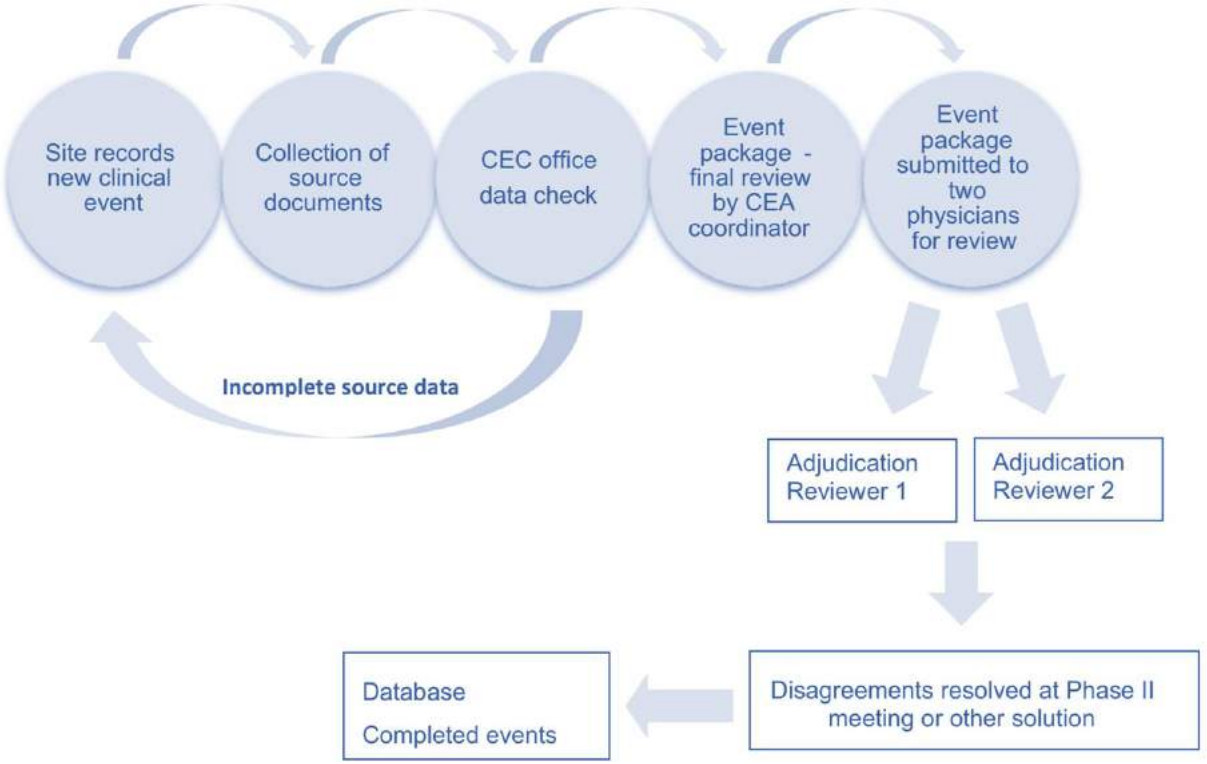
3. Regulatory: FDA/EMA/MHRA interpretation of evidence quality

Clinical endpoint adjudication (CEA):



Held: Upsala J Med Sci. 2019;124:42-45

Limitations of routine data capture

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

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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)**	**1.13 (0.98-1.30)**
Tertiary outcome (CV mortality, MI, USA, cerebro+periph vasc)		
Hazard ratio	**1.20 (1.02-1.39)**	**1.15 (1.01-1.32)**

Kjoller: Am Heart J 2014;168:197-204

Limitations of routine data capture

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

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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)

