SPIRRIT-HFpEF: opportunities and challenges in a large registry-based randomized clinical trial

NIH Collaboratory Grand Rounds
February 4, 2022

Adam DeVore, Associate Professor of Medicine, Duke University and Duke Clinical Research Institute

Lars Lund, Professor of Cardiology, Karolinska Institute and Karolinska University Hospital

SPIRRIT-HFpEF: Overview

SPIRRIT HF-pEF

- Large, pragmatic registry-based RCT of spironolactone or eplerenone in heart failure with preserved ejection fraction (HFpEF) conducted primarily in Sweden and partially in the US

- Why we need these data now for heart failure patients

- Why this approach and study design

NIH National Heart, Lung, and Blood Institute

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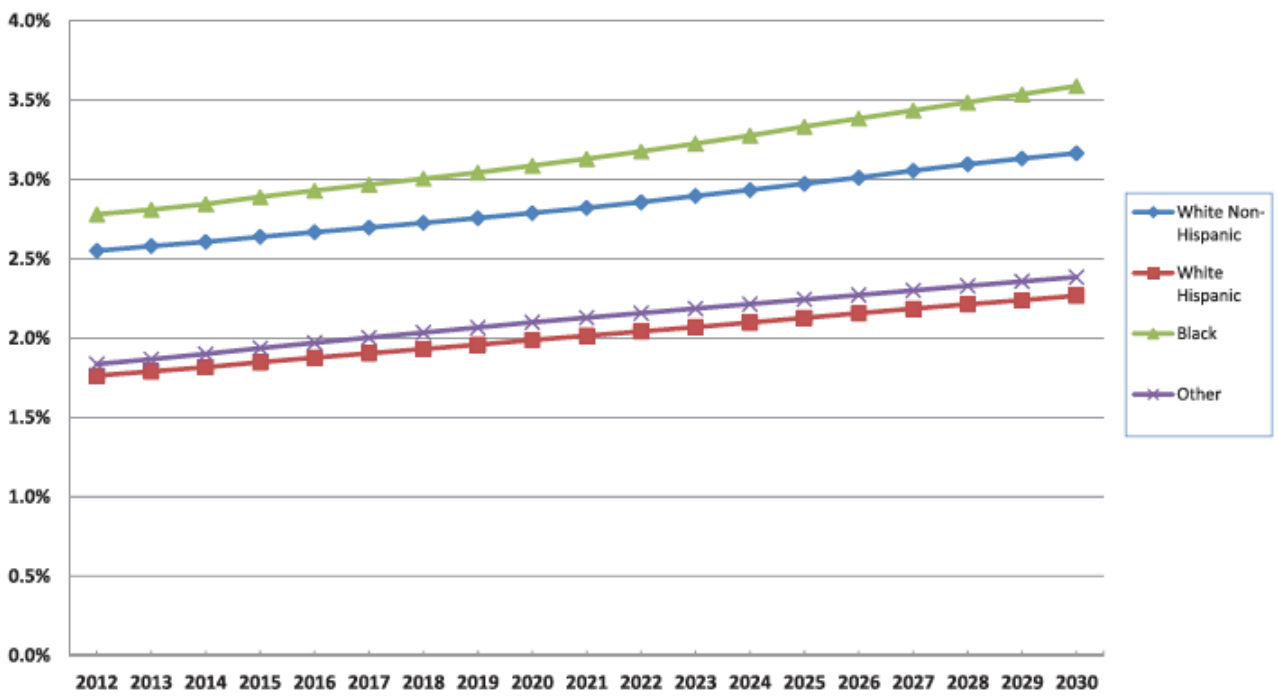
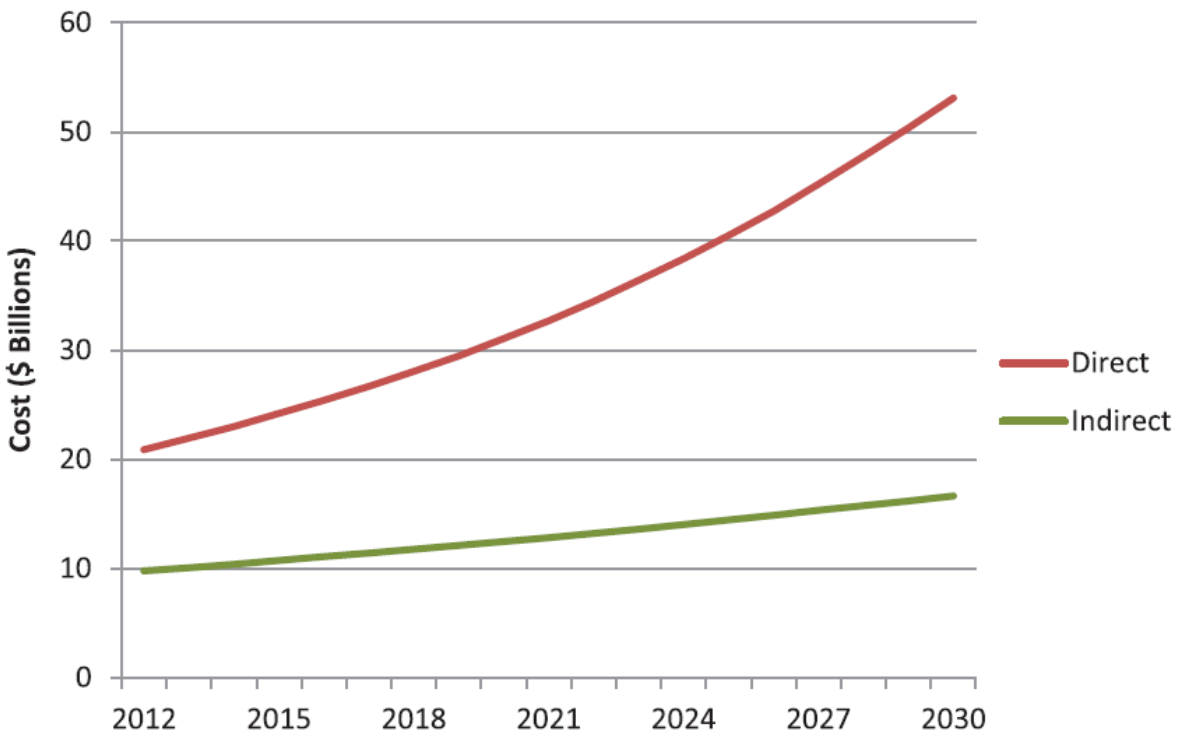
TRIAL INNOVATION NETWORK

