Training course:  
All About Clinical Trials

SwedeHF and registry-based trials in heart failure

Lars Lund

Disclosures:

Industry: Grants, consulting, honoraria: AstraZeneca, Novartis, Bayer, Relypsa, Vifor-Fresenius, Sanofi, Abbott, Merck, Pharmacosmos, Orion Pharma

Non-industry: Grants: NIH, Swedish Heart-Lung Foundation, Swedish Research Council, SLL ALF, Erling Persson Foundation
Heart failure (HFrEF) history and current understanding

→ 1980
Pump failure → Heart replacement: Transplant, MCS/LVAD
Stimulants: inotropes, digoxin
Diuretics

1970s - 1990s
Load hypothesis → Vasodilators

1980s – 2014
Neurohormonal hypothesis:
- Explained why HF did not heal, but got worse spontaneously
  → ACEi/ARB, beta-blocker, MRA: neurohormonal BLOCKADE

2000s → Devices
Heart failure (HFrEF) history and current understanding

→ 1980  
  Pump failure  
  Heart replacement: Transplant, MCS/LVAD  
  Stimulants: inotropes, digoxin  
  Diuretics

1970s - 1990s  
  Load hypothesis  
  Vasodilators

1980s – 2014  
  Neurohormonal hypothesis:  
  - Explained why HF did not heal, but got worse spontaneously  
  → ACEi/ARB, beta-blocker, MRA: neurohormonal BLOCKADE

2000s  
  Devices

2014  
  Maladaptive and adaptive neurohormonal compensation:  
  ARNi  → neurohormonal MODULATION

2019  
  More complex: SGLT2-inhibitors  → load, energetics, remodelling

2020  
  sGC stimulators (and activators)  → cGMP  → multiple targets (e.g. vasorelax,  
  ↓hypertrophy, fibrosis, ↑compliance)
Heart Failure Challenges 2019 – how can a registry address these?

HFrEF
- Innovation
- Implementation

HFmrEF
- Innovation
- Expansion of HFrEF therapy?

HFrEF
- Innovation
- Understanding phenotype(s)
- Novel targets

ADHF / Post-WHF
- Innovation
- Understanding AHF / WHF course
- Type and timing of therapy
Heart Failure Challenges 2019 – how can a registry address these?

- **HFrEF**
  - Innovation
  - Implementation

- **HFmrEF**
  - Innovation
  - Expansion of HFrEF therapy

- **HFP EF**
  - Innovation
  - Understanding phenotype(s)
  - Novel targets

- **ADHF / Post-WHF**
  - Innovation
  - Understanding AHF / WHF course
  - Type and timing of therapy
Swedish Heart Failure Registry (SwedeHF):

- 2000 → ongoing, continuous enrollment
- Inclusion criterion: physician-judged heart failure, in-patient or out-patient
- Key variables: EF, NT-proBNP, loop diuretic use, eGFR, Hb, K
- Online eCRF, managed by UCR

- Automatic outcomes from national registries:
  - Death monthly
  - ICD-10 codes for death and hospitalization and causes, new onset morbidity, yearly
  - Medication adherence continuously
- Minimal loss to follow-up, known vital status

- 120,000 registrations from 80,000 unique individuals
- Coverage: 12% of incident HF, 53% of prevalent HF in Sweden
- From ~68 of Sweden's ~75 hospitals
Registration in the Swedish Heart Failure Registry is associated with lower mortality
The reason is better use of evidence based HF therapy
Risk-adjusted use of therapy over time

Use of evidence-based therapy and survival in heart failure in Sweden 2003–2012

<table>
<thead>
<tr>
<th>% target dose RASi</th>
<th>% patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤50%</td>
<td>42%</td>
</tr>
<tr>
<td>51-99%</td>
<td>12%</td>
</tr>
<tr>
<td>≥100%</td>
<td>46%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>During follow-up</th>
<th>% patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-treated</td>
<td></td>
</tr>
<tr>
<td>Started</td>
<td>31%</td>
</tr>
<tr>
<td>RASi</td>
<td></td>
</tr>
<tr>
<td>MRA</td>
<td>23%</td>
</tr>
<tr>
<td>Treated</td>
<td></td>
</tr>
<tr>
<td>Stopped</td>
<td>9%</td>
</tr>
<tr>
<td>RASi</td>
<td></td>
</tr>
<tr>
<td>MRA</td>
<td>30%</td>
</tr>
</tbody>
</table>
Risk-adjusted survival over time
Factors associated with underuse of mineralocorticoid receptor antagonists in

