Training course:
All About Clinical Trials

SwedeHF and registry-based trials in heart failure

Lars Lund

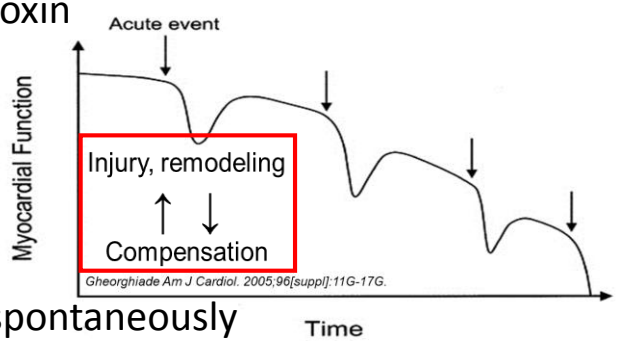
ESC Working Group Cardiovascular Pharmacotherapy

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

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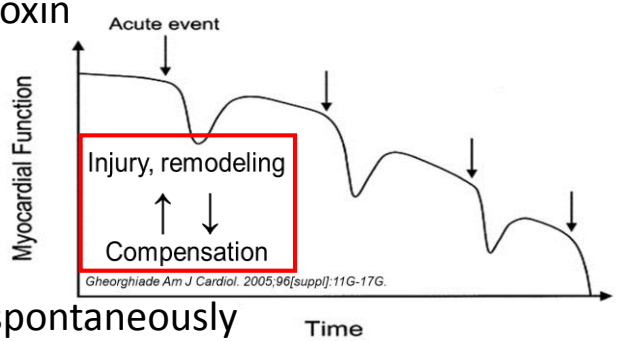

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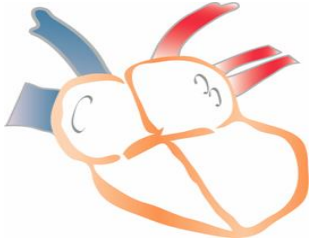
2000s → Devices

2014 → Maladaptive *and adaptive* neurohormonal compensation:
ARNi → neurohormonal MODULATION

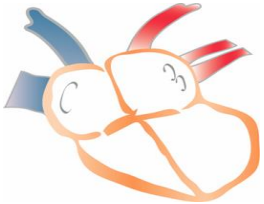
2019 → More complex: SGLT2-inhibitors → load, energetics, remodelling
2020 → sGC stimulators (and activators) → cGMP → multiple targets (e.g. vasorelax, ↓hypertrophy, fibrosis, ↑compliance)

Heart Failure Challenges 2019 – how can a registry address these ?



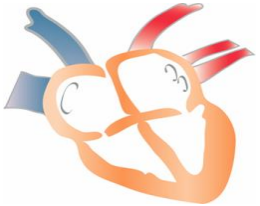
HFrEF

- Innovation
- Implementation



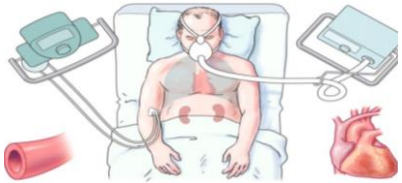
HFmrEF

- Innovation
- Expansion of HFrEF therapy ?



HFpEF

- Innovation
- Understanding phenotype(s)
- Novel targets



ADHF / Post-WHF

- Innovation
- Understanding AHF / WHF course
- Type and timing of therapy

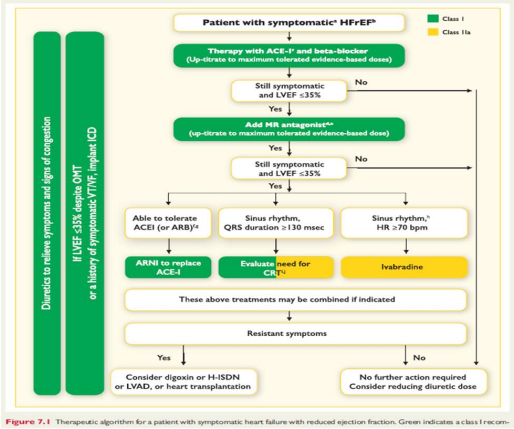


Figure 7.1 Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction. Green indicates a class I recom-

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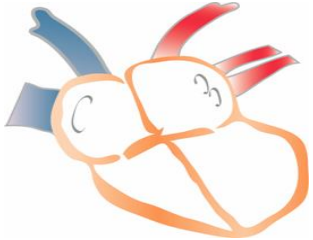
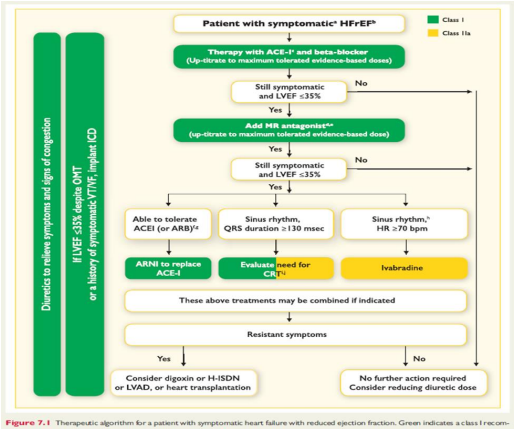