Forecasting the Impact of Heart Failure in the United States

Increase in Prevalence Over Time

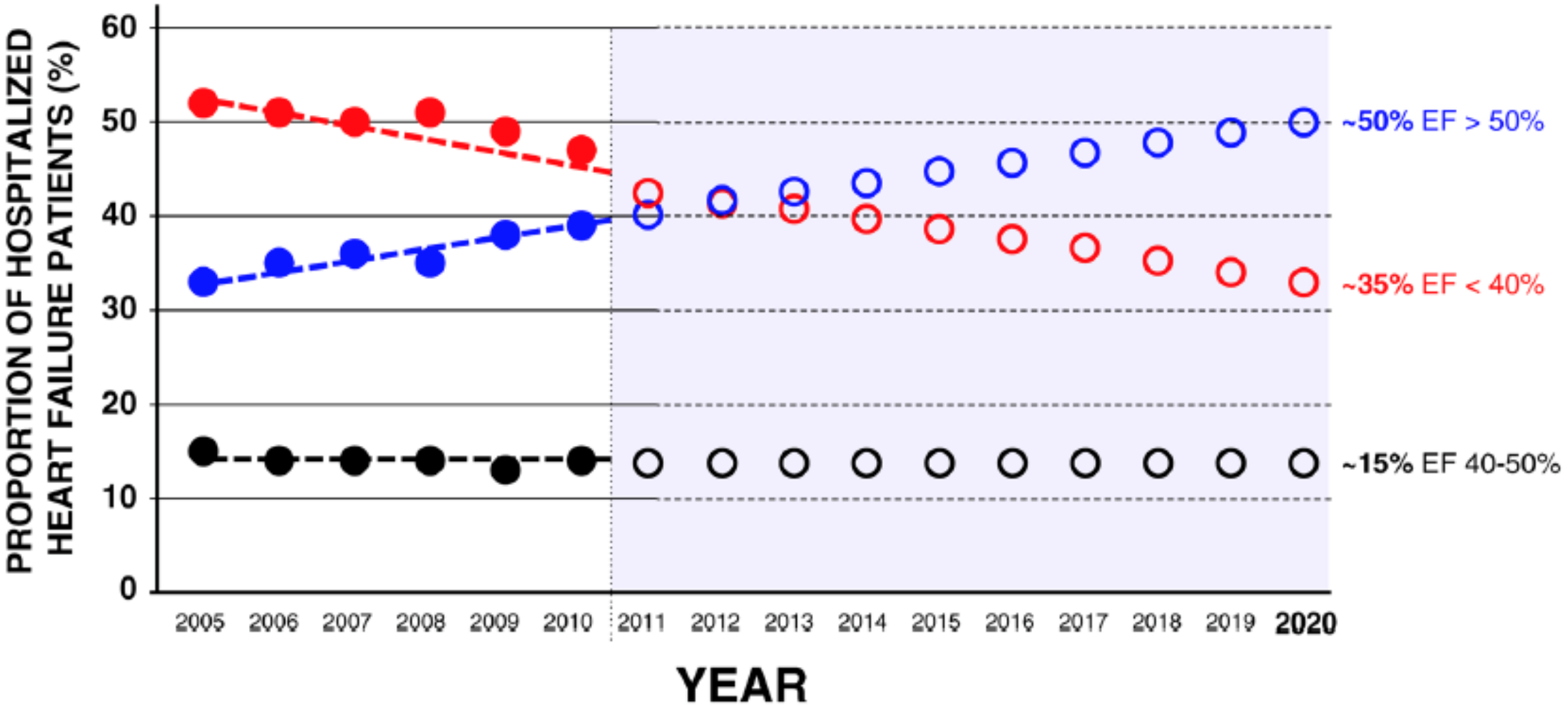


Projected Cost Increases



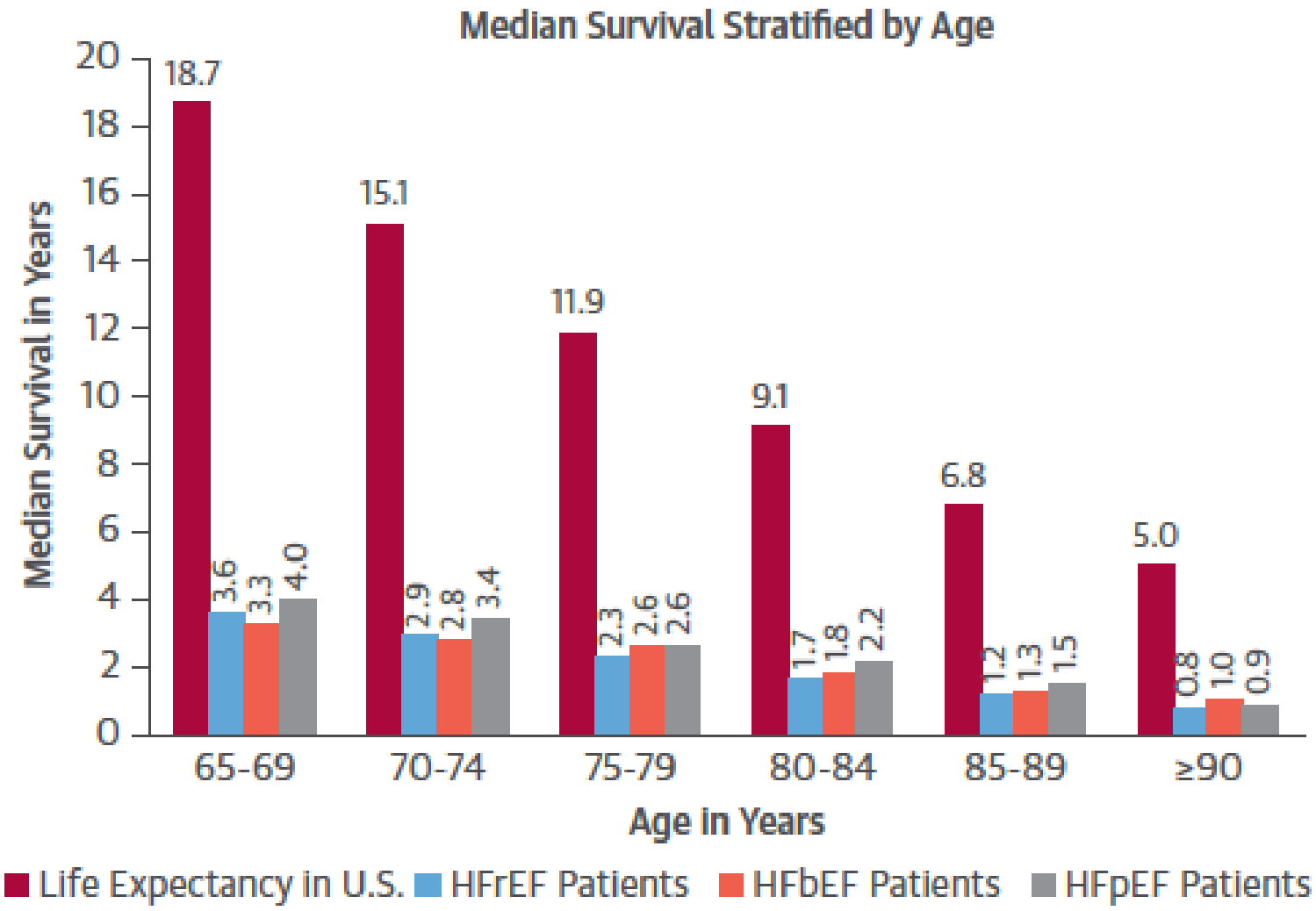
Heidenreich PA et al. *Circ Heart Failure*. 2013;6(3):606-19

The Changing Epidemiology of Heart Failure



Steinberg et al. Circulation. 2012; 126(1):65–75
Oktay et al. Curr Heart Fail Rep. 2013 Dec;10(4):401-10

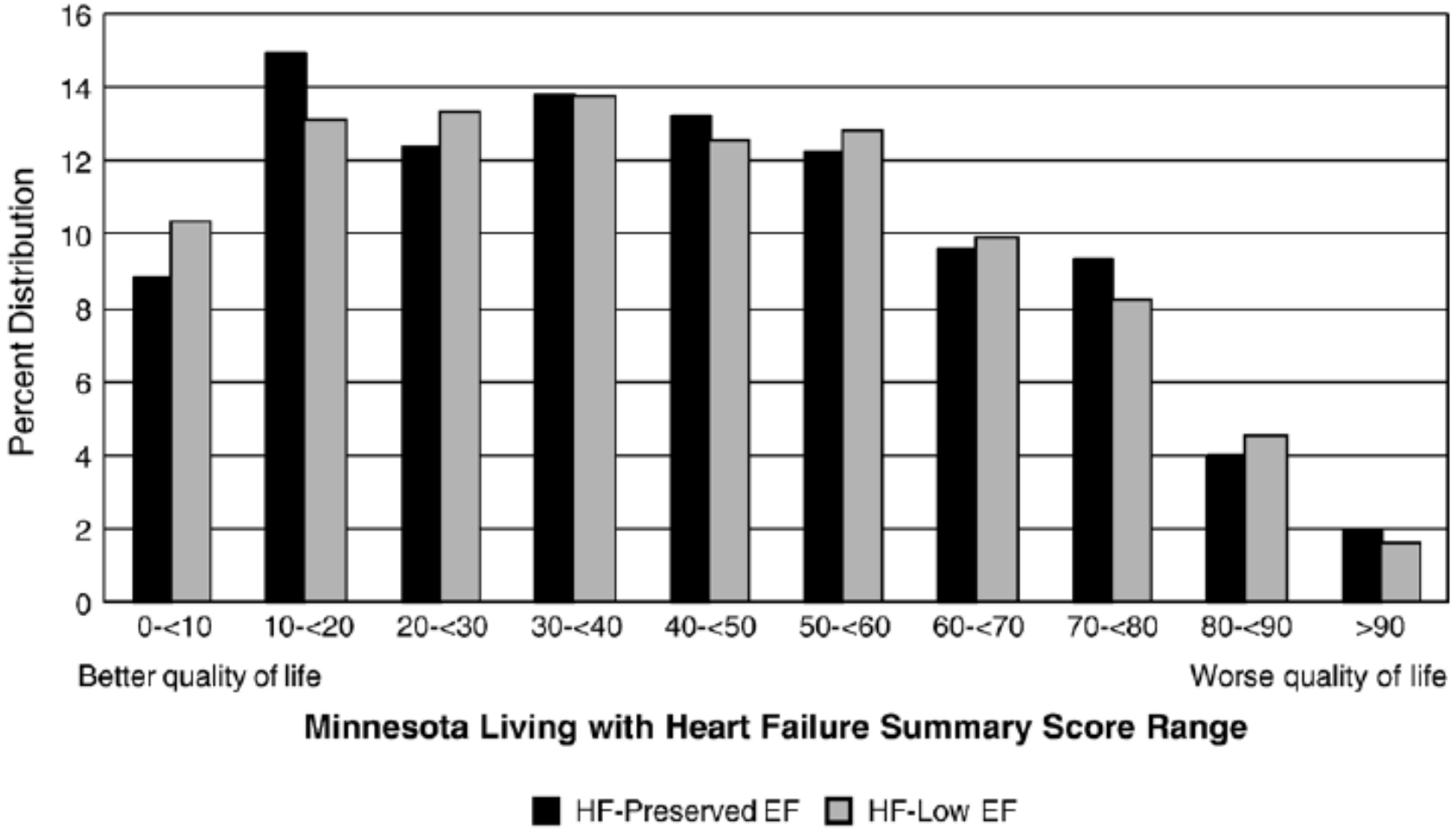
HF Survival by Age Compared with US Life Expectancy



American Heart Association. life is why™ | GET WITH THE GUIDELINES. HEART FAILURE

Shah K et al. *J Am Coll Cardiol* 2017;70:2476–86

CHARM data: Health-related QOL in HFpEF vs HFrEF



Lewis E et al. *Eur J Heart Fail*. 2007 Jan;9(1):83-91

Key Steps in Management of HFpEF

- Does the patient have HFpEF or a condition that mimics HFpEF?
- Are filling pressures optimized to manage symptoms?
- Can we reduce risk of future HF events with medical or non-pharmacologic interventions?
- Are therapies for his comorbid conditions (including CV conditions) optimized? [AF, CAD, HTN, T2DM]

