



# LIFE risk score bij hartfalen

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Cardioloog

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# LIFE-HF risk score bij hartfalen

## Voorjaarsbijeenkomst Hartfalen 2023

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# Disclosures

- Received unrestricted research grants or consultant fees from Bayer, Boehringer Ingelheim, Amgen, Vifor, Novartis.

# Hartfalen – what’s in a name.

## Consensus Statement

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### **Universal Definition and Classification of Heart Failure**

A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure

*Endorsed by Canadian Heart Failure Society, Heart Failure Association of India, the Cardiac Society of Australia and New Zealand, and the Chinese Heart Failure Association*

“a *clinical syndrome* characterized by *typical signs and symptoms*, caused by a *structural and/or functional cardiac abnormality*, resulting in a *reduced cardiac output and/or elevated intracardiac pressures* at rest or during stress”

Bozkurt et al, JCF, 2021

# Voorgestelde definitie voor hartfalen.

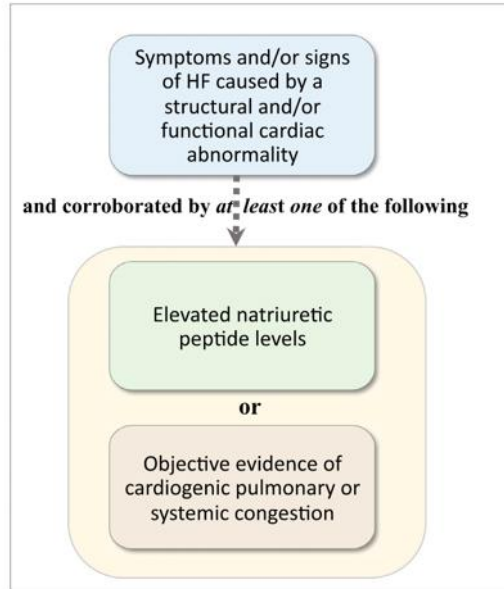
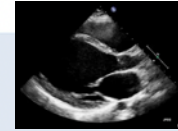


Figure 1. Universal definition of HF.

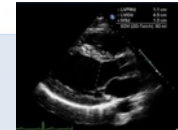
## HF with reduced EF (HFrEF):

- HF with LVEF  $\leq 40\%$



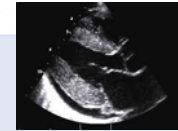
## HF with mildly reduced EF (HFmrEF):

- HF with LVEF 41-49%



## HF with preserved EF (HFpEF):

- HF with LVEF  $\geq 50\%$



## HF with improved EF (HFimpEF):

- HF with a baseline LVEF  $\leq 40\%$ , a  $\geq 10$  point increase from baseline LVEF, and a second measurement of LVEF  $> 40\%$

# Cardiomyopathie en hartfalen – niet uitwisselbaar.

CARDIOMYOPATHIE  
PATHOLOGISCHE DIAGNOSE  
SPECIFIEK

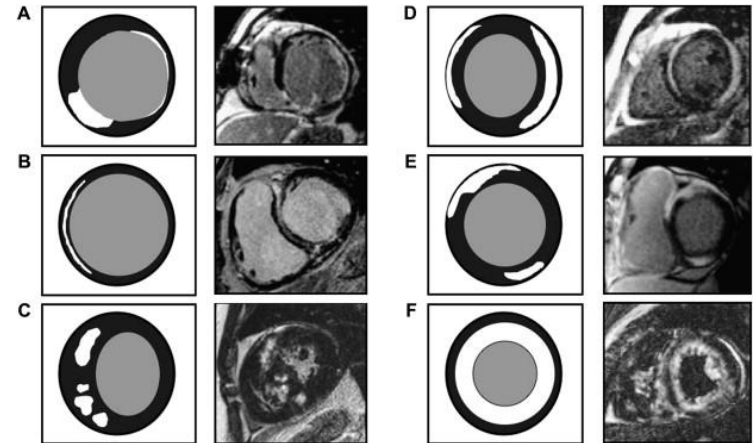
≠

HARTFALEN  
KLINISCHE DIAGNOSE  
ALGEMEEN/BESCHRIJVEND



Vroeger:  
Cardiomyopathie = hartfalen = dezelfde behandeling.

Toekomst:  
generieke hartfalen behandeling  
+ specifieke cardiomyopathie behandeling



J. White et al, MRI Clinic NA, 2007

# Machine learning zal alle aspecten van MRI beïnvloeden.

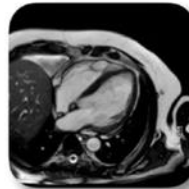
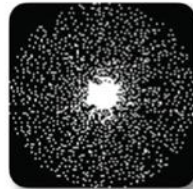
Indication & Patient Scheduling



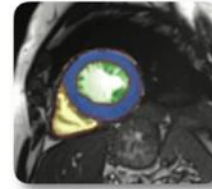
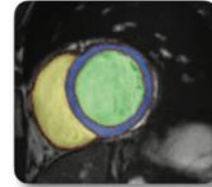
Acquisition



Image Reconstruction & Image Quality



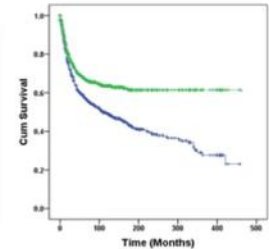
Segmentation, Quantification & Radiomics



Classification & Reporting



Prognosis



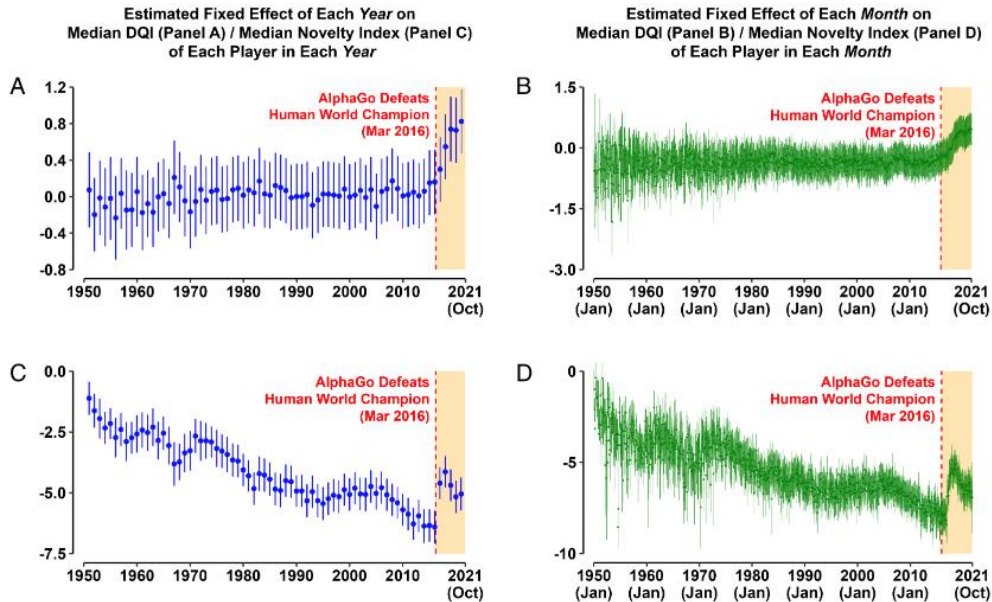
T Leiner et al, J CMR 2019



# Superhuman artificial intelligence can improve human decision-making by increasing novelty

Minkyu Shin<sup>a,1</sup>, Jin Kim<sup>b,c,1</sup>, Bas van Opheusden<sup>a,1</sup>, and Thomas L. Griffiths<sup>d,e</sup>

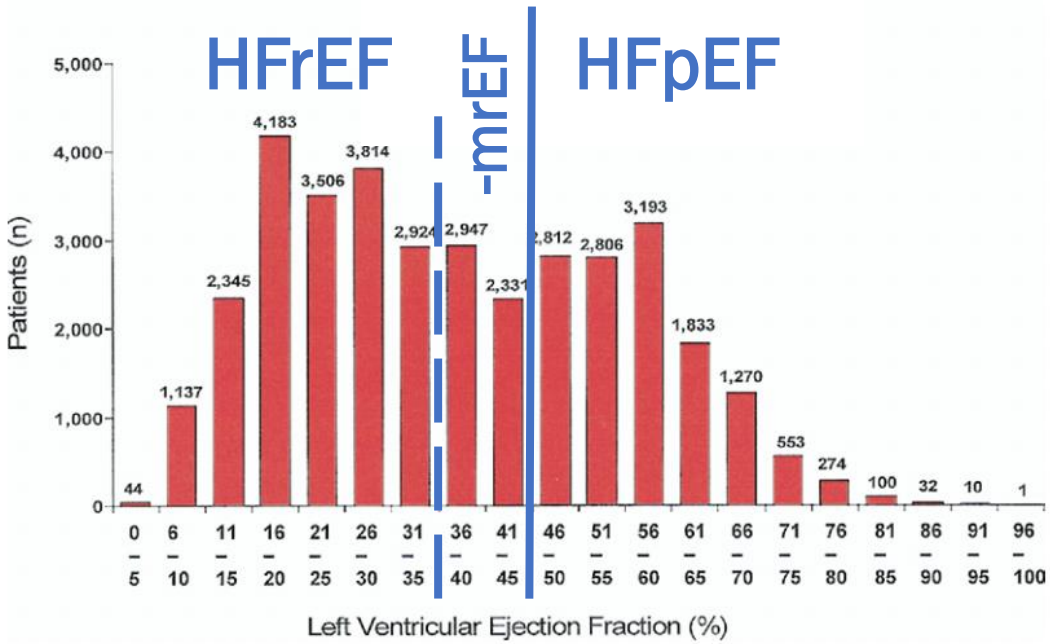
Edited by Michael Gazzaniga, University of California Santa Barbara College of Letters and Science, Santa Barbara, CA; received August 31, 2022; accepted December 19, 2022