HFrEF

- Innovation
- Implementation

REGISTRY



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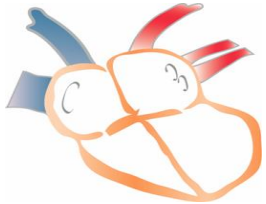

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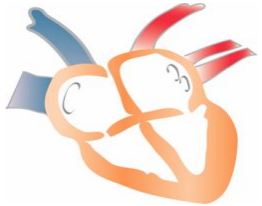

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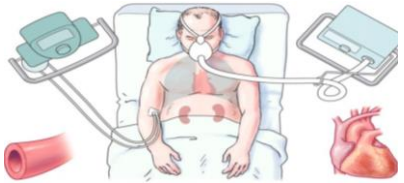

ADHF / Post-WHF

- Innovation
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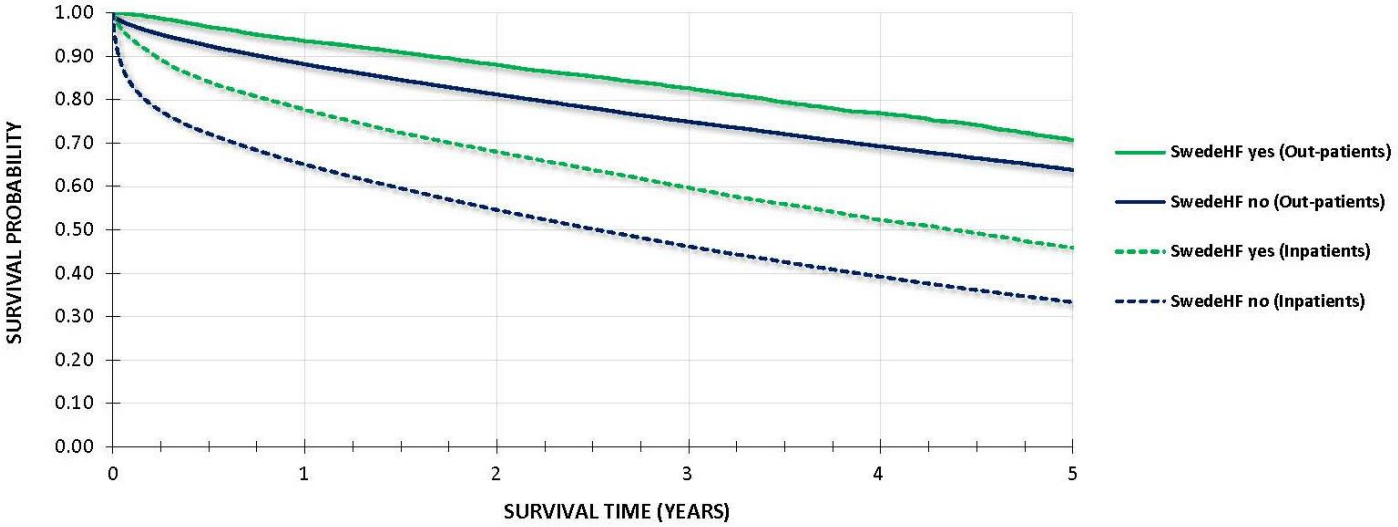
Swedish Heart Failure Registry (SwedeHF) :