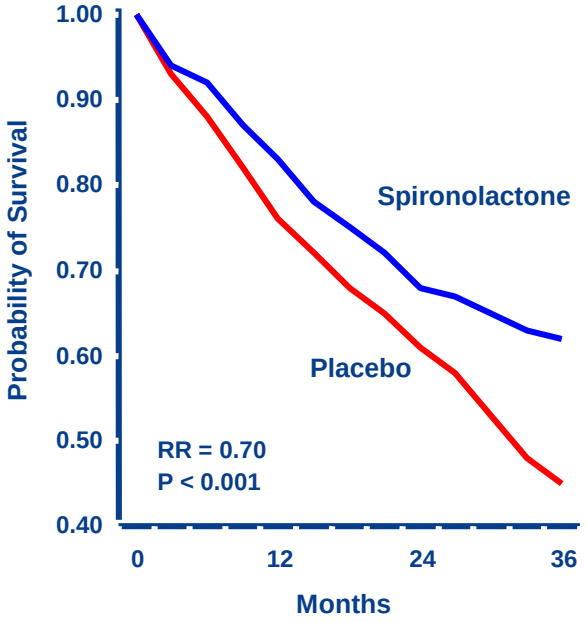
HFpEF Potential Cardiac Mechanisms

- Left ventricular hypertrophy and fibrosis (reduced chamber compliance)
- Impaired diastolic relaxation and elevated left-sided filling pressures
- Systolic dysfunction (sometimes subclinical)
- Abnormal ventricular-vascular coupling
- Chronotropic incompetence and cardiovascular reserve
- Increased oxidative stress and depressed NO signaling (i.e., inflammation) leading to endothelial dysfunction
- Comorbidity-induced systemic inflammation

MRAs Beneficial in HFrEF and Post-MI LVSD

RALES
(Severe HFrEF)

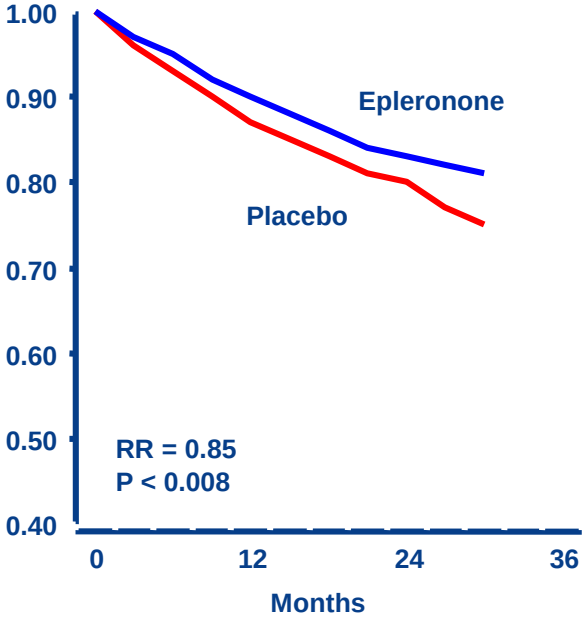
30% Risk Reduction



Pitt NEJM 1999

EPHESUS
(Post-MI)

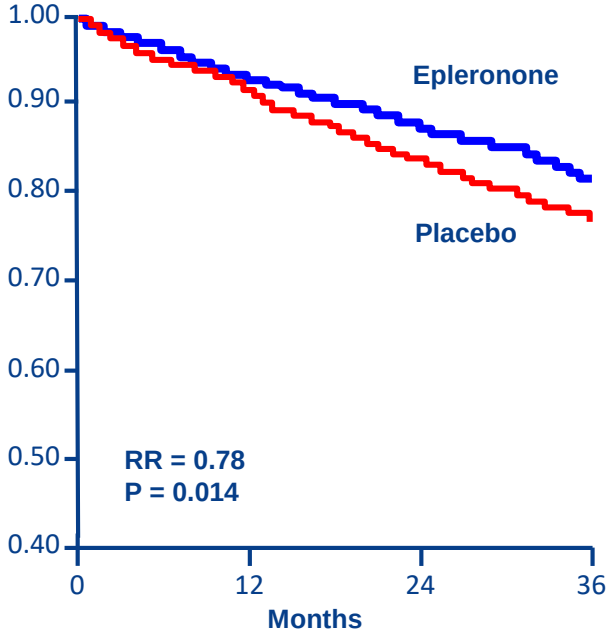
15% Risk Reduction



Pitt NEJM 2003

EMPHASIS
(HFrEF + ↓ NYHA Class)

22% Risk Reduction



Zannad NEJM 2011

MRAs in HFpEF

TOPCAT
Funded by the NHLBI

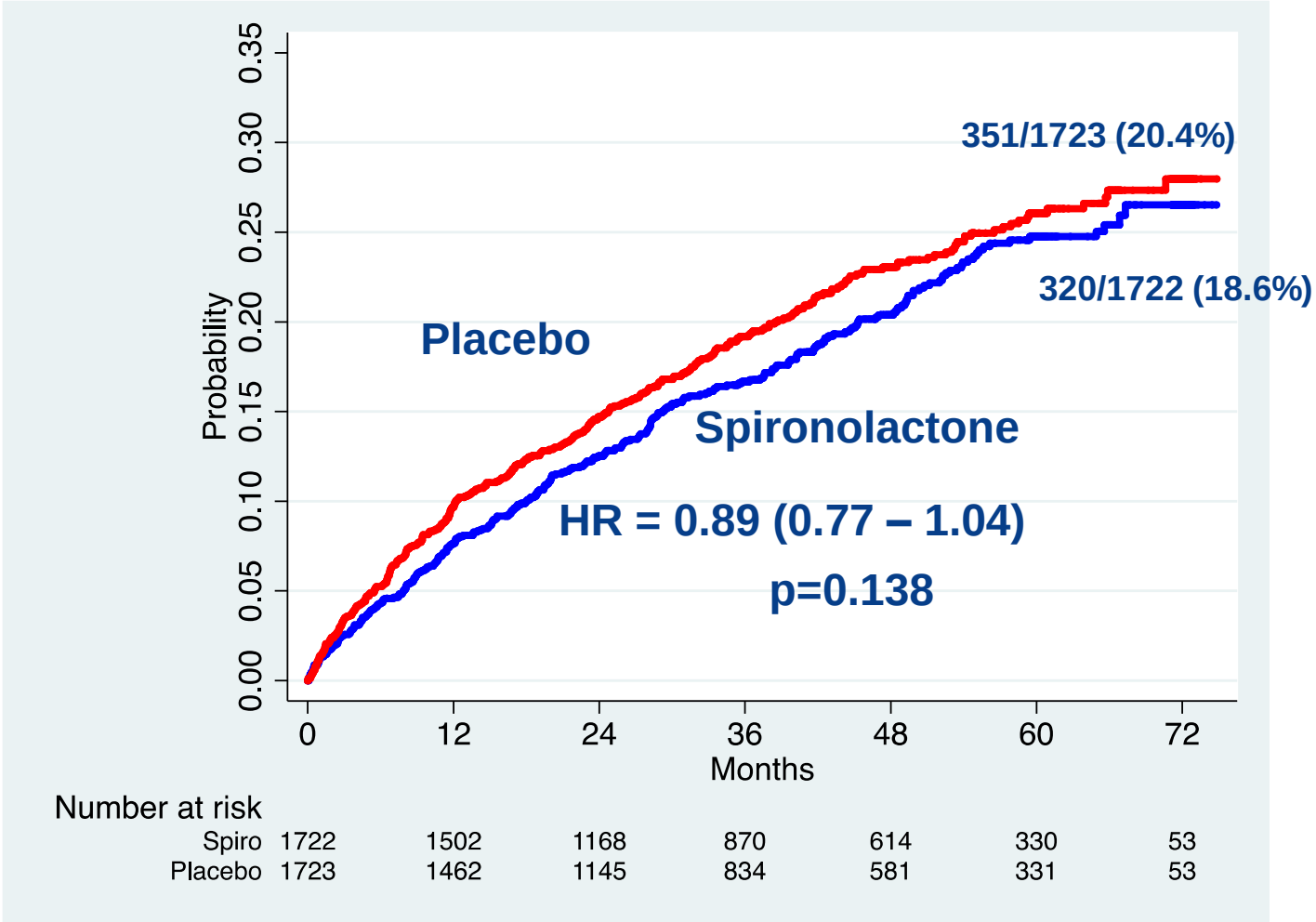
- Objective
  - To determine if treatment with spironolactone can produce a clinically meaningful reduction in the composite endpoint of cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of heart failure, compared with placebo, in adults with HF-Preserved EF.
- Inclusions:
  - Symptomatic Heart Failure, Age ≥ 50, LVEF ≥ 45%, stratified according to:
    - Hospitalization within the past year for management of heart failure, or
    - Elevated natriuretic peptides (BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL)
- Major Exclusions:
  - eGFR<30 mL/min/1.7m^2, serum potassium ≥5 mmol/L, uncontrolled hypertension, AF with rate > 90/min, recent ACS, restrictive, infiltrative, or hypertrophic cardiomyopathy