Bovenmenselijke kunstmatige intelligentie stimuleert mensen tot het afscheid nemen van traditionele strategieën en adopteren met nieuwe strategieën



# Rond 60-50% van HF opnames betreft patiënten met HFrEF (LVEF<40%)



Fonarow, JACC, 2007

# Fenotypes van hartfalen- HFrEF, HFmrEF, en HFpEF

	HFrEF	HFmrEF	HFpEF
<b>Phenotype</b>			
Age	↑	↑↑	↑↑↑
Women	↓↓	↓	↑
Ischaemic heart disease	↑↑↑	↑↑↑	↑
Atrial fibrillation	↑	↑↑	↑↑↑
Hypertension	↑	↑↑	↑↑↑
Chronic kidney disease	↑↑	↑↑	↑↑↑
Natriuretic peptide levels	↑↑↑	↑	↑
<b>Prognosis</b>			
Cardiovascular risk	↑↑↑	↑	↑
Non-cardiovascular risk	↑	↑	↑↑
<b>Treatment</b>			
RAS inhibitors, β-Blockers, MRA, ARNI, SGLT2i	Relative effect	+++ (Ongoing trials on MRA and SGLT2i)	±
	Absolute effect	+++	± (Ongoing trials on MRA and SGLT2i)
	ICD, CRT	+++	±

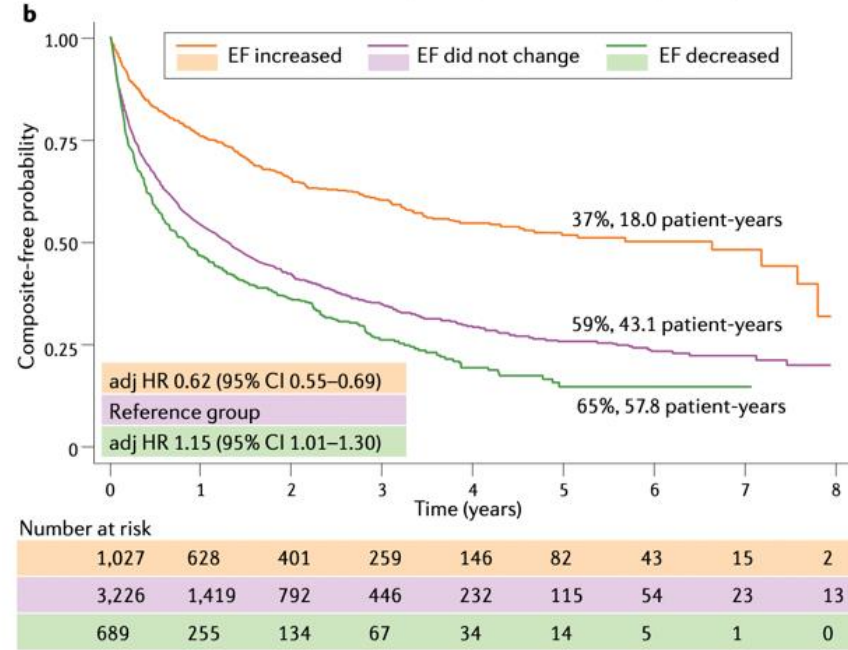
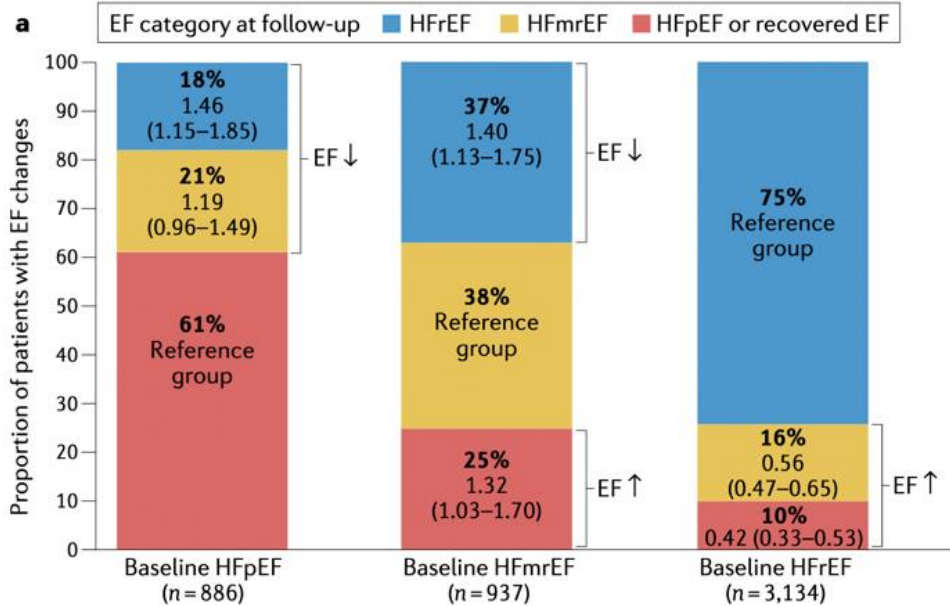
■ HFrEF characteristics   
 ■ HFpEF characteristics   
 ■ Intermediate characteristics

HFrEF vs -mrEF en -pEF:

- Vaker mannen
- Jongere leeftijd
- Minder atriumfibrilleren en hypertensie
- Hogere spiegels natriuretische peptides

Savarese et al, Nat Reviews Card, 2022

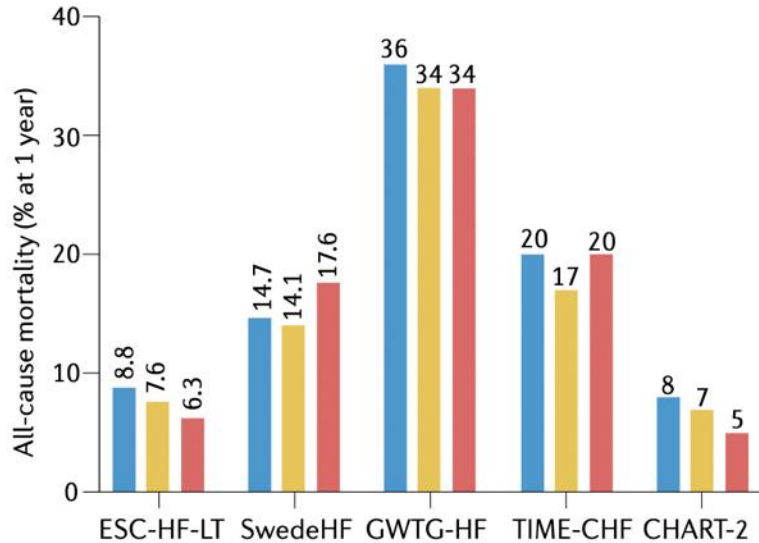
# Patiënt en ziektebeloop door EF stadia heen



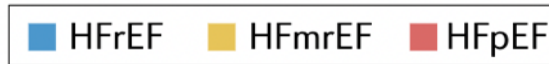
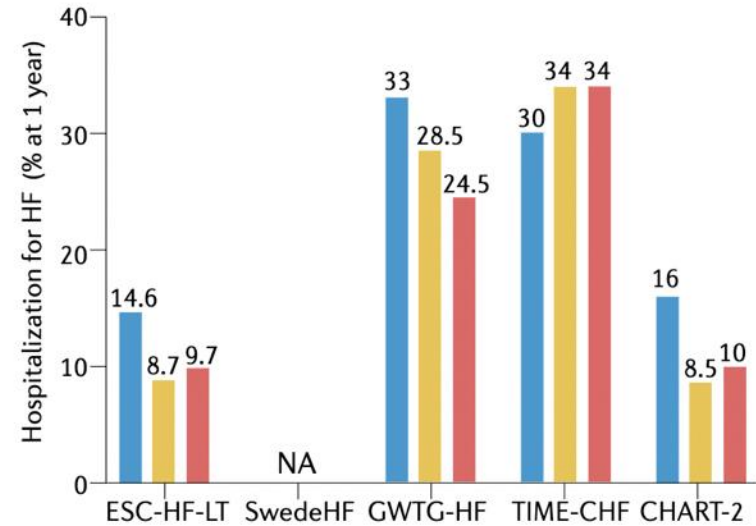
Savarese et al, Nat Reviews Card, 2022