- 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



Lund EJHF 2017

The reason is better use of evidence based HF therapy

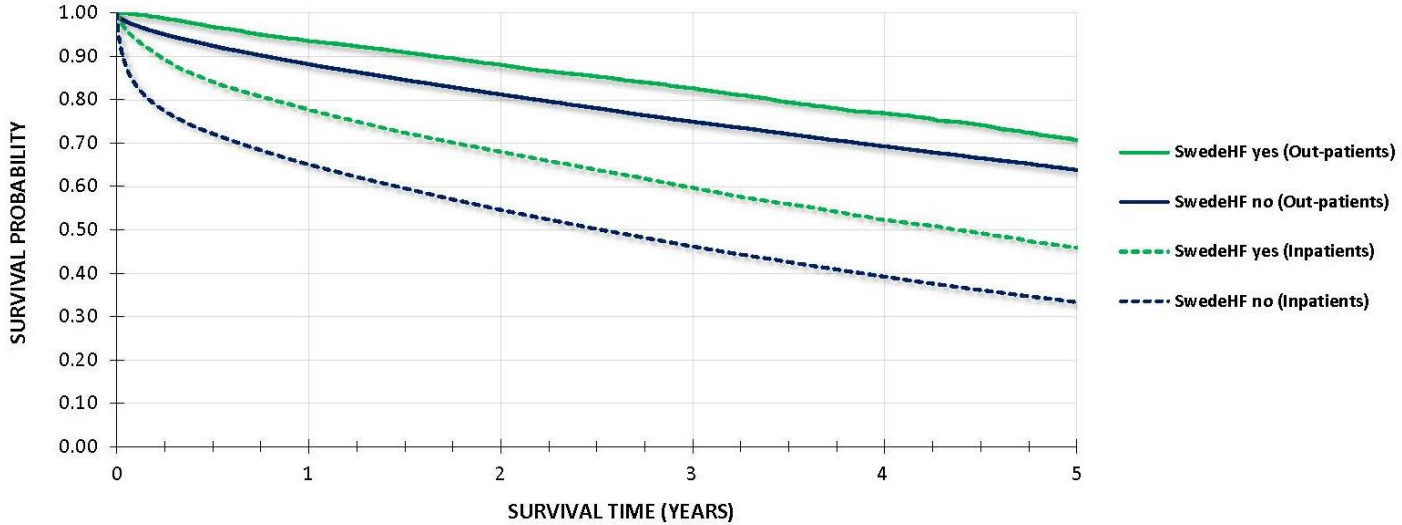


Table 1 **Baseline characteristics in the intervention (enrolled in SwedeHF) vs. control group (not enrolled)**

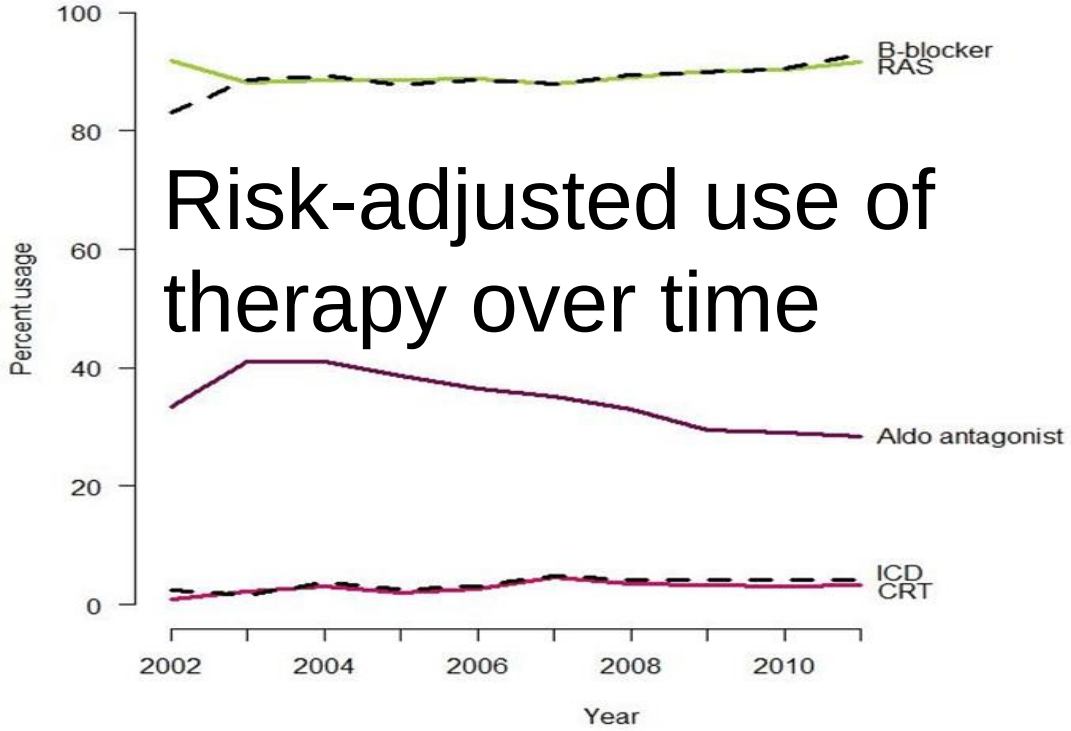
	Enrolled ($n = 21\,888$)	Not enrolled ($n = 209\,549$)	*P*-value
Medications			
HF medications, proven life-prolonging			
RAS antagonist (ACEI and or ARB)	17 878 (82%)	116 487 (56%)	<0.001
Beta blocker	18 481 (84%)	126 095 (60%)	<0.001
MRA	7182 (33%)	38 271 (18%)	<0.001

Lund EJHF 2017

European Journal of Heart Failure (2016)
doi:10.1002/ejhf.496

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

Tonje Thorvaldsen[1,2]*, Lina Benson[3], Ulf Dahlström[4], Magnus Edner[1], and Lars H. Lund[1,2]



Risk-adjusted use of therapy over time

% target dose RASi	% patients
≤50%	42%
51-99%	12%
≥100%	46%

During follow-up	% patients
Non-treated **Started**	
RASi	31%
MRA	23%
Treated **Stopped**	
RASi	9%
MRA	30%