MRAs in HFpEF

TOPCAT
Funded by the NHLBI

1° Outcome

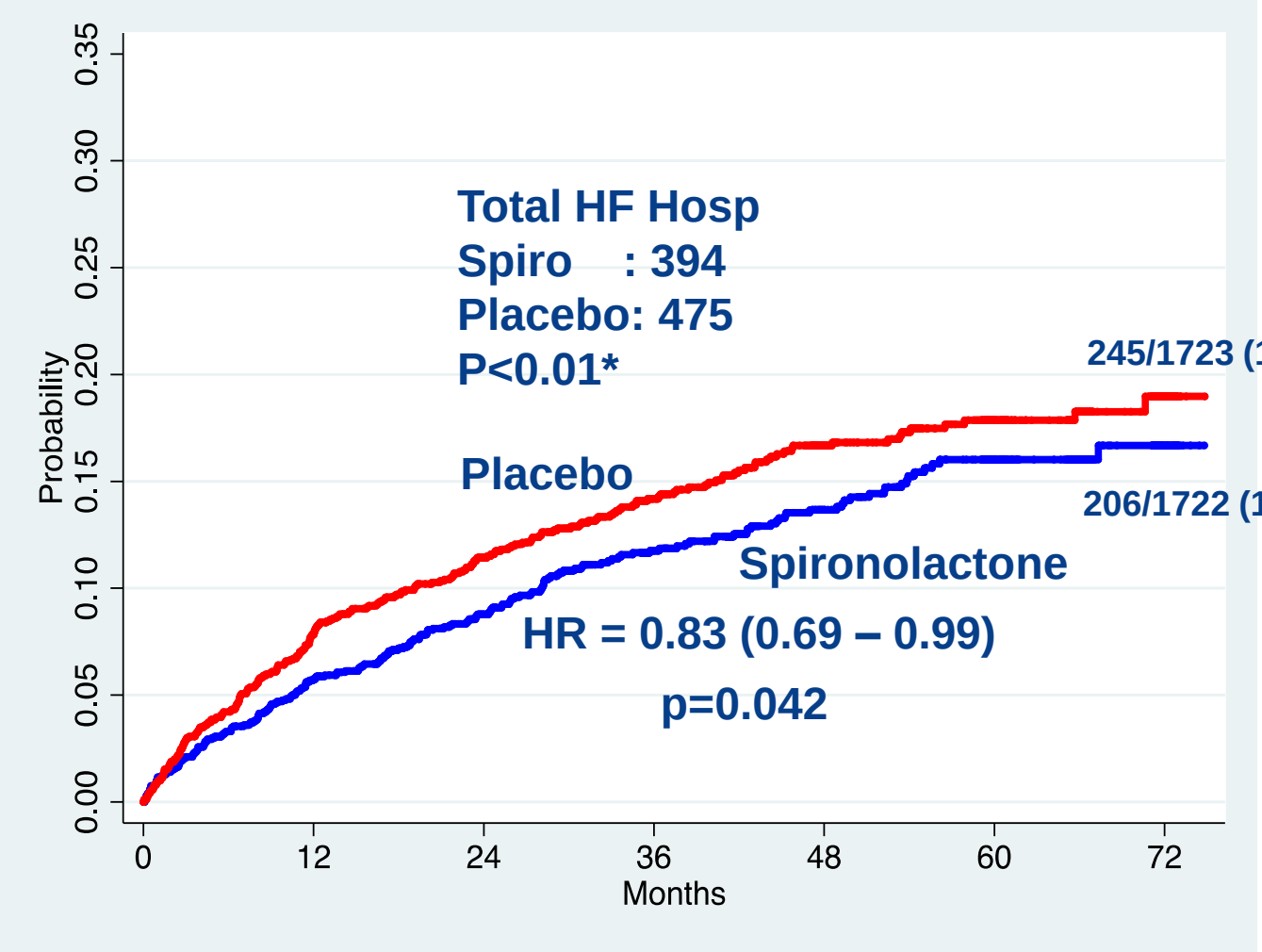
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)