# Impact van HF-EF stadiering op prognose

**a** 1-year all-cause mortality

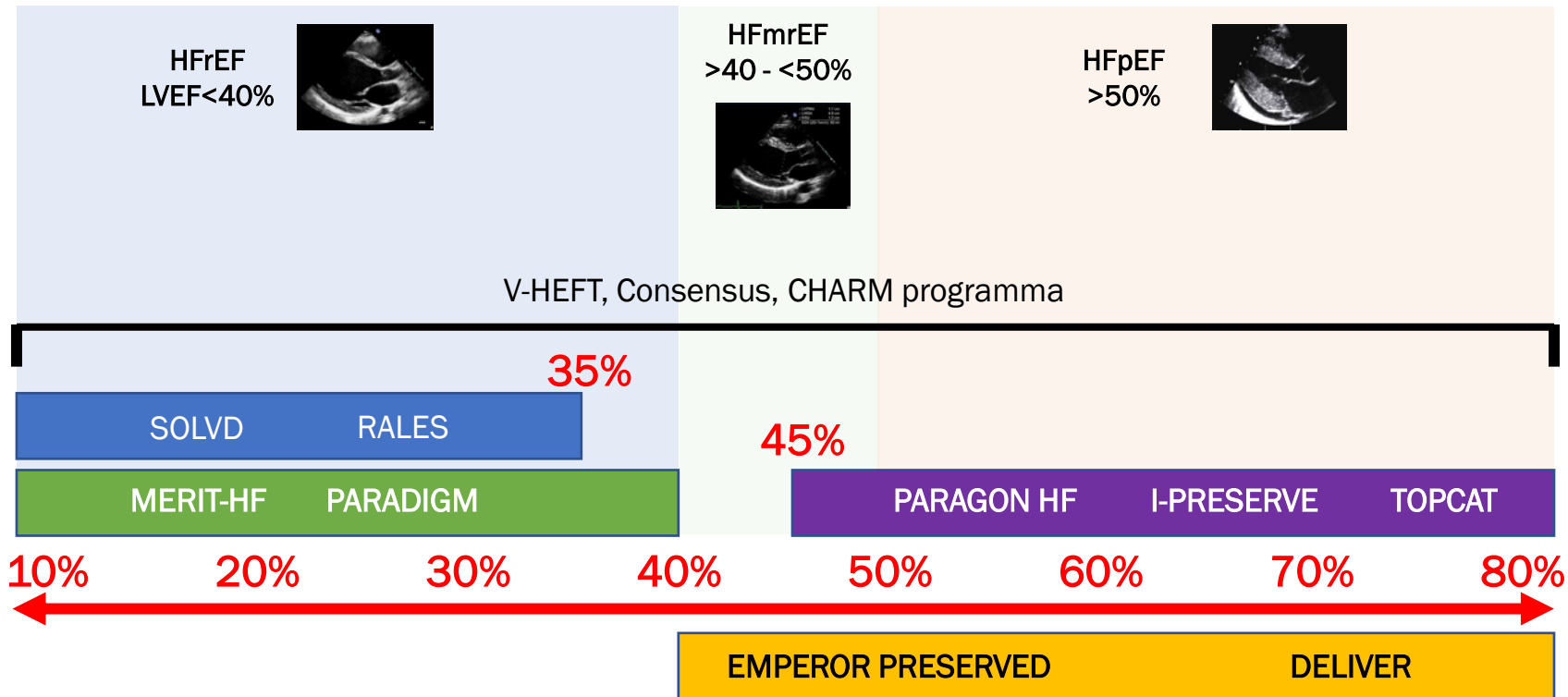


**c** 1-year rate of hospitalization for HF



Savarese et al, Nat Reviews Card, 2022

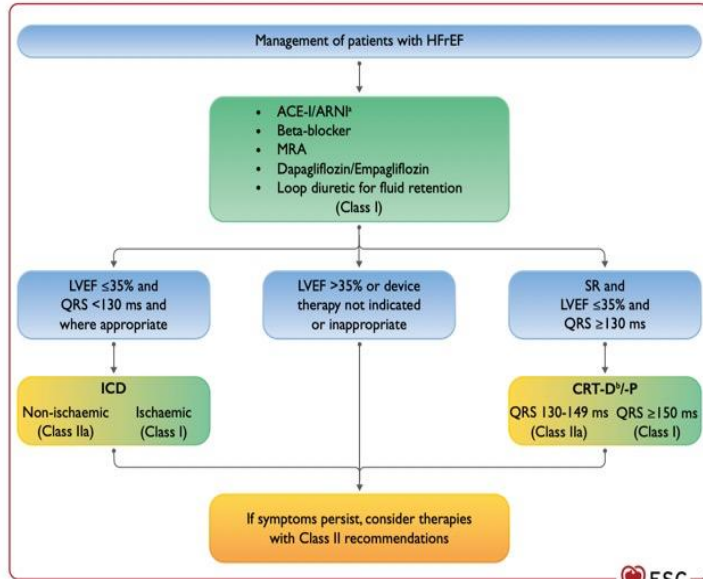
# LV Ejectiefractie en Ontwikkeling van Clinical Trial Programma in Hartfalen



# Major breakthroughs in Heart Failure Care – HFrEF (LVEF<40%)

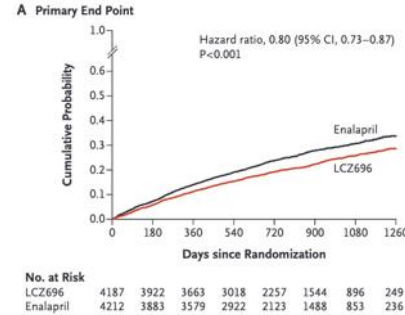
## GUIDELINE RECOMMENDED MEDICAL TREATMENT