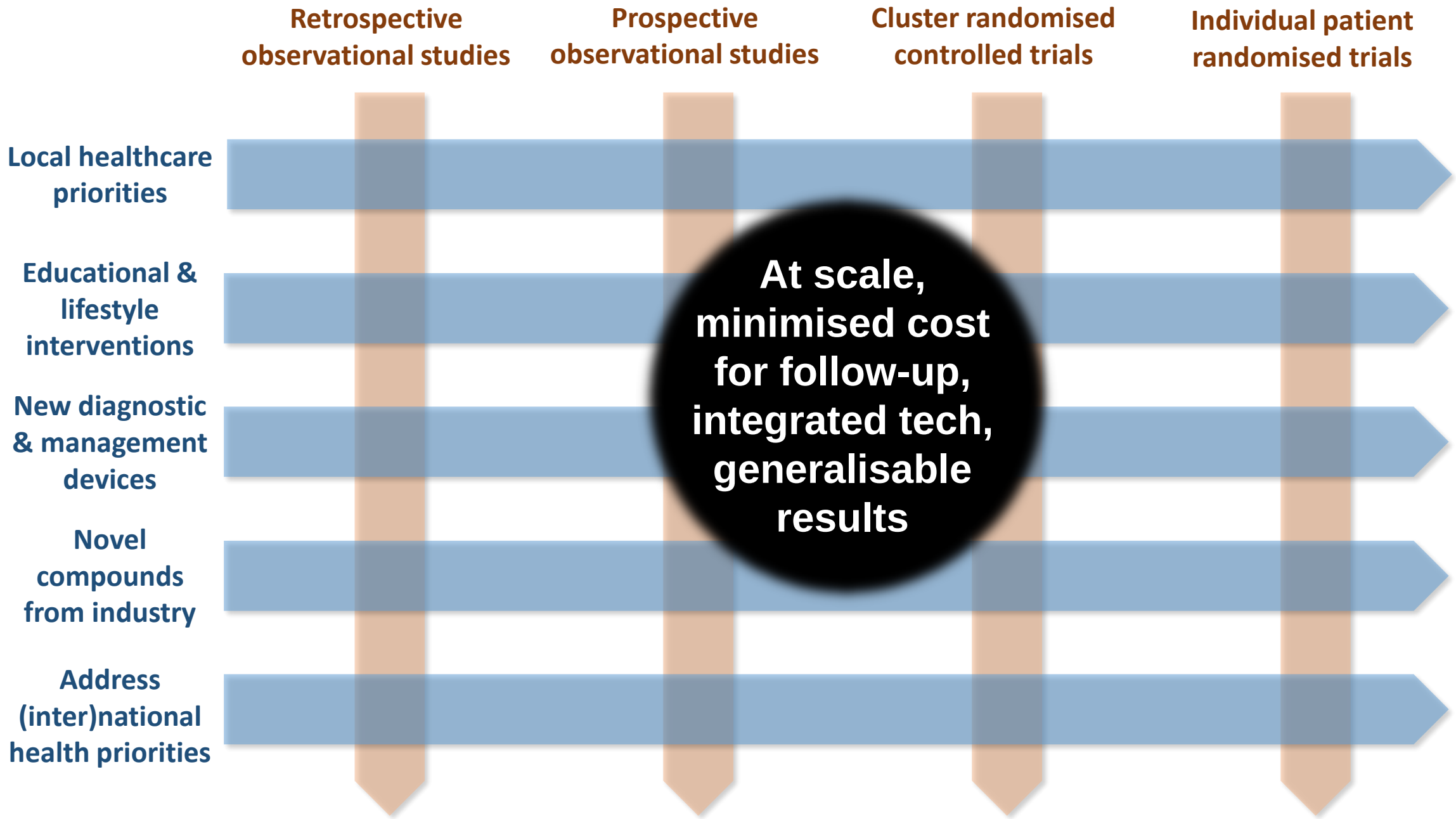
FDA adverse event reporting

137,026 HF patients

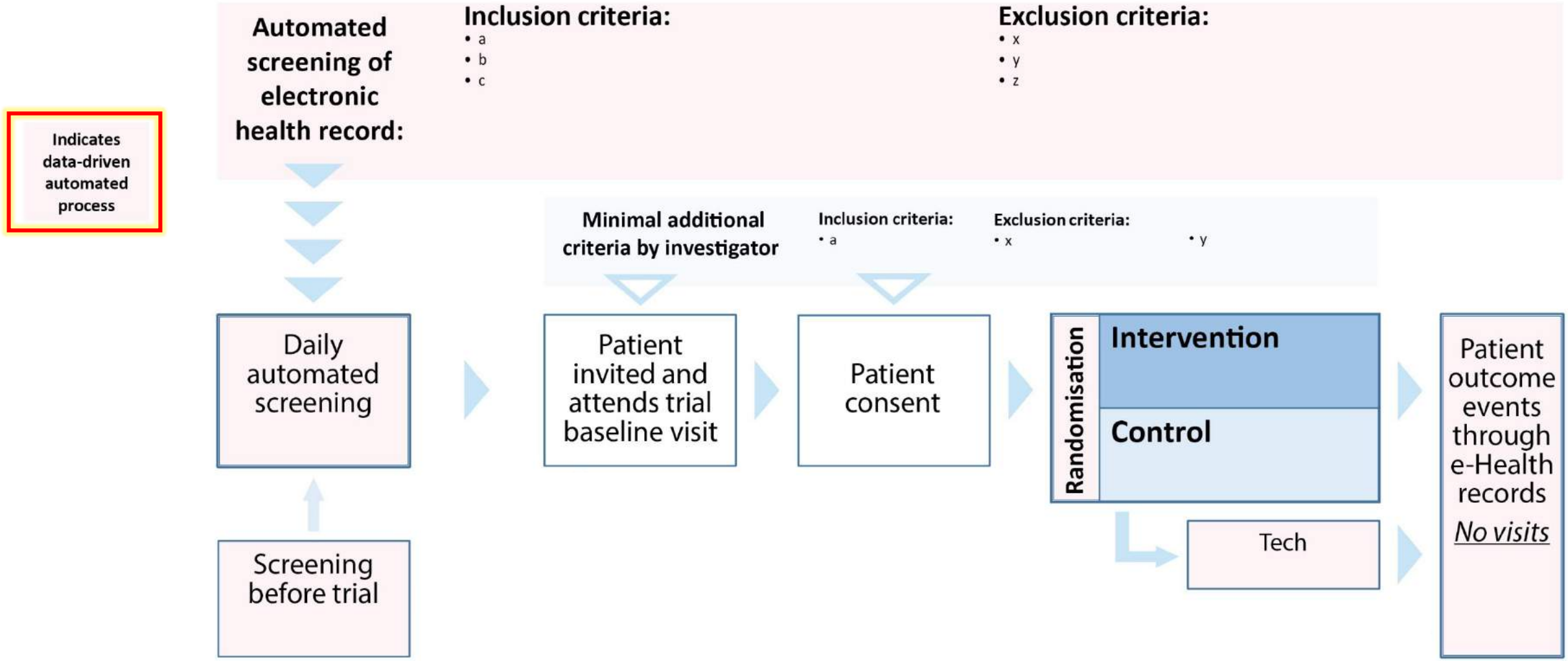
Warfarin inferior to NOACs for all efficacy outcomes

Granger: NEJM 2011; Ntaios: Stroke 2017 Leuder, Kotecha, Agewall, Atar: Am J Ther 2019

Flexible and robust pipeline for the development of pragmatic, efficient research for patient benefit



Data-driven EHR trials…. pipe dream ?



Data-driven EHR trials…. reality ! (proposed; not yet funded)

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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