MRAs in HFpEF

TOPCAT
Funded by the NHLBI

Heart Failure Hospitalizations



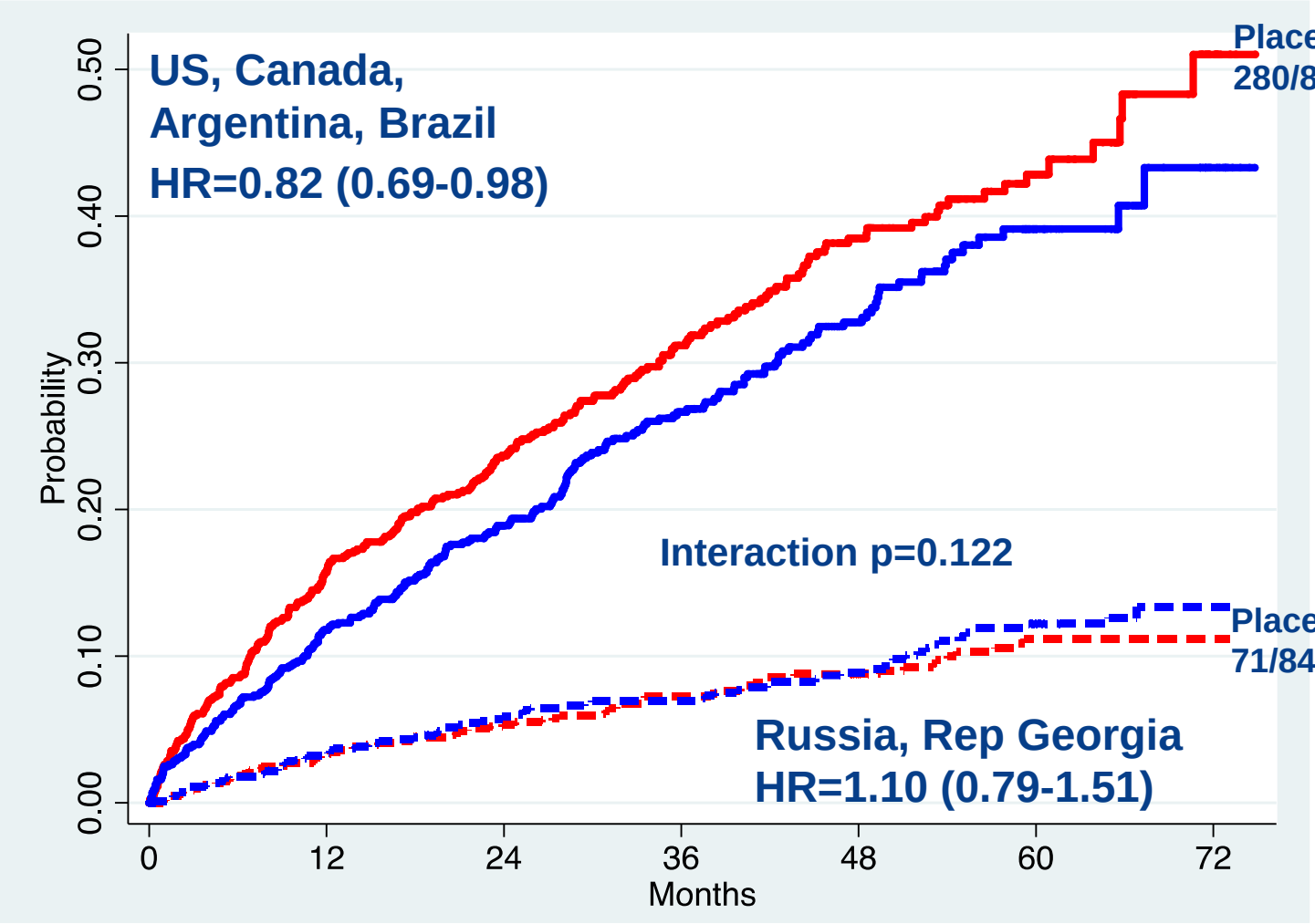
*poisson regression

MRAs in HFpEF

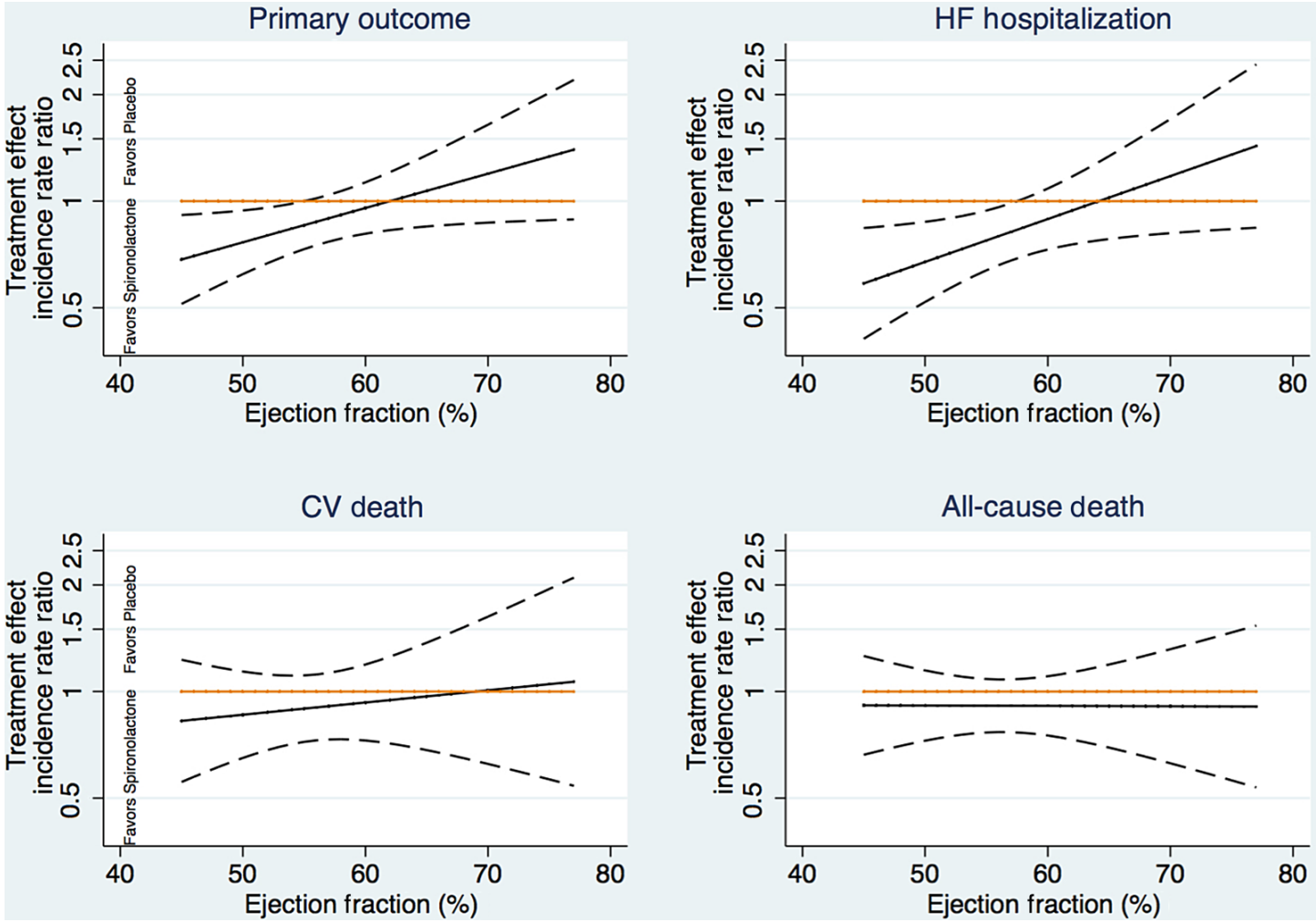
TOPCAT
Funded by the NHLBI

Exploratory (post-hoc):

Placebo vs. Spiro by region



Greater Benefit with Impaired LVEF

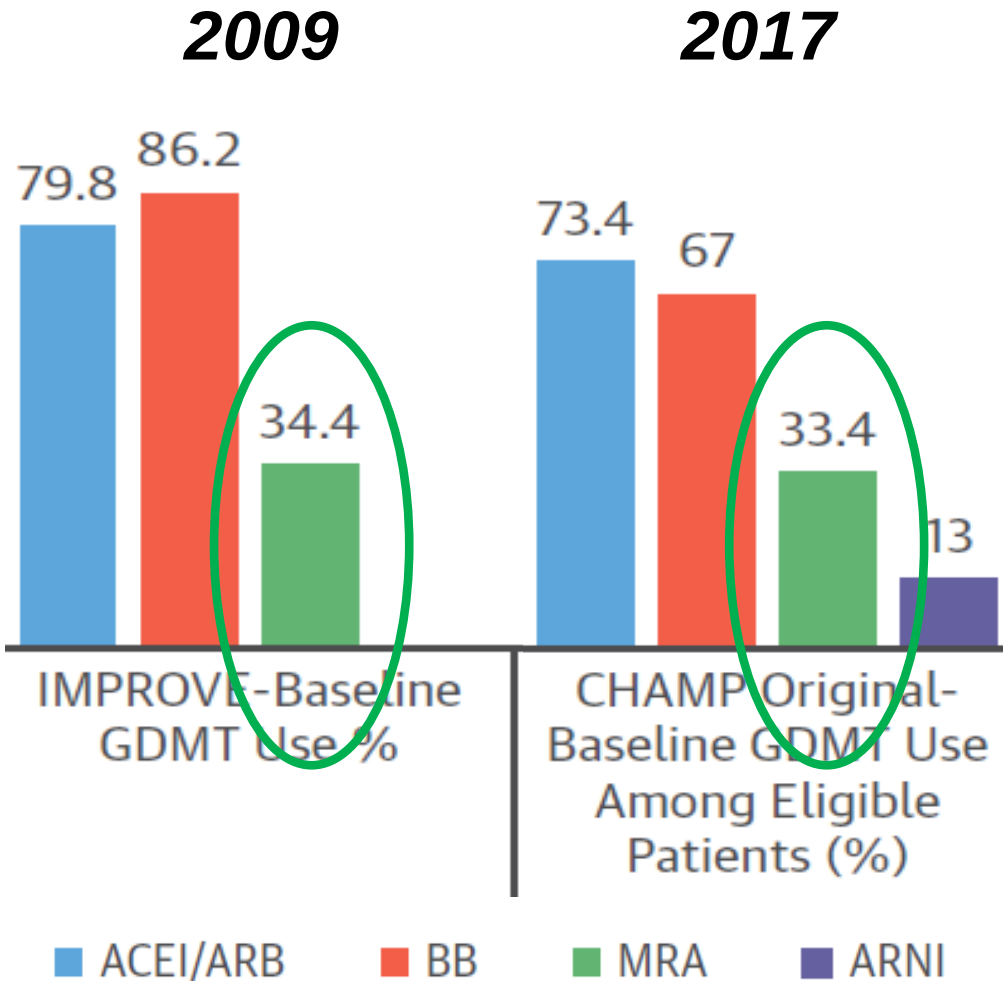


Solomon SD et al. *Eur Heart J*. 2016 Feb 1;37(5):455-62.

Pharmacological Treatment for Stage C HF With Preserved EF: COR IIb

COR	LOE	Recommendations	Comment/ Rationale
IIb	B-R	In appropriately selected patients with HF*p*EF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.	NEW: Current recommendation reflects new RCT data.

Medical Therapy for Heart Failure with Reduced EF



Bozkurt B. *J Am Coll Cardiol.* 2019 May 21;73(19):2384-2387

HFpEF Today

SPIRRIT HF-pEF

- HFpEF is increasing in prevalence with a high burden of symptoms, HF hospitalizations, and death
- In TOPCAT, treatment with spironolactone did not alter the primary composite in the overall trial
  - ➢ MRAs are a generic and widely-available therapy with conflicting data on efficacy in HFpEF
- Prior use of MRAs in HF has been low

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Curr Heart Fail Rep
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]

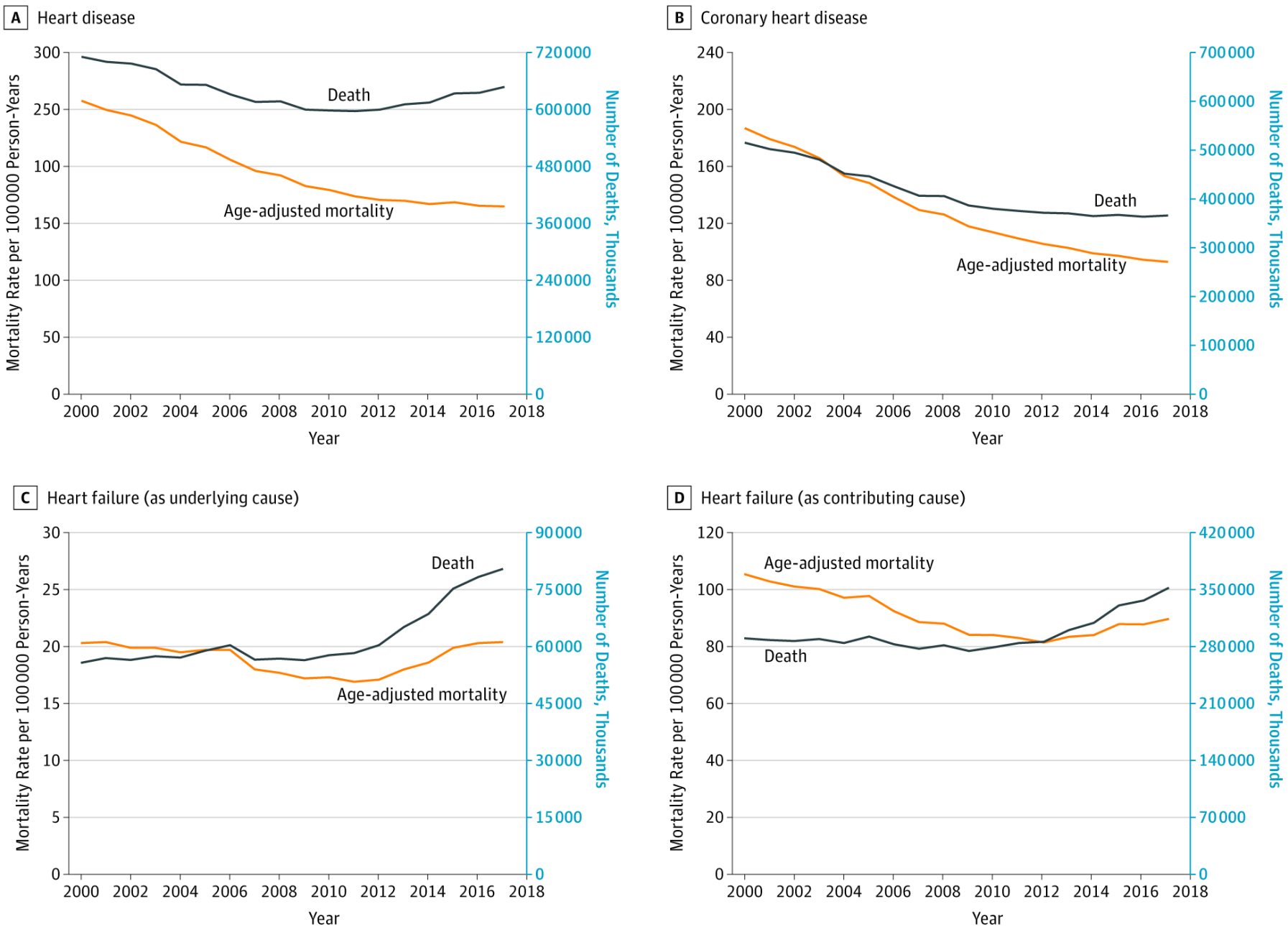
RCT

- 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

RCTs in HF are complex and expensive and results not implemented: CVD in 2021: Death ↓ from CCS but ↑ from HF !