Five major pathways; Four drug classes

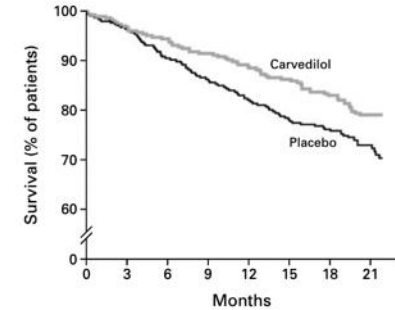


T McDonagh et al, Eur Heart J, 2021

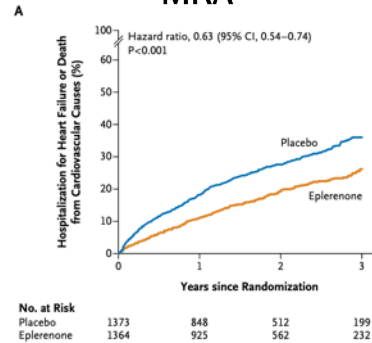
### ARNI



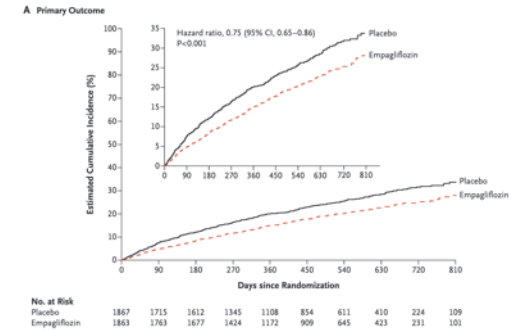
### Betablocker



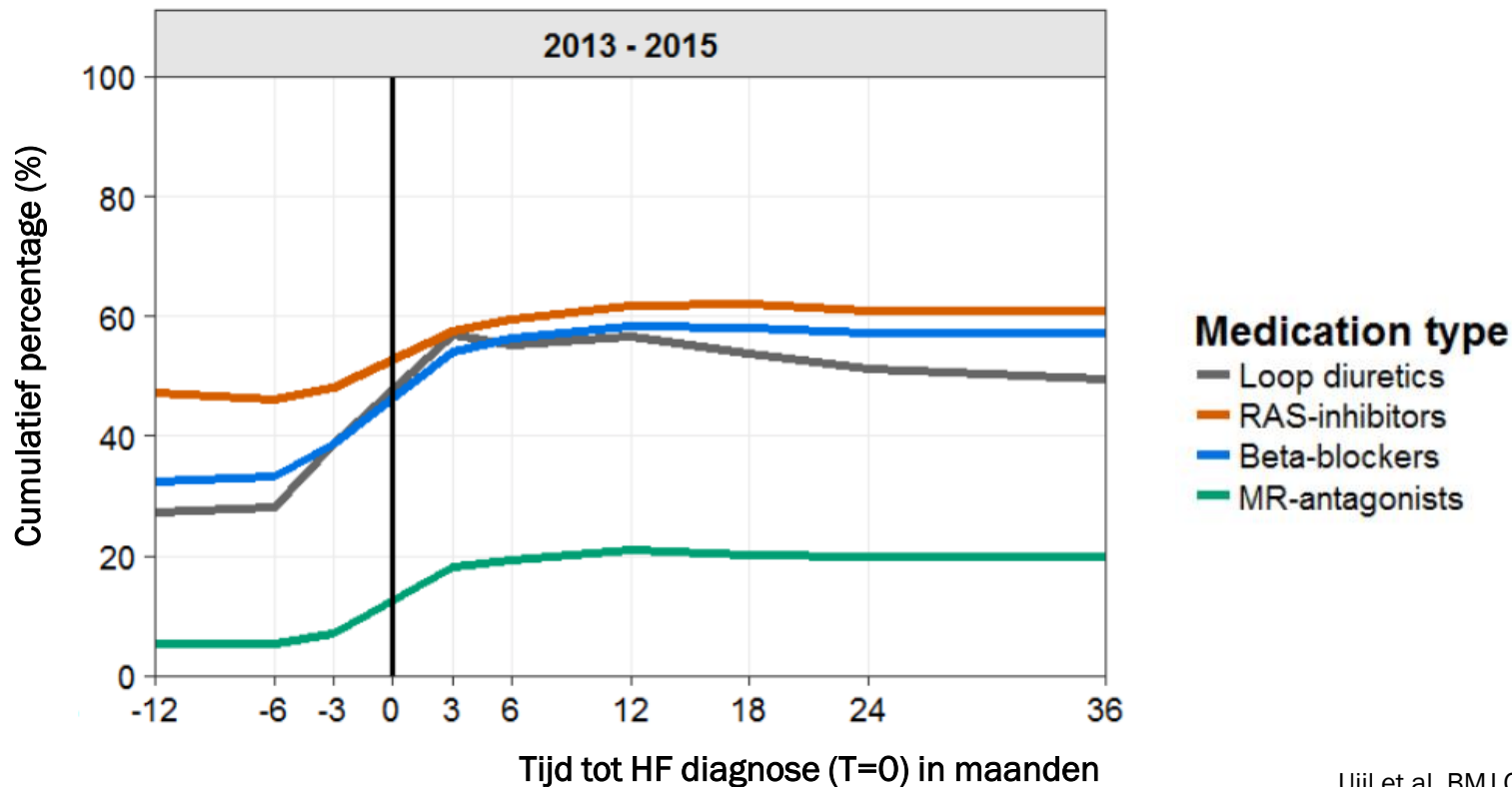
### MRA



### SGLT2i



# Medicatiewijzigingen in de tijd voor, kort na, en jaren na een hartfalen diagnose.

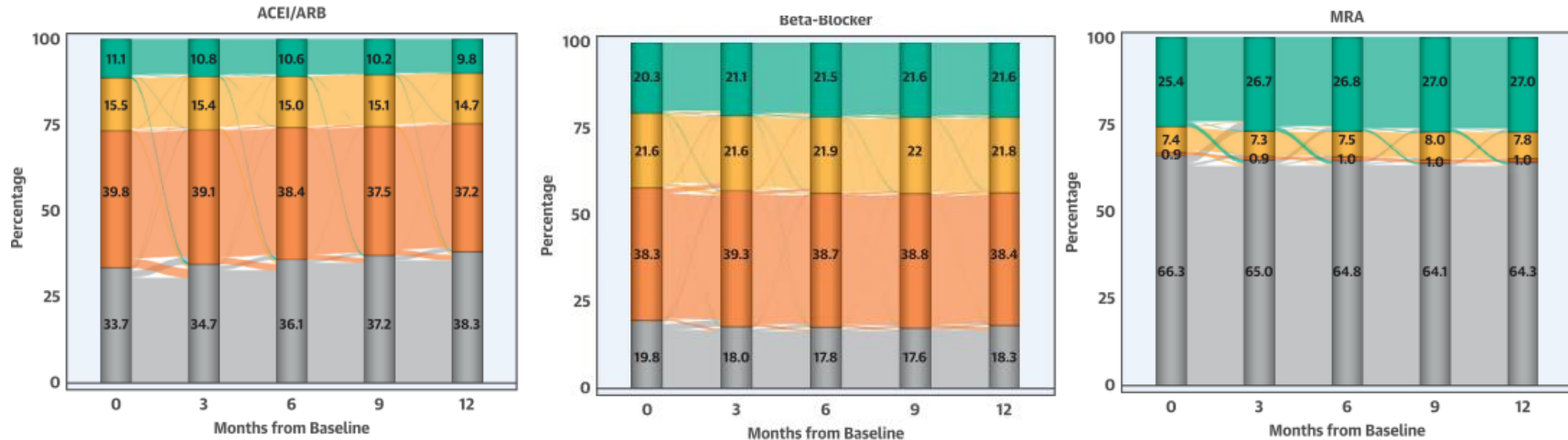


Uijl et al, BMJ Open, 2020

# Titration of Medical Therapy for Heart Failure With Reduced Ejection Fraction



Stephen J. Greene, MD,<sup>a,b</sup> Gregg C. Fonarow, MD,<sup>c</sup> Adam D. DeVore, MD, MHS,<sup>a,b</sup> Puza P. Sharma, MBBS, MPH, PhD,<sup>d</sup> Muthiah Vaduganathan, MD, MPH,<sup>e</sup> Nancy M. Albert, PhD,<sup>f</sup> Carol I. Duffy, DO,<sup>d</sup> C. Larry Hill, PhD,<sup>a</sup> Kevin McCague, MA,<sup>d</sup> J. Herbert Patterson, PHARM.D,<sup>g</sup> John A. Spertus, MD, MPH,<sup>h</sup> Laine Thomas, PhD,<sup>a</sup> Fredonia B. Williams, EdD,<sup>i</sup> Adrian F. Hernandez, MD, MHS,<sup>a,b</sup> Javed Butler, MD, MPH, MBA<sup>j</sup>

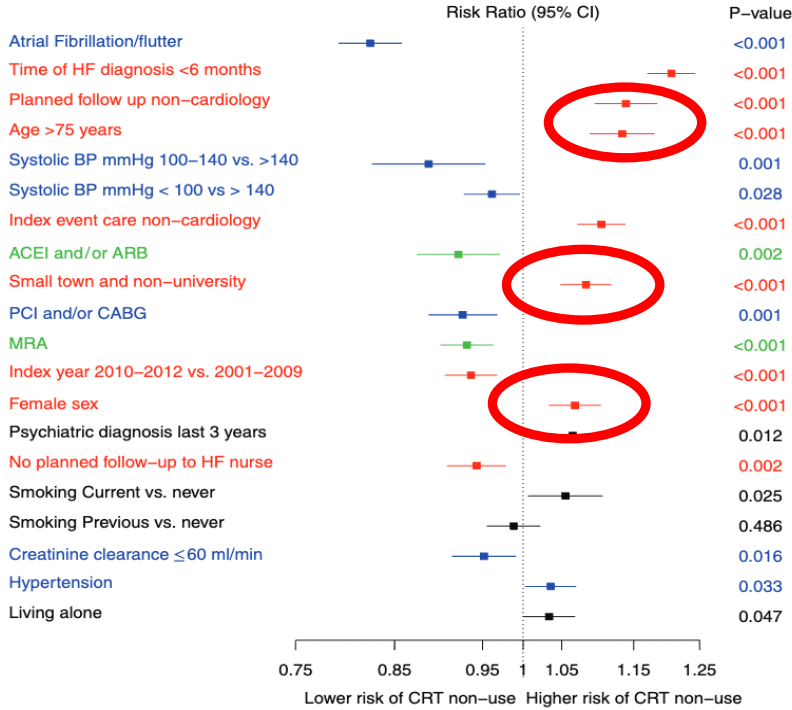


**US based CHAMP-HF registry showed that most eligible HFrEF patients did not receive target doses of medical therapy at any point during follow-up, and few patients had doses increased over time.**



# Study implementation using HF registries: non-use of CRT and ICD therapy

A



European Journal of Heart Failure (2017) 19, 1270-1279  
doi:10.1002/ehf.781

RESEARCH ARTICLE

## 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<sup>1,2\*</sup>, Frieder Braunschweig<sup>1,2</sup>, Lina Benson<sup>3</sup>, Marcus Ståhlberg<sup>1,2</sup>, Ulf Dahlström<sup>4</sup>, and Cecilia Linde<sup>1,2</sup>

Lund et al, Eur J Heart Failure, 19;1270-1279, 2017

## Differential Impact of Heart Failure With Reduced Ejection Fraction on Men and Women



**TABLE 2** Continued

	Women (n = 3,357)	Men (n = 12,058)	p Value
Digitalis	1,089 (32.4)	3,692 (30.6)	0.048
Beta-blocker	3,075 (91.6)	11,168 (92.6)	0.049
MRA	1,555 (46.3)	5,718 (47.4)	0.2599
ACE inhibitor	2,842 (84.7)	10,697 (88.7)	<0.0001
ARB	551 (16.4)	1,434 (11.9)	<0.0001
CCB§	330 (9.8)	1,035 (8.6)	0.0245
Statins	1,598 (47.6)	6,787 (56.3)	<0.0001
Aspirin	1,557 (46.4)	6,393 (53.0)	<0.0001
Anticoagulants	897 (26.7)	3,906 (32.4)	<0.0001
In patients with atrial fibrillation on ECG	67.1	71.2	0.029
In patients with atrial fibrillation history	60.6	66.6	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥2	67.1	71.5	0.019
Pacemaker	310 (9.2)	1,490 (12.4)	<0.0001
ICD (including CRT-D)	290 (8.6)	2,001 (16.6)	<0.0001
ICD only	196 (5.8)	1,371 (11.4)	<0.0001
CRT-P or CRT-D	137 (4.1)	830 (6.9)	<0.0001