European Journal of Heart Failure (2016)
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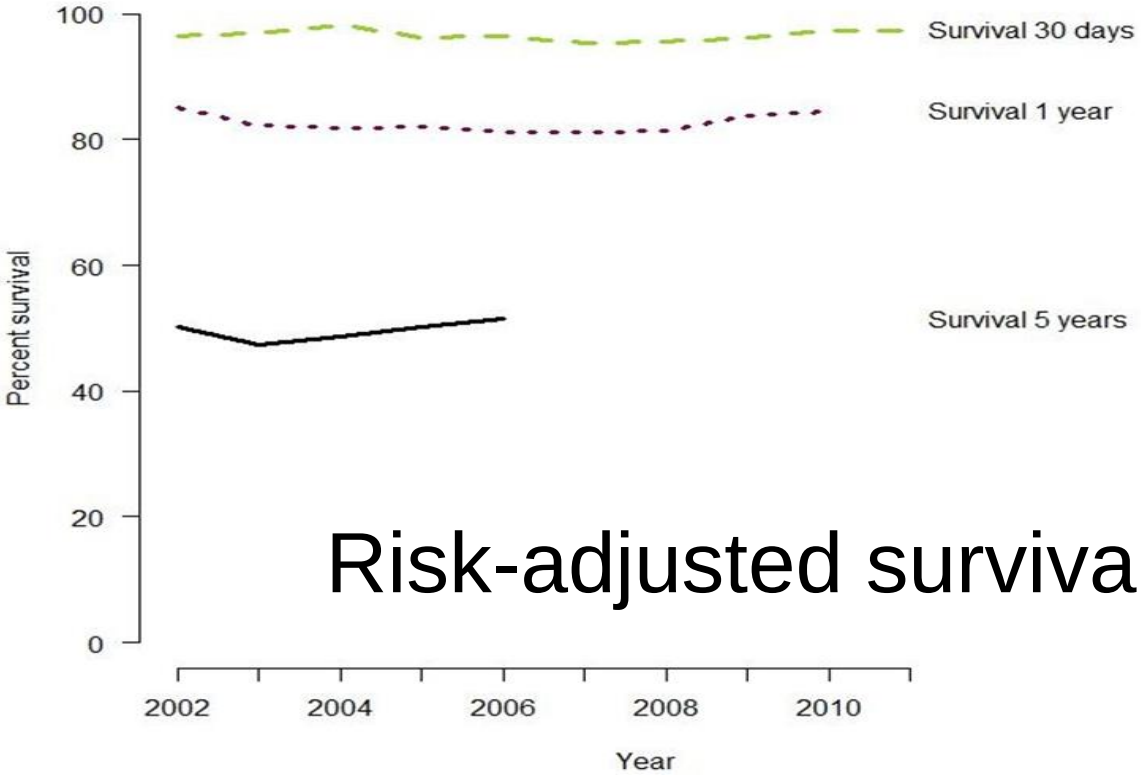


Risk-adjusted survival over time

ESC European Society of Cardiology
European Journal of Heart Failure (2018) 20, 1326–1334
doi:10.1002/ejhf.1182
RESEARCH ARTICLE

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

Study	MRA use
GWTG-HF[5]	32% of the eligible population.
IMPROVE HF[13]	36% of the eligible population.
EuroHeart Failure Survey II[14]	47.5% of patients discharged after a hospital admission for HF.
ESC-HF Pilot Survey[15]	~50% in inpatients at discharge and 44% in outpatients.
BIOSTAT-CHF[7]	56% of eligible patients before and 63% after HF treatment optimization.
ESC-HF-LT[16]	53.9% of patients hospitalized for acute HF received MRA at discharge and 56.5% at 1 year from hospitalization.
SwedeHF (current study)	40% of the eligible population.

Why MRA underuse?

European Journal of Heart Failure (2018)
doi:10.1002/ejhf.1182

RESEARCH ARTICLE

Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry

Gianluigi Savarese[1]*, Juan-Jesus Carrero[2], Bertram Pitt[3], Stefan D. Anker[4,5], Giuseppe M.C. Rosano[6,7], Ulf Dahlström[8], and Lars H. Lund[1,9]

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)