From US CDC
Sidney JAMA 2019

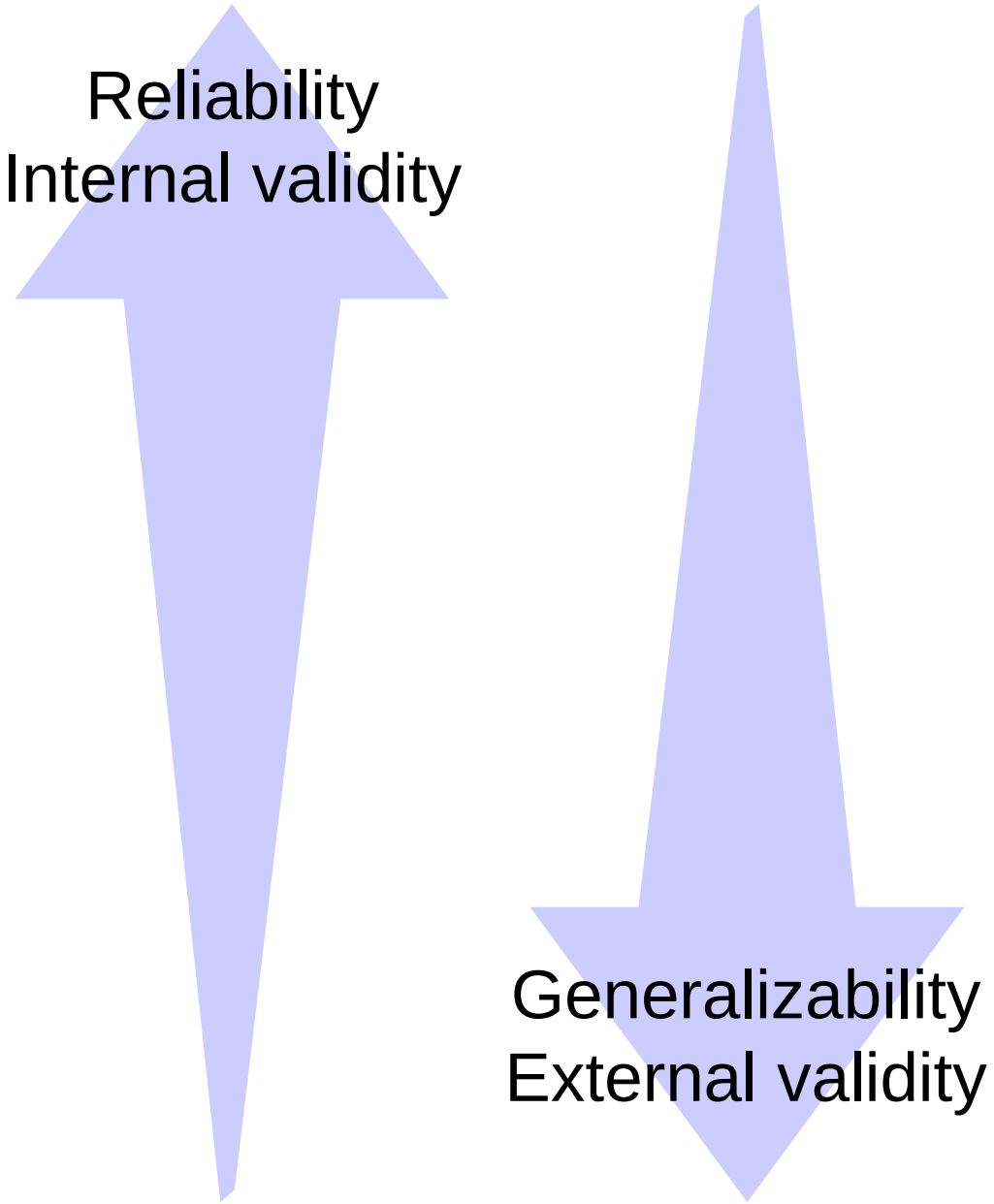
What are other study forms and their characteristics?

RCT database

Prospective cohort

Registry - combines broad coverage with sufficient data detail

Surveys, claims databases - epidemiology



Swedish Heart Failure Registry (SwedeHF) :

- Voluntary quality registry
- 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 mandatory national administrative 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

- 150,000 registrations from 110,000 unique individuals
- Coverage: ~30%
- From ~68 of Sweden's ~75 hospitals

Registries improve (are associated with) better outcomes by better use of evidence based HF therapy

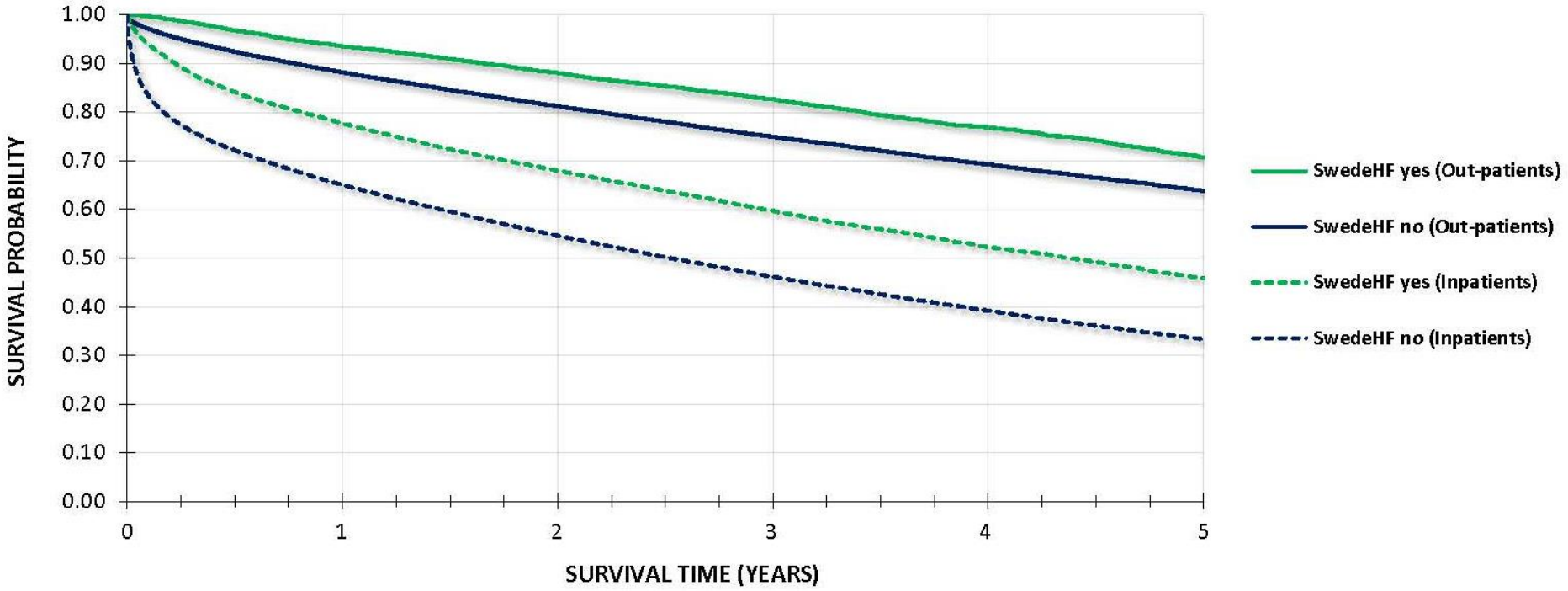


Table 1 Baseline characteristics in the intervention (enrolled in SwedeHF) vs. control group (not enrolled)

	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

Curr Heart Fail Rep
DOI 10.1007/s11897-017-0325-0

CLINICAL TRIALS (J BUTLER, SECTION EDITOR)

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

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 ?