*Women with HFrEF live longer, but have poorer quality, higher self-reported psychological and physical disability. Women are undertreated, without a compelling reason for this shortfall.*

# Wetenschappelijke evolutie - roadmap



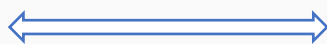
# LIFE HF onderzoeksgroep en acknowledgment

- Over 65,000 patients who consented to participate in the trials and/or registries worldwide used for this study.
- LIFE-HF investigators
  - **Pascal Burger** (UMCU, NL)
  - **Gianluigi Savarese** (Karolinska, Stockholm, Sweden)
  - **Jasper Tromp** (University of Singapore, Singapore)
  - **Carly Adamson** (University of Glasgow, UK)
  - **Pardeep Jhund** (University of Glasgow, UK)
  - **Lina Benson** (Karolinska, Stockholm, Sweden)
  - **Camilla Hage** (Karolinska, Stockholm, Sweden)
  - **Wan Ting Tay** (University of Singapore, Singapore)
  - **Scott Solomon** (Brigham and Women's Hospital, Boston, US)
  - **Milton Packer** (Baylor Heart and Vascular Inst, Dallas, US)
  - **Frank Visseren** (UMCU, NL)
  - **John McMurray** (University of Glasgow, UK)
  - **Carolyn Lam** (National Heart Center Singapore, Singapore)
  - **Lars Lund** (Karolinska Hospital, Stockholm, Sweden)
  - **Jannick Dorresteijn** (UMCU, NL)
  - **Arend Mosterd** (Meander MC, Amersfoort, NL)
- ESC Cardiovascular Risk Collaboration
  - **Xavier Rosello** (Cardiovascular Health Center, Madrid, Spain)
  - **John W. McEvoy** (Institute for Prevention and CV Health, Galway, Ireland)
  - **Dirk De Bacquer** (Dpt. Public Health, Gent, Belgium)
  - **Adam Timmis** (Queen Mary University of London, UK)
  - **Panos Vardas** (Heraklion University Hospital, Greece)
  - **Ian Graham** (Trinity University, Dublin, Ireland)
  - **Emanuele Di Angelantonio** (Cambridge, UK)



# Hoe vertaal je onderzoeksresultaten uit klinische trials naar je patiënt in de spreekkamer?

## GROEPSNIVEAU



## INDIVIDUEEL NIVEAU

- Hazard ratio
- Absoluut risicoreductie
- Number needed to treat
- Overleving (%) op X jaren

- Mediane overleving
- Gewonnen levensjaren per medicijn/ingreep/device

# Levenswinst van quadruple medicatie in hartfalen met LVEF <40%.

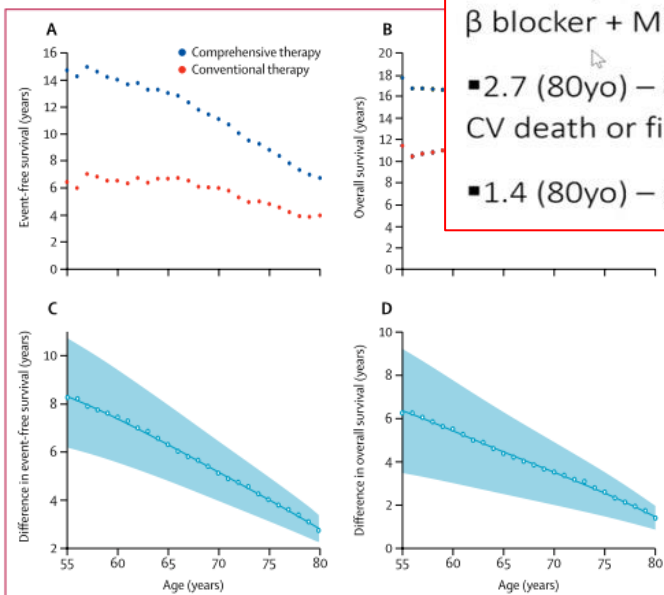
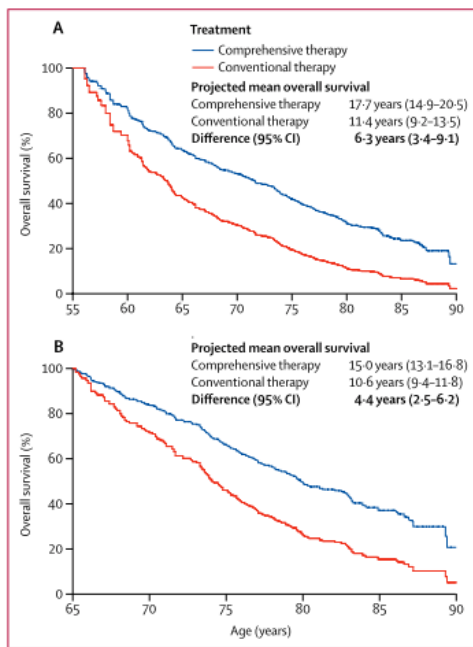


Figure 4: Treatment benefits on overall survival and event-free survival with comprehensive disease-modifying therapy vs conventional therapy

Compared to conventional therapy with ACEi/ARB +  $\beta$  blocker, comprehensive therapy with ARNI +  $\beta$  blocker + MRA + SGLT2i provides

- 2.7 (80yo) – 8.3 (55yo) additional years free from CV death or first hospital admission for HF;
- 1.4 (80yo) – 6.3 (55yo) additional years of survival

# Aims and objectives

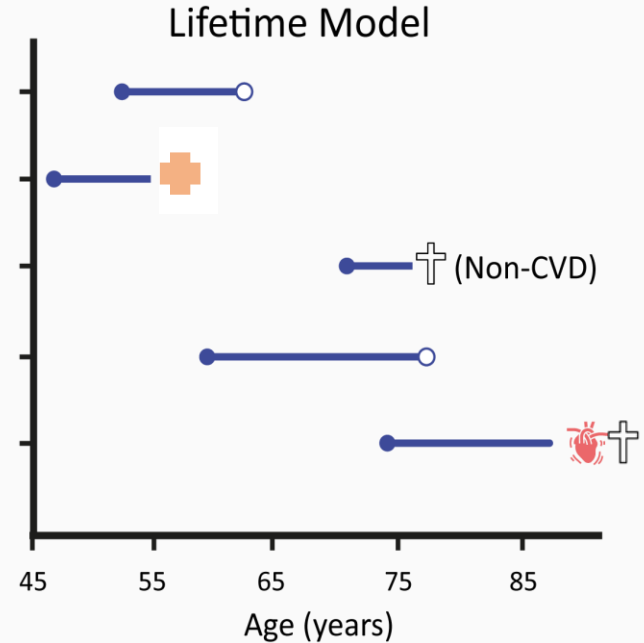
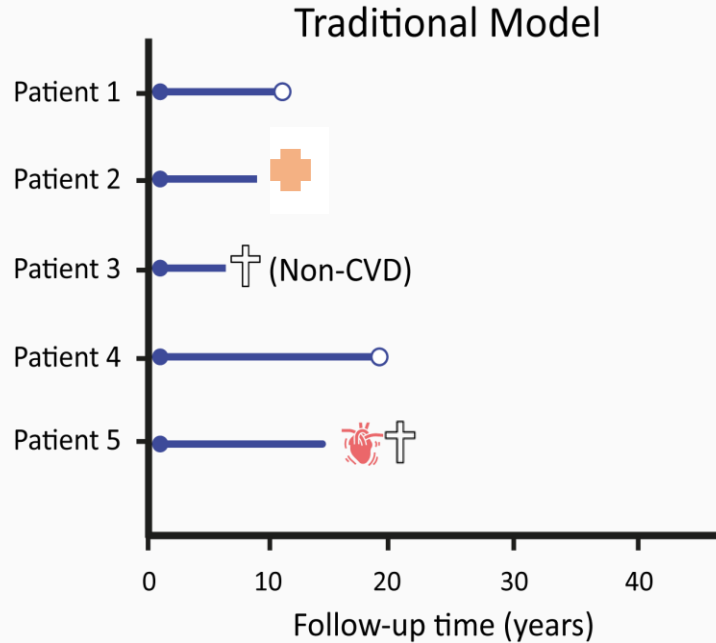
- Een model voor lifetime predictie ontwikkelen om patiënten te informeren over hun individuele overleving zonder ziekenhuisopname voor hartfalen en/of cardiovasculaire mortaliteit.
- Om patiënten te informeren hoe medische behandeling voor HFrEF hun individuele lifetime risico op hartfalenuitkomsten zal beïnvloeden.