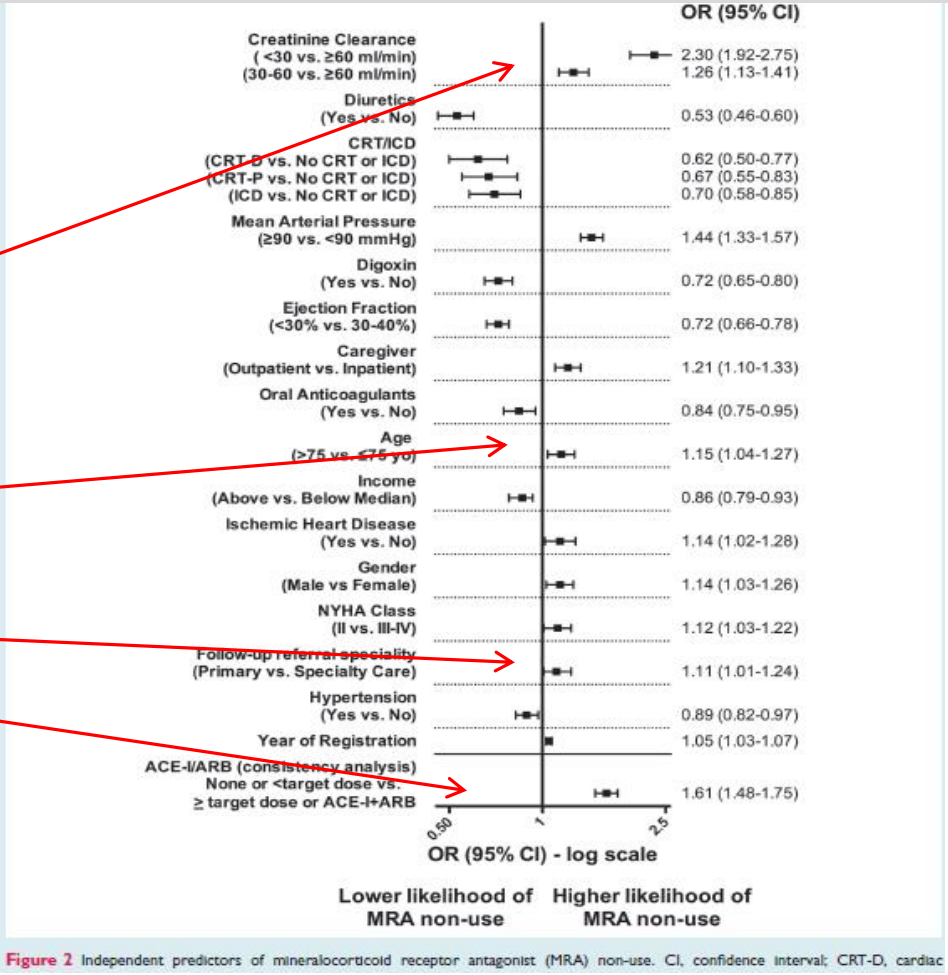


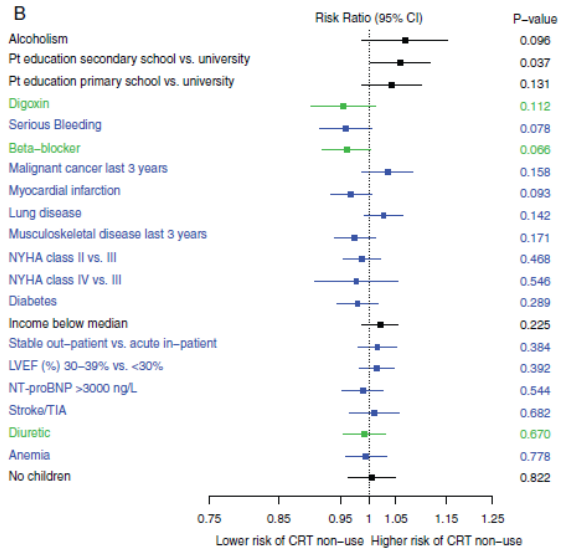
Figure 2 Independent predictors of mineralocorticoid receptor antagonist (MRA) non-use. CI, confidence interval; CRT-D, cardiac