**Table 2** Summary of current evidence on mineralocorticoid receptor antagonist underuse in heart failure with reduced ejection fraction

<table>
<thead>
<tr>
<th>Study</th>
<th>MRA use</th>
</tr>
</thead>
<tbody>
<tr>
<td>GWTG-HF⁵</td>
<td>32% of the eligible population.</td>
</tr>
<tr>
<td>IMPROVE HF¹³</td>
<td>36% of the eligible population.</td>
</tr>
<tr>
<td>EuroHeart Failure Survey II¹⁴</td>
<td>47.5% of patients discharged after a hospital admission for HF.</td>
</tr>
<tr>
<td>ESC-HF Pilot Survey¹⁵</td>
<td>~50% in inpatients at discharge and 44% in outpatients.</td>
</tr>
<tr>
<td>BIOSTAT-CHF⁷</td>
<td>56% of eligible patients before and 63% after HF treatment optimization.</td>
</tr>
<tr>
<td>ESC-HF-LT¹⁶</td>
<td>53.9% of patients hospitalized for acute HF received MRA at discharge and 56.5% at 1 year from hospitalization.</td>
</tr>
<tr>
<td>SwedeHF (current study)</td>
<td>40% of the eligible population.</td>
</tr>
</tbody>
</table>
Causes of non-use are:

- eGFR ≤ 60
- Higher age
- Non-cardiology care
- Poor ACEi/ARB use

(K / BP: neutral, mix cause/effect)

Causes of d/c are:

HyperK, WRF, hypotension (Rosano exp consensus 2018)
Reasons for CRT non-use

Association between demographic, organizational, clinical, and socio-economic characteristics and underutilization of cardiac resynchronization therapy: results from the Swedish Heart Failure Registry

Lars H. Lund¹,², Frieder Braunschweig¹,³, Lina Benson³, Marcus Ståhlberg¹,², Ulf Dahlström⁴, and Cecilia Linde¹,³

B

<table>
<thead>
<tr>
<th>Risk Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism</td>
<td>0.066</td>
</tr>
<tr>
<td>Pe education secondary school vs. university</td>
<td>0.039</td>
</tr>
<tr>
<td>Pe education primary school vs. university</td>
<td>0.131</td>
</tr>
<tr>
<td>Diabetic</td>
<td>0.112</td>
</tr>
<tr>
<td>Sudden death</td>
<td>0.079</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>0.099</td>
</tr>
<tr>
<td>Malignant cancer last 3 years</td>
<td>0.158</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.003</td>
</tr>
<tr>
<td>Lung disease</td>
<td>0.142</td>
</tr>
<tr>
<td>Musculoskeletal disease last 3 years</td>
<td>0.171</td>
</tr>
<tr>
<td>NYHA class II vs. III</td>
<td>0.458</td>
</tr>
<tr>
<td>NYHA class IV vs. III</td>
<td>0.346</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.269</td>
</tr>
<tr>
<td>Income below median</td>
<td>0.225</td>
</tr>
<tr>
<td>Stable out-patient vs. acute in-patient</td>
<td>0.384</td>
</tr>
<tr>
<td>LVEF (%) 30–39% vs. &lt;30%</td>
<td>0.392</td>
</tr>
<tr>
<td>NT-proBNP &gt;500 ng/L</td>
<td>0.544</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>0.622</td>
</tr>
<tr>
<td>Diuretic</td>
<td>0.570</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.778</td>
</tr>
<tr>
<td>No children</td>
<td>0.922</td>
</tr>
</tbody>
</table>

Lower risk of CRT non-use Higher risk of CRT non-use
2016: simple but poor implementation → 2020: complex and ?implementation

HF is the central cardiology space

RASi / BB

All these "difficult", rationed, targeted, etc:
- MRA / K-binder
- ivabradine
- ARNi
- SGLT2i
- sGC stimulator/activator
- Iv iron
- DOAC
- CRT
- ICD
- Levosimendan
- AF ablation
- Mitraclip
- CABG
- CardioMEMS
- Tx
- MCS
- Palliation
Heart Failure Challenges 2019 – how can a registry address these?