# Lifetime risk - Statistical Considerations

- Three cause-specific Cox Proportional Hazard Models.
  - Age as time scale (i.e. left truncation and right censoring).
- Datasets
  - PARADIGM and ATMOSPHERE trials (n= 15,415)
  - External validation in Swede-HF, ASIAN-HF registries, and DAPA-HF trial (n= 51,286)
- Outcome measures
  1. Cardiovascular mortality or first HF hospitalisation.
  2. Cardiovascular mortality.
  3. Non-cardiovascular mortality.
- Predictors
  - 24 candidate predictors backwards selected using AIC.
- Validation
  - Internal validation using C-statistics for discrimination, and calibration plots of the observed vs predicted 2-year risk of outcome.



# Lifetime survival



# Data used to develop LIFE-HF models – PARADIGM and ATMOSPHERE trials. Baseline characteristics

	PARADIGM-HF <sup>1</sup> (n= 8399)	ATMOSPHERE <sup>2</sup> (n= 7016)	Derivation cohort (n = 15,415)
Age (years)	63.8 ±11.4	63.2 ±11.8	63.5 ±11.6
Sex (male)	6,567 (78%)	5,491 (78%)	12,058 (78%)
Ischemic aetiology	4,147 (49%)	3,211 (46%)	7,358 (48%)
NYHA II/III/IV (%)	70 / 24 / 1	63 / 35 / 2	67 / 29 / 1
LVEF (mean, %)	29.5 ±6.2	28.4 ±5.7	29.0 ±6.0
Prior HF Hospitalisation	5,274 (63%)	4,188 (60%)	9,462 (61%)
NT-proBNP (pg/mL) – median (IQR)	1615 (888-3231)	1198 (634-2259)	1418 (770-2774)
Mean systolic BP (mmHg)	128 ±17	127 ±18	128 ±17

<sup>1</sup> McMurray et al, NEJM, 2014;371:993-1004

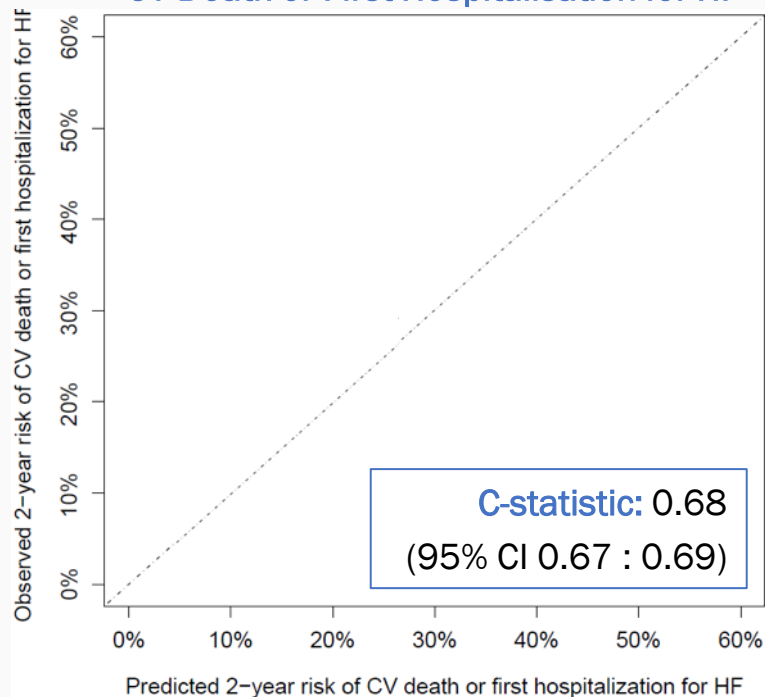
<sup>2</sup> McMurray et al, NEJM, 2016; 374:1521-1532

# Lifetime model - Results

Predictor	CV death or first hospitalization for HF, HR (95% CI)	CV death, HR (95% CI)	Non-CV mortality, HR (95% CI)
Sex (male)	1.19 (1.10-1.29)	1.27 (1.15-1.41)	1.51 (1.20-1.90)
NYHA class (III/IV)	1.32 (1.25-1.41)	1.39 (1.29-1.50)	1.01 (0.84-1.20)
Prior hospitalization for HF	1.30 (1.22-1.39)	1.11 (1.03-1.21)	1.13 (0.95-1.35)
Diabetes mellitus	1.47 (1.38-1.57)	1.26 (1.16-1.37)	1.29 (1.07-1.55)
Extracardiac vascular disease	1.33 (1.23-1.43)	1.30 (1.19-1.43)	1.30 (1.06-1.59)
Systolic blood pressure	0.85 (0.81-0.89)	0.82 (0.77-0.86)	1.01 (0.89-1.15)
LVEF	0.87 (0.82-0.93)	0.90 (0.85-0.95)	0.97 (0.85-1.10)
NT-proBNP	1.72 (1.64-1.79)	1.80 (1.71-1.90)	1.37 (1.22-1.55)
Total bilirubin	1.08 (1.05-1.11)	1.06 (1.02-1.09)	1.07 (0.99-1.16)
Uric acid	1.15 (1.11-1.20)	1.11 (1.06-1.17)	1.05 (0.93-1.18)

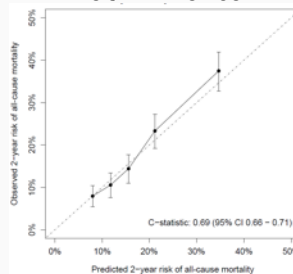
# LIFE-HF Model Performance

## CV Death or First Hospitalisation for HF

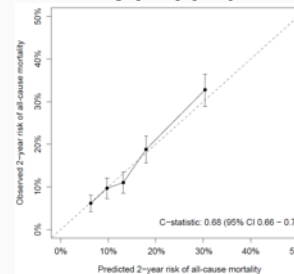


## Geographic Regions

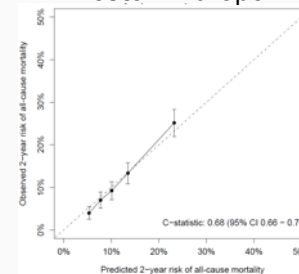
### Latin America



### Asia-Pacific

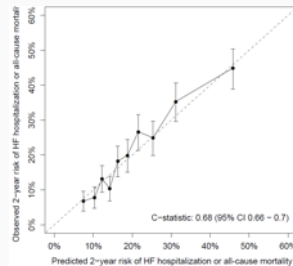


### Western Europe

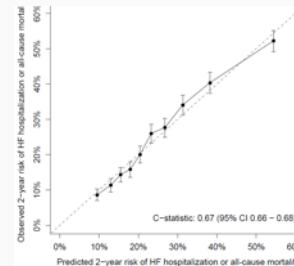


## Sex

### Female



### Male



# External Validation

## Swede-HF registry, Asian-HF registry, DAPA-HF trial

### EXTERNAL VALIDATION

DERIVATION  
(n = 15,415)

Age: 63.5 ±11.6

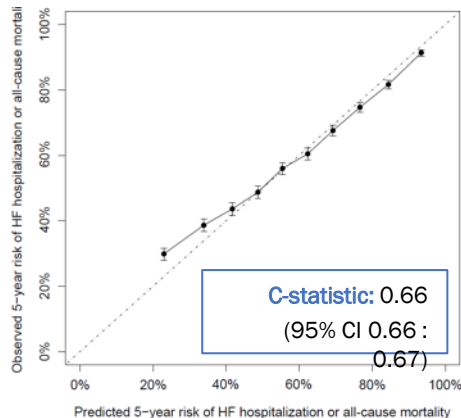
78% male

25% NYHA III/IV

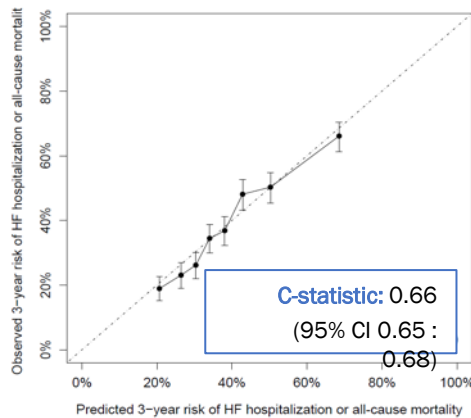
1418 pg/ml

Incidence CV  
mortality and/or  
HHF: 119 /  
1000PY

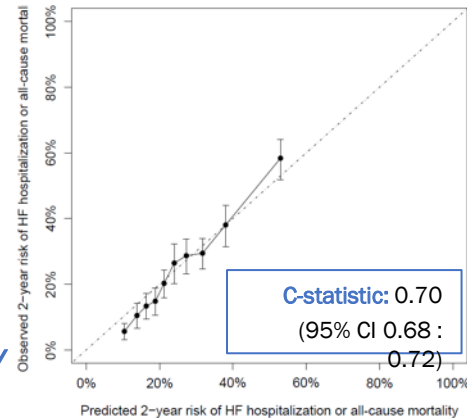
SWEDE-HF<sup>1</sup> (n = 42,063)



ASIAN-HF<sup>2</sup> (n = 4,479)



DAPA-HF<sup>3</sup> trial (n = 4,744)