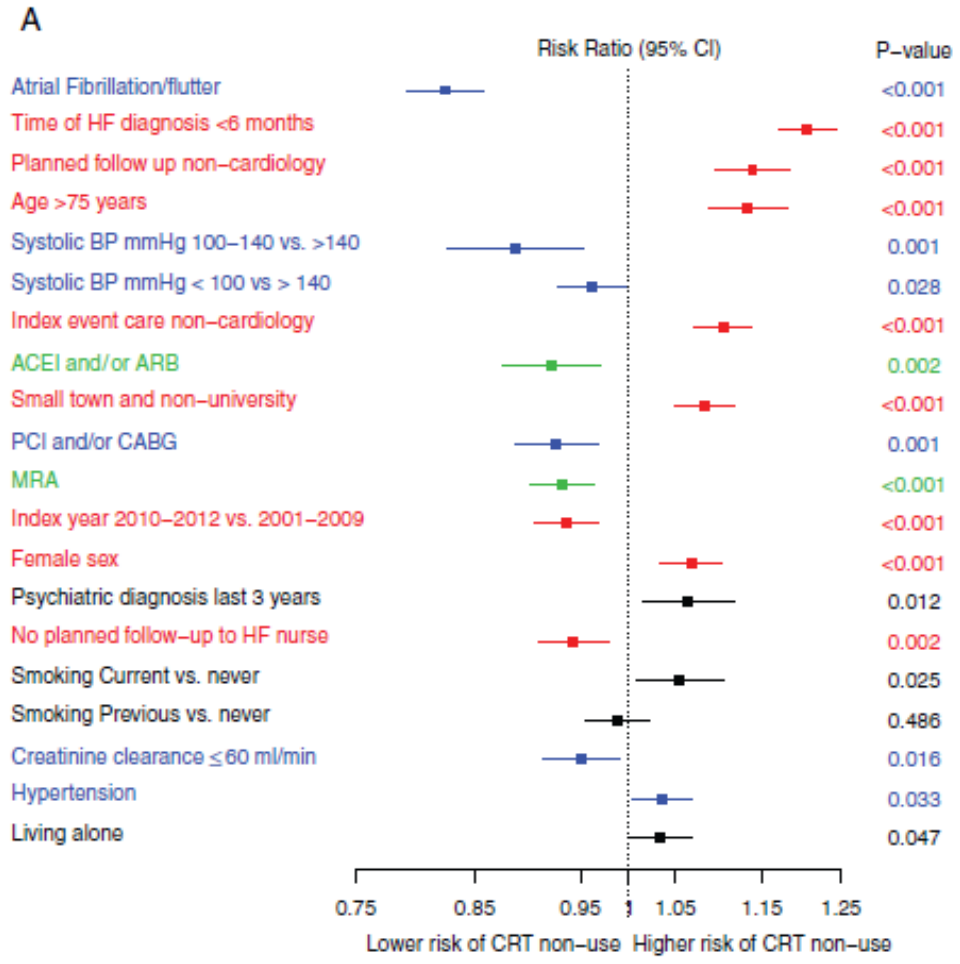
Reasons for CRT non-use

European Journal of Heart Failure (2017)
doi:10.1002/ejhf.781

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

Lars H. Lund[1,2]*, Frieder Braunschweig[1,2], Lina Benson[3], Marcus Ståhlberg[1,2], Ulf Dahlström[4], and Cecilia Linde[1,2]





2016: simple but poor implementation → 2020: complex and ?implementation

HF is the central cardiology space

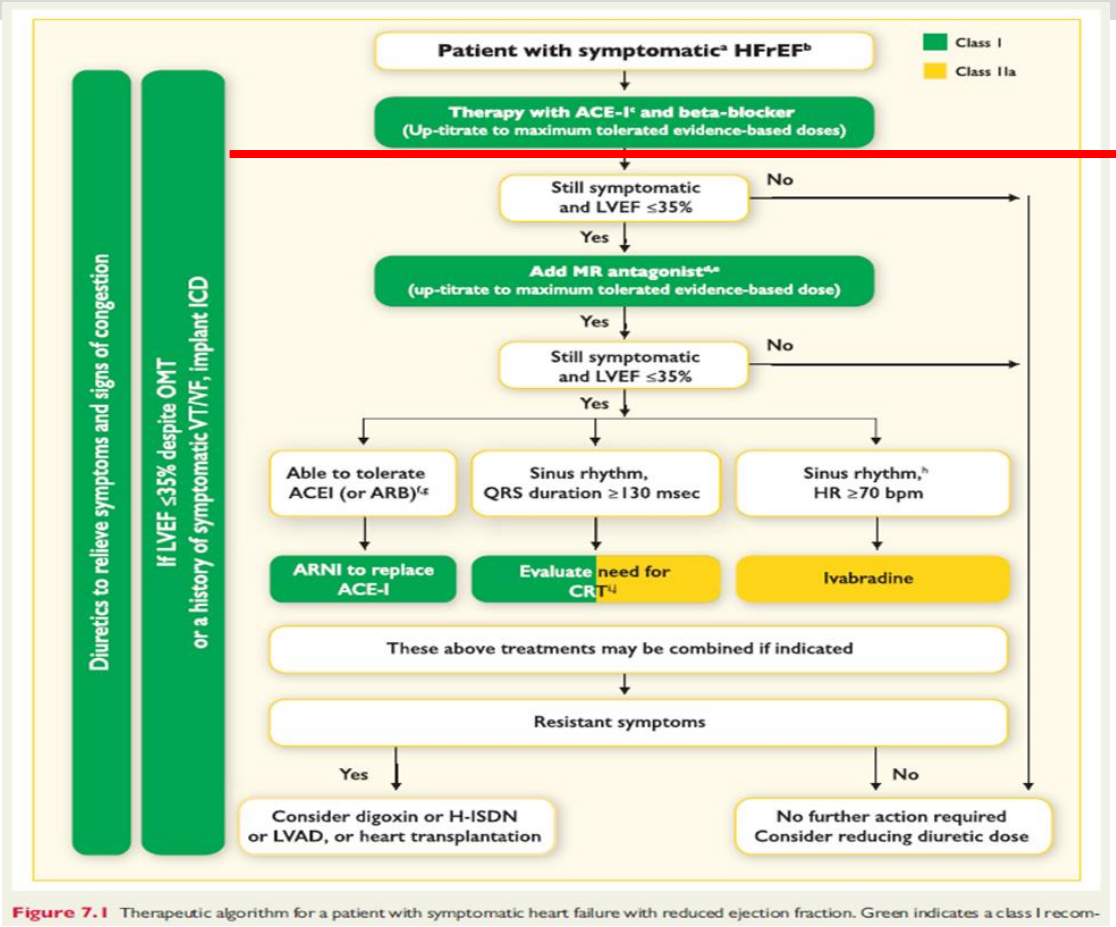


Figure 7.1 Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction. Green indicates a class I recom-

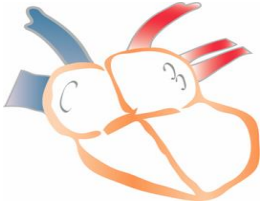
RASi / BB

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

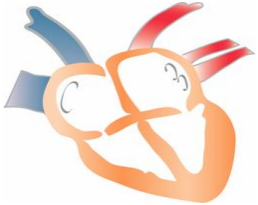
Heart Failure Challenges 2019 – how can a registry address these ?