**HFmrEF**
- Innovation
- Expansion of HFrEF therapy

**HFpEF**
- Innovation
- Understanding phenotype(s)
- Novel targets

*REGISTRY*
HFpEF: 5 trials were neutral but 3 were suggestive of benefit.
**New understanding:** Reduced + mildly reduced is one phenotype and *preserved/normal is another*

<table>
<thead>
<tr>
<th></th>
<th>Reduced</th>
<th>Mid-range/mildly reduced</th>
<th>Preserved/normal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age</strong></td>
<td>65-70</td>
<td>65-75</td>
<td>70-80</td>
</tr>
<tr>
<td><strong>% women</strong></td>
<td>&lt; 1/3</td>
<td>&lt; 1/3</td>
<td>&gt; 1/2</td>
</tr>
<tr>
<td><strong>Chronic coronary syndrome</strong></td>
<td>50-70%</td>
<td>50-70%</td>
<td>20-50%</td>
</tr>
<tr>
<td><strong>AF</strong></td>
<td>25-40%</td>
<td>25-50%</td>
<td>30-60%</td>
</tr>
<tr>
<td><strong>sBP</strong></td>
<td>120-130</td>
<td>125-130</td>
<td>130-140</td>
</tr>
<tr>
<td><strong>CKD</strong></td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>NTproBNP</strong></td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>CV risk</strong></td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Non-CV risk</strong></td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td><strong>ARB, MRA, BB (sinus), ARNi</strong></td>
<td>+++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td><strong>Relative effect</strong></td>
<td>+++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td><strong>Absolute effect</strong></td>
<td>+++</td>
<td>++</td>
<td>-</td>
</tr>
</tbody>
</table>

*SwedeHF, ESC-LT, CHARM*
1. New use of existing HFrEF drugs:
   • Greatest potential for HFmrEF
   • NTproBNP and structural heart disease for diagnosis
   • NTproBNP, loop diuretic use, h/o HF hospitalization for enrichment

Registry Randomized Clinical Trials – RRCTs: MRAs, RAS-antagonists, beta-blockers
Conventional RCTs: ARNi, SGLT2-inhibitors, sGC stimulators/activators

2. Drugs under development and narrower phenotypes:
   E.g. targeting microvascular inflammation (defined e.g. by coronary flow reserve)
   or early changes in left atrium?

SATELLITE: MPO-inhibitor vs. placebo in HFPpEF
So how to conduct a pragmatic RRCT in heart failure?
So how test new *use* of existing therapy?

**Registry**

- Efficient enrolment integrated in real-world health care
- Real-world generalizable descriptive and outcomes data
- Epidemiological characterization
- Utilization of evidence based therapy
- Quality reporting, benchmarking
- Quality improvement
- Equality of care
- Risk markers
- Comparative outcomes → Hypothesis generating
  - Efficient
  - Inexpensive

**But:**

- Lack of randomization → NOT comparative effectiveness
So how test new use of existing therapy?

**RCT**
- Randomized evidence
- Complex regulatory requirements
- Collection of non-essential data
- For-profit CROs
- Multiple ethics approvals
- Complex consent forms
- Many unknowns for power calculation
- In-feasible: (pre-)screening is manual, inefficient and unpredictable
- Enrolment slow
- Trial population unpredictable
- Outcomes assessment manual, inefficient
- Selective $\rightarrow$ not generalizable to real world
- Expensive to conduct: in HF: 5,000 patients, >$200M, ~$50,000 per patient
- Industry must recoup drug development and trial costs
  - $\rightarrow$ Delivers novel patented expensive therapy: e.g. sacubitril/valsartan: $5-15$ per day

**Registry**
- Efficient enrolment integrated in real-world health care
- Real-world generalizable descriptive and outcomes data
- Epidemiological characterization
- Utilization of evidence based therapy
- Quality reporting, benchmarking
- Quality improvement
- Equality of care
- Risk markers
- Comparative outcomes $\rightarrow$ Hypothesis generating
- Efficient
- Inexpensive
  - But: Lack of randomization $\rightarrow$ NOT comparative effectiveness
So how test new **use** of existing therapy?