<sup>1</sup> Å Jonsson et al, EJHF;12:25-31;

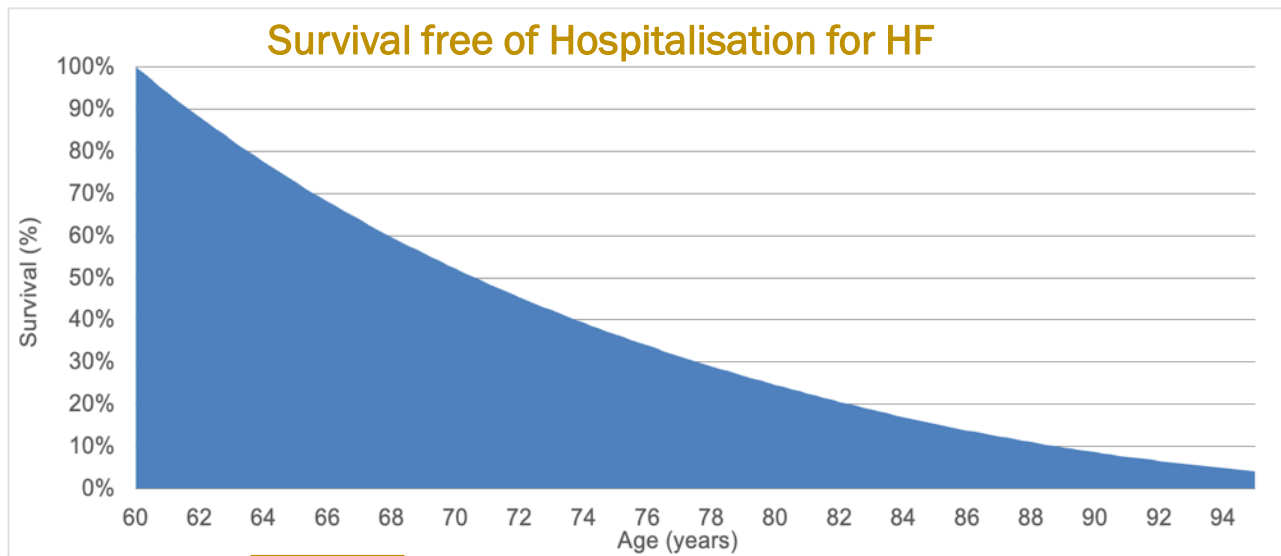
<sup>2</sup> CS Lam et al, EJHF, 2013; 15:928-936; <sup>3</sup> JJV McMurray et al, NEJM;381;1995-2008

# Prediction of Individual Risk and Life Expectancy

Age	Cumulative HF hospitalization-free survival	Risk of CV death or hospitalization for HF (%)	Non-CV mortality risk (%)
60	1		
60.25	0.984		
60.5	0.969		
60.75	0.954		
61	0.939		
61.25	0.924		
61.5	0.909		
61.75	0.895		
62	0.881		
.....			
70	0.522		
70.25	0.513		
70.5	0.504		
70.75	0.495		
71	0.487		

## INDIVIDUAL LIFE TABLES

patient



70,6

Current HF hospitalization-free life expectancy

Life-years gained

$$e_{t+1} - e_t \wedge (1 - a_t - u_t)$$

# Hazard ratios for estimation of benefit from recommended therapies

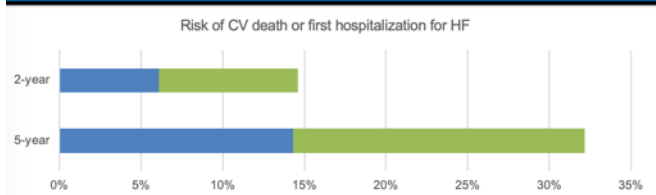
Treatment	Trial(s)/meta-analysis	HR CV death or first hospitalization for HF	HR CV death
ACE inhibitor / ARB	Pooled based on: - SOLVD-T trial - CHARM-Alternative	0.74	0.84
Beta-blocker	Pooled based on meta-analysis (11 RCTs)	0.77	0.76
MRA	Pooled based on: - RALES trial - EMPHASIS-HF trial	0.67	0.72
ARNI	PARADIGM-HF trial	0.80	0.80
SGLT2 inhibitor	Meta-analysis, including: - DAPA-HF trial - EMPEROR-Reduced trial	0.74	0.86

# LIFE-HF interactive calculator

## Patient example 1: Hoog risico, jonge patiënt

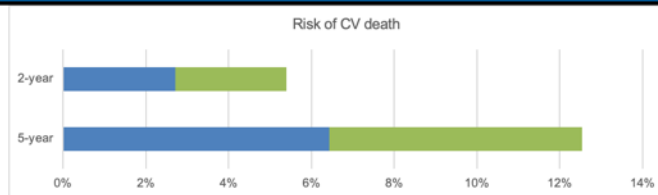


### LIFE-HF Calculator



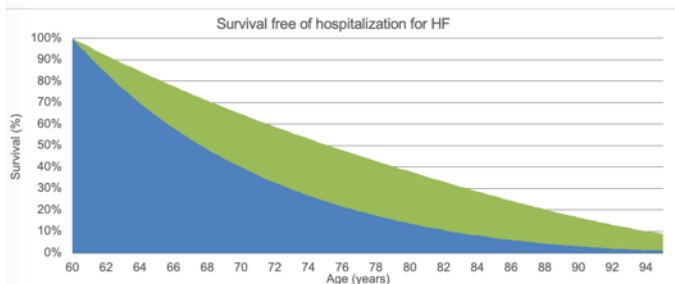
14,6%      8,5%      32,2%      17,9%

Current 2-year risk      2-year ARR      Current 5-year risk      5-year ARR



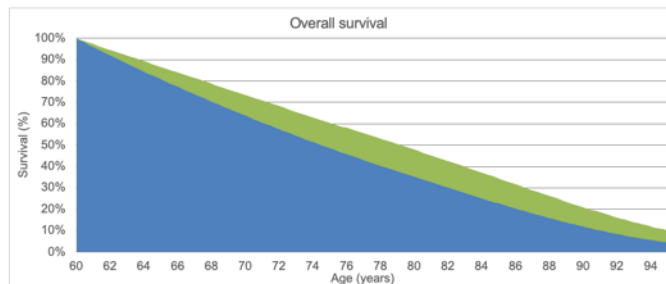
5,4%      2,7%      12,5%      6,1%

Current 2-year risk      2-year ARR      Current 5-year risk      5-year ARR



67,6      7,6

Current HF hospitalization-free life expectancy      Life-years gained



74,5      4,7

Current overall life expectancy      Life-years gained

### Current treatment:

- ACEi
- Betablocker

### Intended treatment:

- ARNI
- Betablocker
- MRA
- SGLT2i



# LIFE-HF interactive calculator

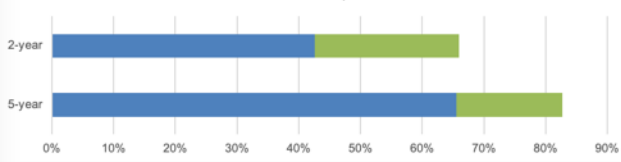
## Patient example 2: Hoog risico cardiogeriatrische patiënt

Groene Hart  
Open



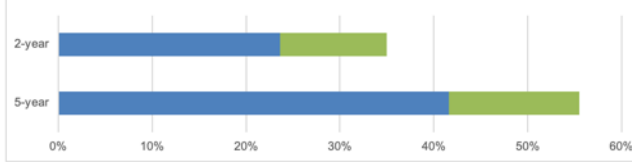
### LIFE-HF Calculator

Risk of CV death or first hospitalization for HF



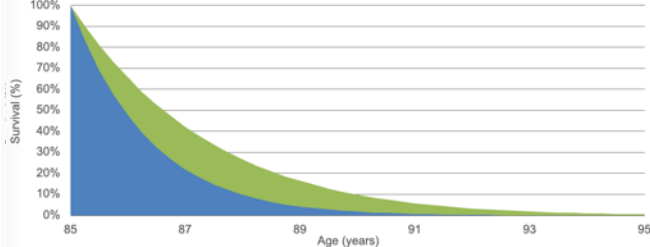
66,0% Current 2-year risk  
23,4% 2-year ARR  
82,7% Current 5-year risk  
17,1% 5-year ARR

Risk of CV death



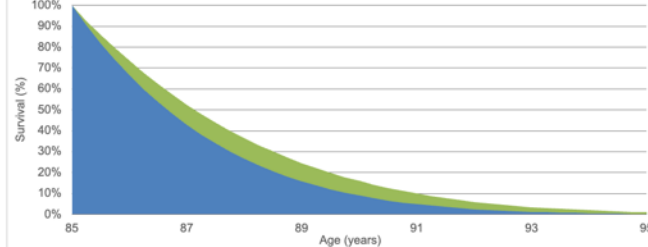
35,0% Current 2-year risk  
11,3% 2-year ARR  
55,5% Current 5-year risk  
13,9% 5-year ARR