HFmrEF

- Innovation
- Expansion of HFrEF therapy

RRCT

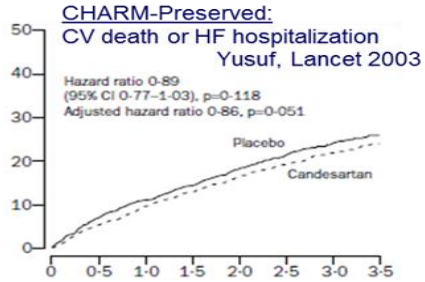


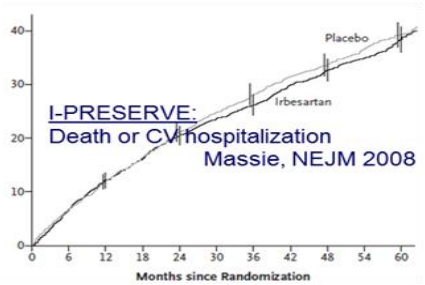
HFpEF

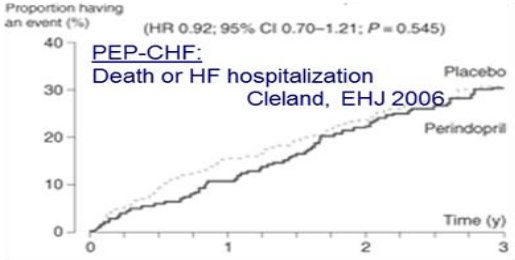
- Innovation
- Understanding phenotype(s)
- Novel targets

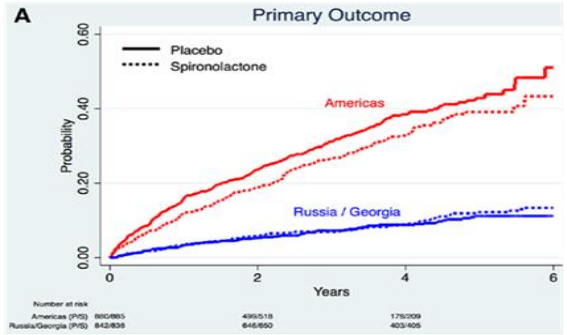
REGISTRY

HFpEF: 5 trials were neutral but 3 were suggestive of benefit





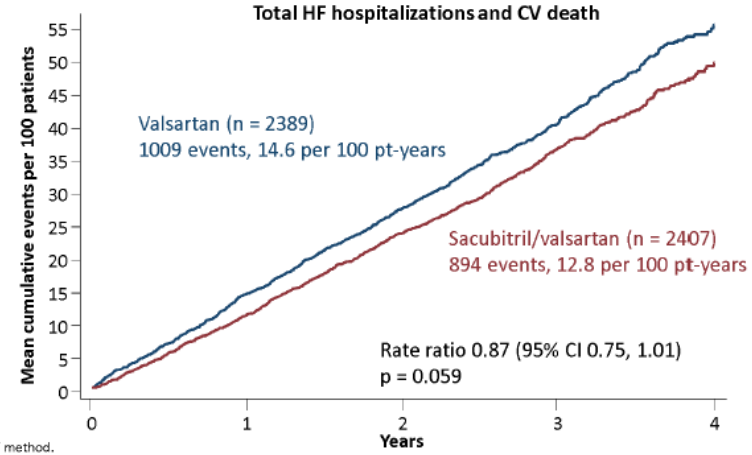




TOPCAT:
CV Death or HF Hospitalization
Pitt NEJM 2014, Pfeffer Circ 2014

PARAGON-HF primary results

Recurrent event analysis of total HF hospitalizations and CV death*



*Semiparametric LWYY method.

New understanding: Reduced + mildly reduced is one phenotype and ***preserved/normal is another***

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

SwedeHF, ESC-LT, CHARM

”How To” for HFpEF and HFmrEF phenotyping and trials ?

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 HFpEF

So how to conduct a pragmatic RRCT in heart failure ?

Curr Heart Fail Rep (2017) 14:59–70
DOI 10.1007/s11897-017-0325-0

CLINICAL TRIALS (J BUTLER, SECTION EDITOR)

Registry-Based Pragmatic Trials in Heart Failure: Current Experience and Future Directions

Lars H. Lund[1,2] · Jonas Oldgren[3] · Stefan James[3]

So how test new ***use*** of existing therapy ?