**RCT**
- Randomized evidence
- Complex regulatory requirements
- Collection of non-essential data
- For-profit CROs
- Multiple ethics approvals
- Complex consent forms
- Many unknowns for power calculation
- In-feasible: (pre)-screening is manual, inefficient and unpredictable
- Enrolment slow
- Trial population unpredictable
- Outcomes assessment manual, inefficient
- Selective → not generalizable to real world
- Expensive to conduct: in HF: 5,000 patients, >$200M, ~$50,000 per patient
- Industry must recoup drug development and trial costs
  - Delivers novel patented expensive therapy: e.g. sacubitril/valsartan: $5-15 per day

**RRCT**
- Simplified regulatory procedures
- Focus on essential baseline and outcome data
- Non-profit AROs
- Single ethics approval
- Simplified consent forms
- For power calculation: know eligible sample and event rates
- Feasible: Have lists of existing and know n new eligible patients
- (Pre)-screening is automated, efficient and predictable
- Outcomes assessment automatic
- Non-selective: both efficacy and effectiveness
- Inexpensive to conduct: ~$5M = ~$1,000 per patient
- Non-selective → real world evidence
- Promotes adoption of evidence into practice
- Delivers new use of existing drug: generic HF drug: e.g spironolactone 10 cents per day

**Registry**
- Efficient enrolment integrated in real-world health care
- Real-world generalizable descriptive and outcomes data
- Epidemiological characterization
- Utilization of evidence based therapy
- Quality reporting, benchmarking
- Quality improvement
- Equality of care
- Risk markers
- Comparative outcomes → Hypothesis generating
- Efficient
- Inexpensive
  - Lack of randomization → NOT comparative effectiveness

---

Registry-Based Pragmatic Trials in Heart Failure: Current Experience and Future Directions
Lars H. Lund1,2 • Jonas Oldgren3 • Stefan James3
**Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction**

- **HF discharge from hospital**
- **HF Outpatient**

**Registry (data) platform**

- The Swedish Heart Failure Registry (SwedeHF)
- **TRIAL INNOVATION NETWORK**

**Academic partners**

- Uppsala Clinical Research Center
- UPPSALA UNIVERSITY
- Karolinska Institutet
- Duke Clinical Research Institute

**Funding agencies**

- **Hjärt-Lungfonden**
- **THE ERLING-PERSSON FAMILY FOUNDATION**
- **National Heart, Lung, and Blood Institute**

**n=3200 patients** (2550 Swe; 650 US)

- HFpEF (EF ≥40%)
- NTproBNP ≥ 300 SR; ≥ 750 AF
- eGFR ≥ 30; K ≤ 5.0
- Regular loop diuretics*

**Spironolactone (eplerenone)**
- Dosed according to investigator + Usual care

**Usual care alone**

- K + eGFR at local lab → telephone contact
- 4 times over 1st year
- Mean FU 3.5 years

**Primary EP:** CV death and total HF hospitalizations (adjudicated)
- Powered for key secondary: CV death (632 events)

*protocol amendment 2019
Design: Swe registries
USA: DCRI Trial Innovations Network

Board of Health and Welfare
- Outcomes:
  - Death
  - Hospitalization / causes
  - Safety
  - Medication adherence and use

RRCT platform
- ID number
- Baseline data
- Outcomes
  - Electronic data capture
- Data management
  - Data analysis

SwedeHF
- Platform screens and determines eligibility
- Platform randomizes

Patients
- Enrolled in routine care
- Existing or new Patient data
- Investigator collects Informed consent
- Implement assigned intervention

Clinicians

Guideline

Publication

DMC

Lund, Curr Heart Fail Rep 2017
Registries improve outcomes by analyzing and improving implementation.

Registries improve understanding of clinical phenotypes.

Registries can conduct RRCTs.