Curr Heart Fail Rep
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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

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Rationale RRCT

Perspective

The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

- Conventional trials too complex, too expensive, enrollment too slow

- Swedish registries and have the RRCT concept in place
- SPIRRIT:
  - Pragmatic, efficient, inexpensive
  - Existing registry provides data for power and feasibility
  - Generalizable results
  - New *use* of inexpensive generic drug
  - ***First RRCT in HF and among the first in chronic condition***

    (ADAPTABLE, ABC-AF, DELIVER are chronic but not HF)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 24, 2013 VOL. 369 NO. 17

Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction

ORIGINAL ARTICLE

Outcomes 1 Year after Thrombus Aspiration for Myocardial Infarction

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 11, 2017 VOL. 376 NO. 19

Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI

ORIGINAL ARTICLE

Oxygen Therapy in Suspected Acute Myocardial Infarction

ORIGINAL ARTICLE

Bivalirudin versus Heparin Monotherapy in Myocardial Infarction

... and many ongoing

Pragmatic trial chronic intervention: ADAPTABLE: digital features
No patient monitoring

JAMA Cardiology | Special Communication

Rationale and Design of the Aspirin Dosing—A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) Trial

Figure 1. Recruitment Approaches

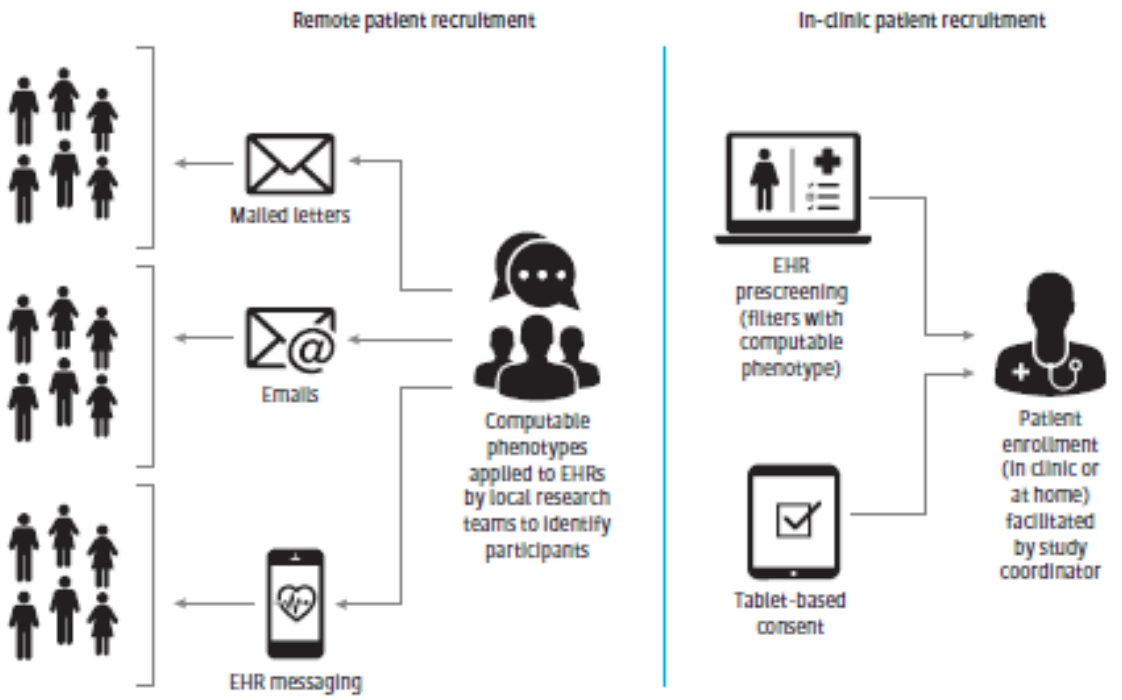
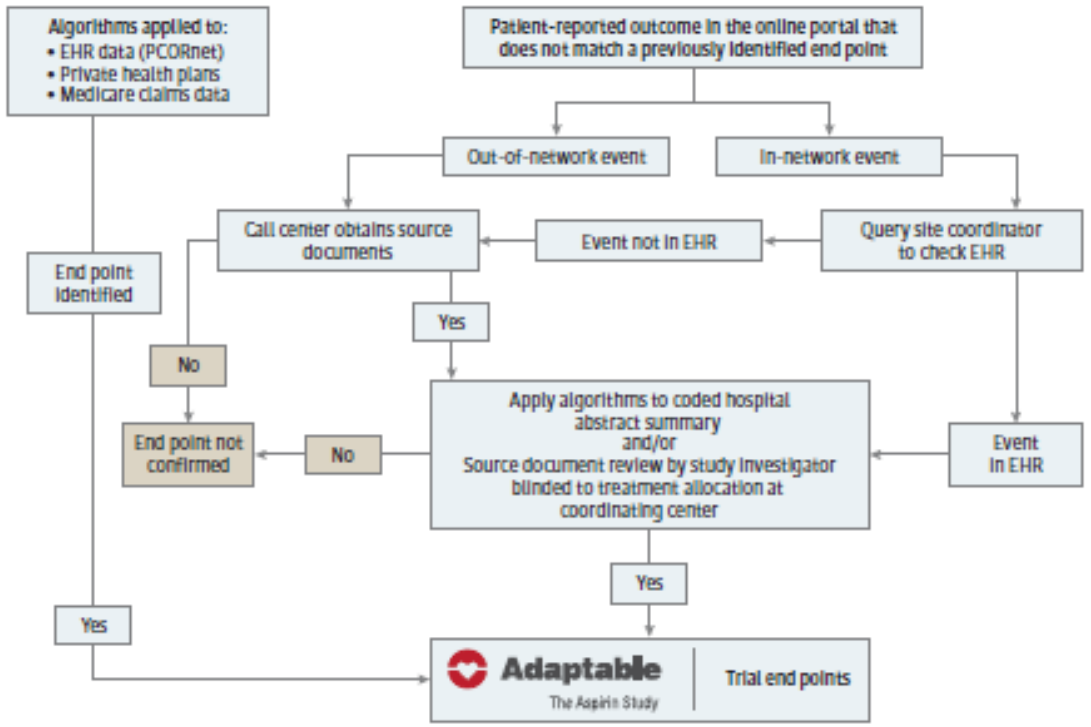


Figure 4. End Point Ascertainment and Reconciliation



Patients pre-screened in EHRs → letter / email / message → electronic consent

Endpoints from EHR or study portal – NOT adjudicated

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

SPIRRIT HF-pEF

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
Powered for key secondary: CV death (632 events)

Registry (data) platform

RiksSvikt
nationellt hjärtsviktsregister

The Swedish Heart Failure Registry (SwedeHF)