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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

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RCT

- Randomized evidence

But:

- 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

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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
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- Comparative outcomes → Hypothesis generating
- Efficient
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But:

- Lack of randomization → NOT comparative effectiveness

Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction

SPIRRIT HF-pEF

Registry (data) platform

RiksSvikt nationellt hjärtsviktsregister

The Swedish Heart Failure Registry (SwedeHF)

TRIAL INNOVATION NETWORK

Academic partners

UCR Uppsala Clinical Research Center

UPPSALA UNIVERSITET

Karolinska Institutet

KAROLINSKA Universitetssjukhuset

Duke Clinical Research Institute

HF discharge from hospital

HF Outpatient

Existing patients in SwedeHF

New registrations in SwedeHF or US sites

n=3200 patients (2550 Swe; 650 US)
- HFpEF (EF ≥40%)
- NTproBNP ≥ 300 SR; ≥ 750 AF
- eGFR ≥ 30; K ≤ 5.0
- Regular loop diuretics*

Randomized open label blinded endpoint (PROBE)

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)

Trial

*protocol amendment 2019

Funding agencies

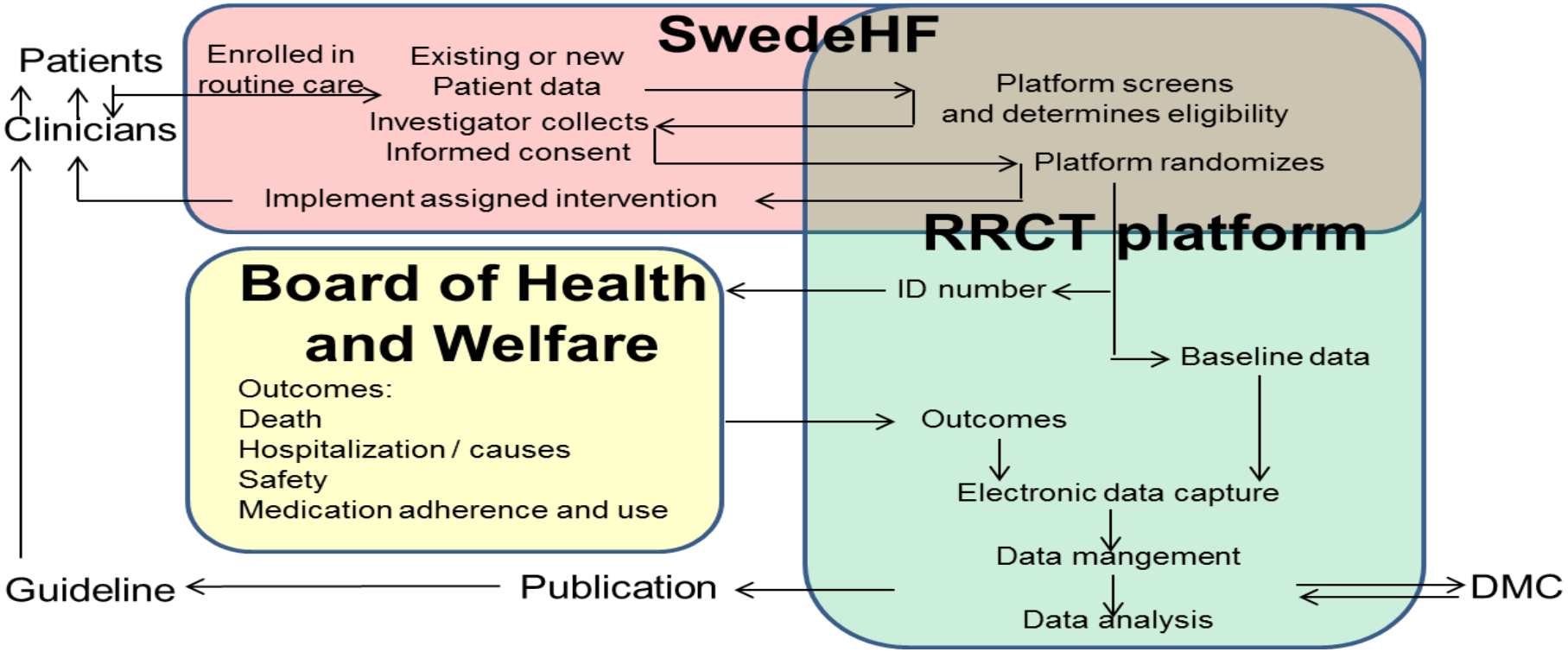
Hjärt Lungfonden

Vetenskapsrådet

THE ERLING-PERSSON FAMILY FOUNDATION

NIH National Heart, Lung, and Blood Institute

Design: Swe registries
USA: DCRI Trial Innovations Network



Lund, Curr Heart Fail Rep 2017

Summary SwedeHF and registry-based trials in heart failure

- Registries improve outcomes by analyzing and improving *implementation*
- Registries improve *understanding of clinical phenotypes*
- Regsitries can *conduct RRCTs*