Survival free of hospitalization for HF



85,9 Current HF hospitalization-free life expectancy  
0,7 Life-years gained

Overall survival



86,7 Current overall life expectancy  
0,4 Life-years gained

### Current treatment:

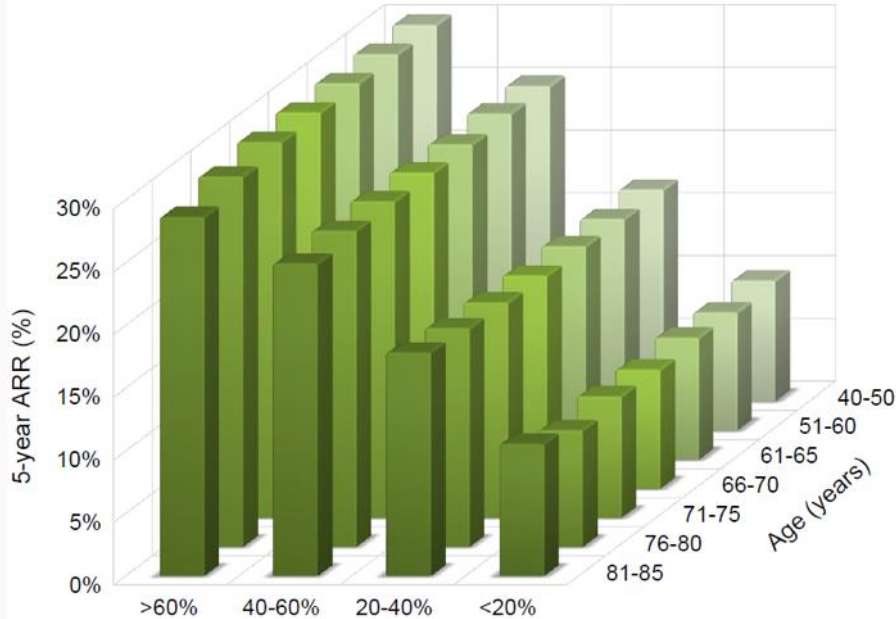
- ACEi
- Betablocker

### Intended treatment:

- ACEi (ARNI failed)
- Betablocker
- MRA
- SGLT2i

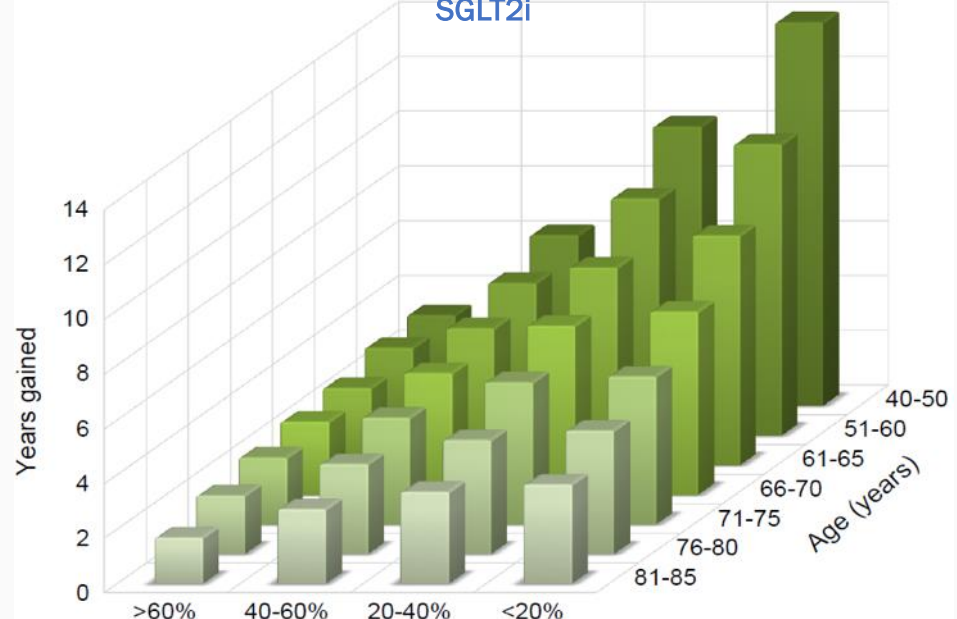
# Winst van behandeling gestratificeerd voor leeftijd en risico

5-year Absolute Risk Reduction MRA + ARNI + SGLT2i

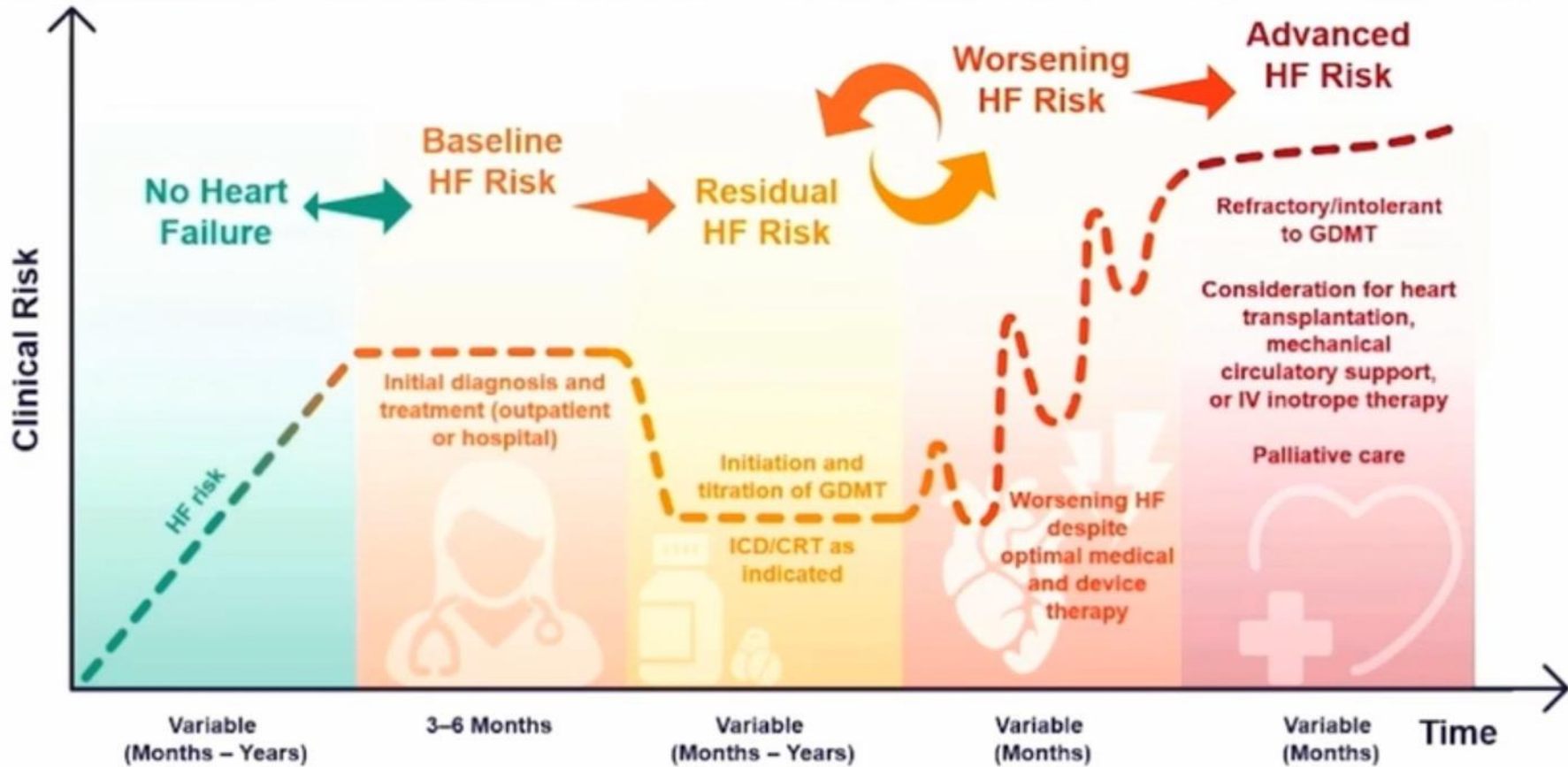


5-year baseline risk of CV death or HF hospitalization

HF Hospitalisation-free life-years gained from MRA + ARNI + SGLT2i



5-year baseline risk of CV death or HF hospitalization



Ference, JACC, 2018:1141-56  
 Greene, Circulation Heart Fail, 2020

# Conclusies

- Hartfalen wordt een generieke syndroombehandeling in combinatie met een cardiomyopathie-behandeling.
- Er bestaan vier klassen medicatie voor hartfalen met verminderde LV-ejectiefractie om mortaliteit en ziekenhuisopnames te voorkomen.
- LIFE-HF schat redelijk accuraat de levensverwachting vrij van hartfalen-opnames in en kan hazard ratio's van klinische trials 'vertalen' naar gezondheidswinst voor de individuele patiënt.
- LIFE-HF kan patiënten met hartfalen beter te informeren over hun prognose en behandel-effect van deze medicatie.

# Conceptueel raamwerk voor HFrEF zorg in Nederland.

## Positie van LIFE-HF