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Funding agencies

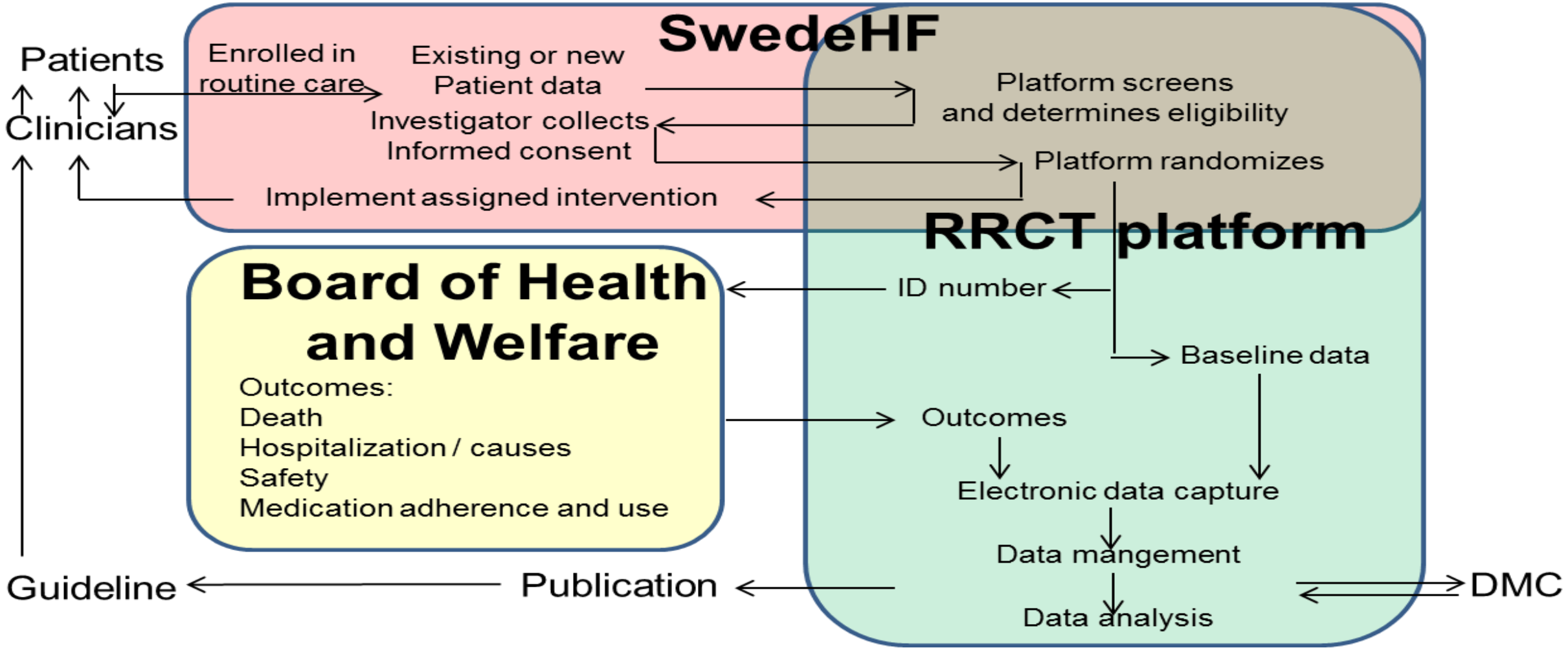
Hjärt Lungfonden

Vetenskapsrådet

THE ERLING-PERSSON FAMILY FOUNDATION

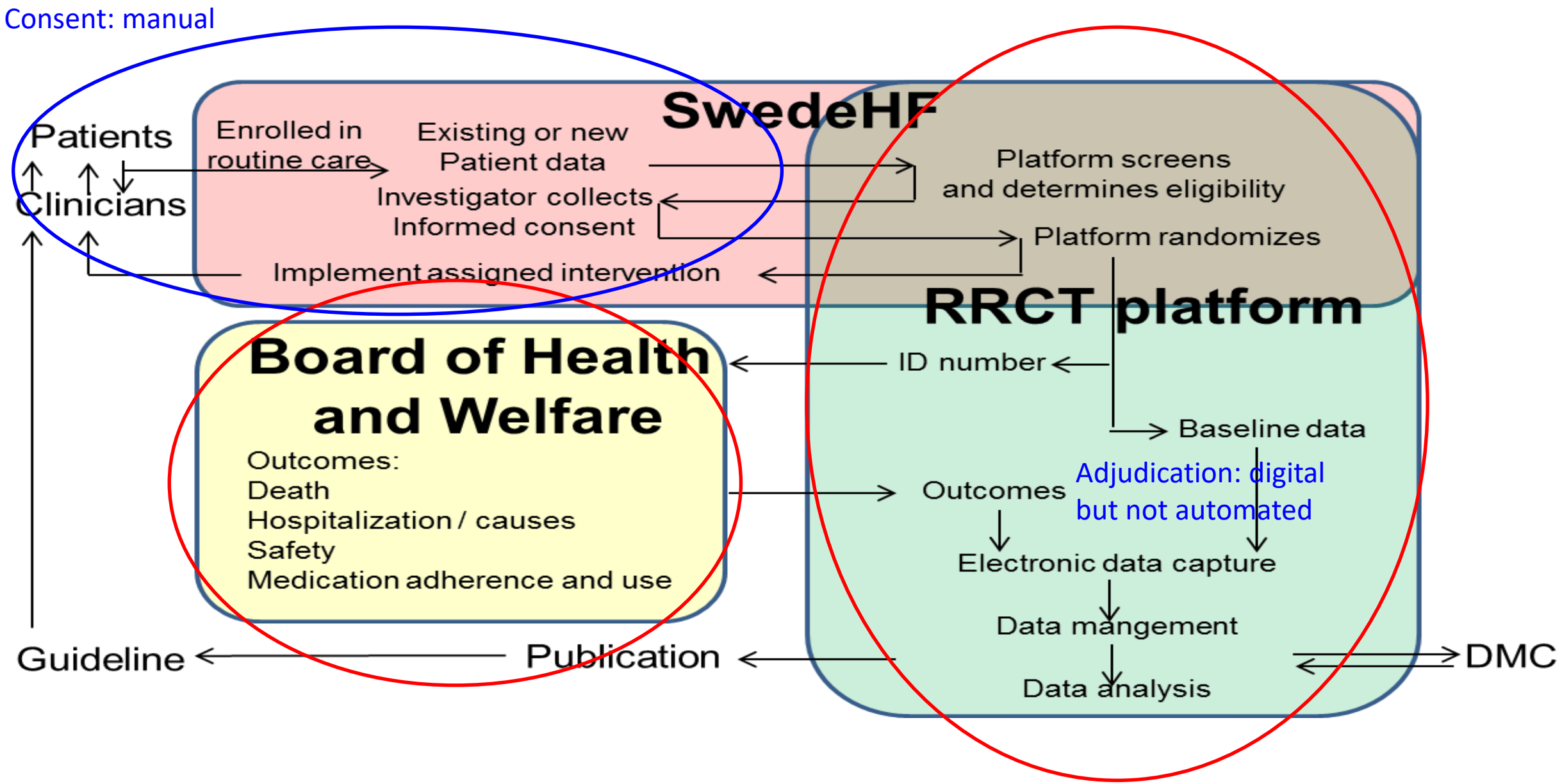
NIH National Heart, Lung, and Blood Institute

Design: Swe registries
USA: DCRI Trial Innovations Network



Lund, Curr Heart Fail Rep 2017

SPIRRIT-HFpEF is pragmatic but both digital and conventional



Lund, Curr Heart Fail Rep 2017

Pre-specified patient-level metaanalysis

SPIRRIT HF-pEF

n = 3200

TOPCAT

n = 3445

n = 7945 (8745)

n = 1300 (2100)

SPIRIT-HF
DZHK TRIAL 08

Funded by:

NIH
National Heart, Lung, and Blood Institute

The next registry based trials: Implementation trials using digital *screening*

Swedish Universal SGLT2i Screen - SUSIS

National Patient Registry: ICD code HF / CKD / T2DM

↓

Randomized to offer NT-proBNP / eGFR / HbA1c (not treatment, thus no consent) yes vs. no

↓ → Outcomes from registries

Digital informed consent and home NT-proBNP / eGFR / HbA1c

↓

- NT-proBNP > 300 non-AF / 900 AF (ICD code)
- eGFR 25-75
- HbA1C >6.5%

↓

Offered SGLT2i

↓

Outcomes from registries

Summary RCTs, SwedeHF and registry-based trials in heart failure

- RCTs provide causality and evidence of *efficacy*
- Registries are observational but improve outcomes by analyzing and *improving implementation*
- Registries can now also *conduct RRCTs*
- Future: *implementation trials ?*

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- Large, pragmatic registry-based RCT of spironolactone or eplerenone in heart failure with preserved ejection fraction (HFpEF) conducted primarily in Sweden and partially in the US

- Why we need these data now for heart failure patients

- Why this approach and study design

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SPIRRIT-HFpEF: Points for Discussion

- Swedish enrollment: “retrospective” pre-screening of living eligible patients in SwedeHF and “prospective” pre-screening of patients enrolled in SwedeHF during the trial

- Open-label intervention of generic medication with site monitoring of potassium and creatinine

- Outcome ascertainment: Swedish National Patient + Population Registry and in US data collected by sites and centralized call center - both with blinded adjudication

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	TOPCAT	SPIRRIT-HFpEF
Study Design	Double-blind, placebo-controlled randomized trial	Registry-based Randomized Clincial Trial with open-label intervetion
Location	6 countries	Sweden and US
Eligibility Criteria-LVEF	LVEF ≥ 45%	LVEF ≥ 40%
Eligibility Criteria	HF Hosp or BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL	NT-proBNP >300ng/L (>750 in AF) or BNP >100 pg/mL (>250 in AF)
Enrollment	3445	3200
Dosing	Spiro 15-45mg	Spiro or Eplerenone with dosing determined by PI
Primary Outcome	CV Death, HF Hosp, or Resuscitated Cardiac Arrest	CV Death or HF Hosp
Follow-up	Traditional Study Visits	Limited Study Visits for safety with centralized outcome collection

SPIRRIT HF-pEF

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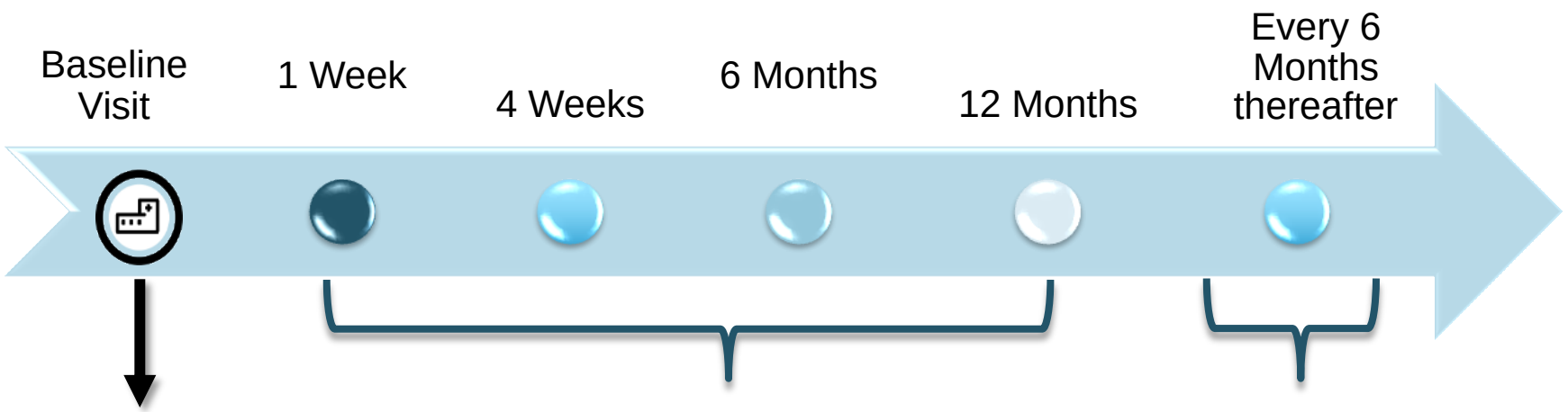
Outcome Collection in the US



Site Enrollment

- Baseline Data
- Randomization
- Creatinine, eGFR, and K^+

Site Study Visits

- No in-person visits required
- Creatinine, eGFR, and K^+
- Mediation adherence and cross-over
- Outcomes

DCRI Call Center

- Medication adherence and cross-over
- Outcomes