Cardiovasculaire casuïstiek en innovatie

Een interactief avondprogramma

Behandelrichtlijnen voor hartfalen: Toepassingen in de praktijk

Woensdag 9 oktober 2024

Introductie

De behandeling van hartfalen

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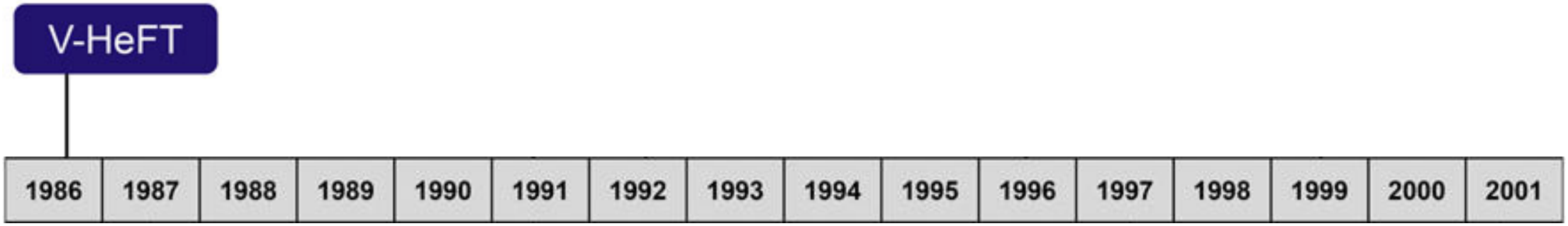
Cardioloog, UMC Groningen

Hoe is de behandeling van hartfalen begonnen?

- Digoxine (nog geen bewijs)
- Furosemide (geen bewijs)
- Spironolactone (nog geen bewijs)
- Nitraat



Eerste studies in patiënten met ernstig hartfalen

- Digoxine (nog geen bewijs)
- Furosemide (geen bewijs)
- Spironolactone (nog geen bewijs)
- Nitraat

+ ACE-inhibitor??

The New England
Journal of Medicine

Volume 316 JUNE 4, 1987 Number 23

EFFECTS OF ENALAPRIL ON MORTALITY IN SEVERE CONGESTIVE HEART FAILURE

Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

THE CONSENSUS TRIAL STUDY GROUP*

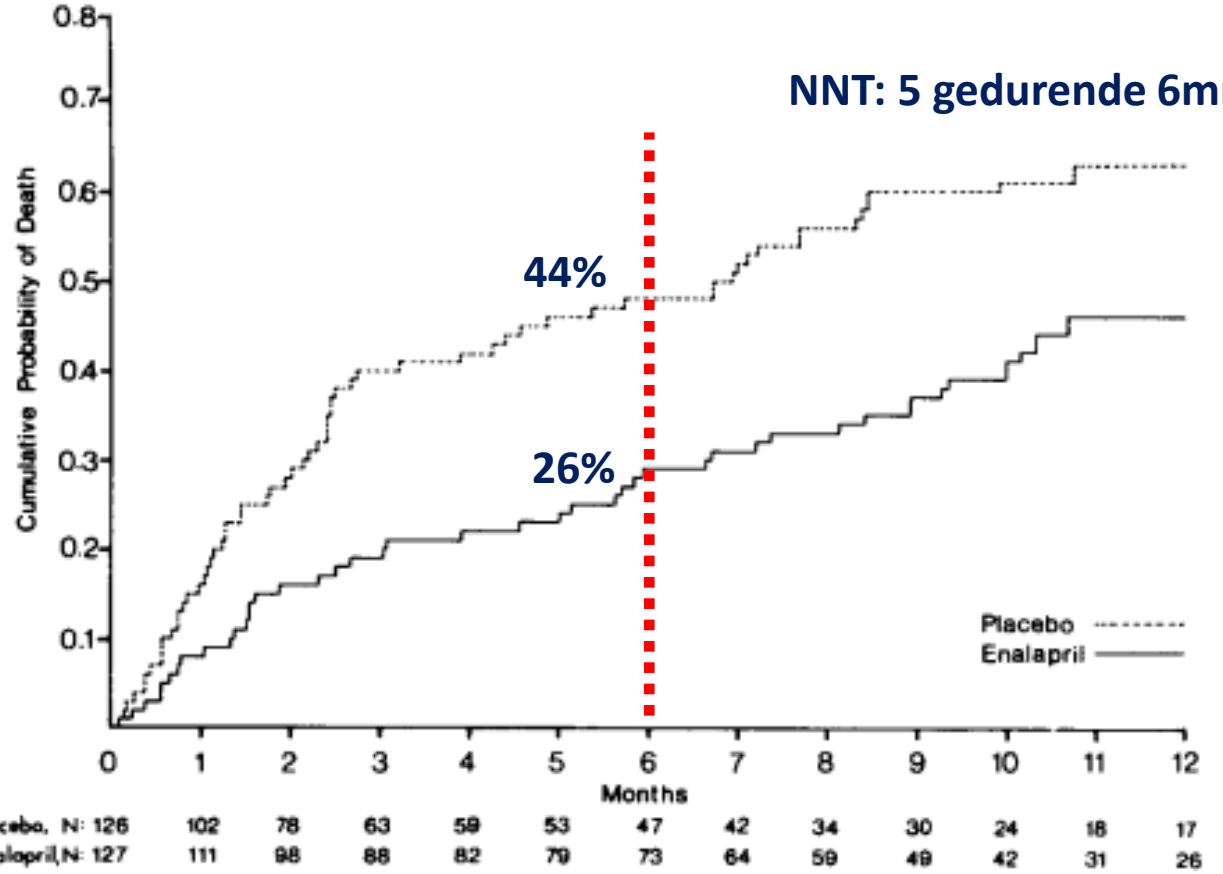
Abstract To evaluate the influence of the angiotensin-converting-enzyme inhibitor enalapril (2.5 to 40 mg per day) on the prognosis of severe congestive heart gressive heart failure (a reduction of 50 percent), whereas no difference was seen in the incidence of sudden cardiac death.

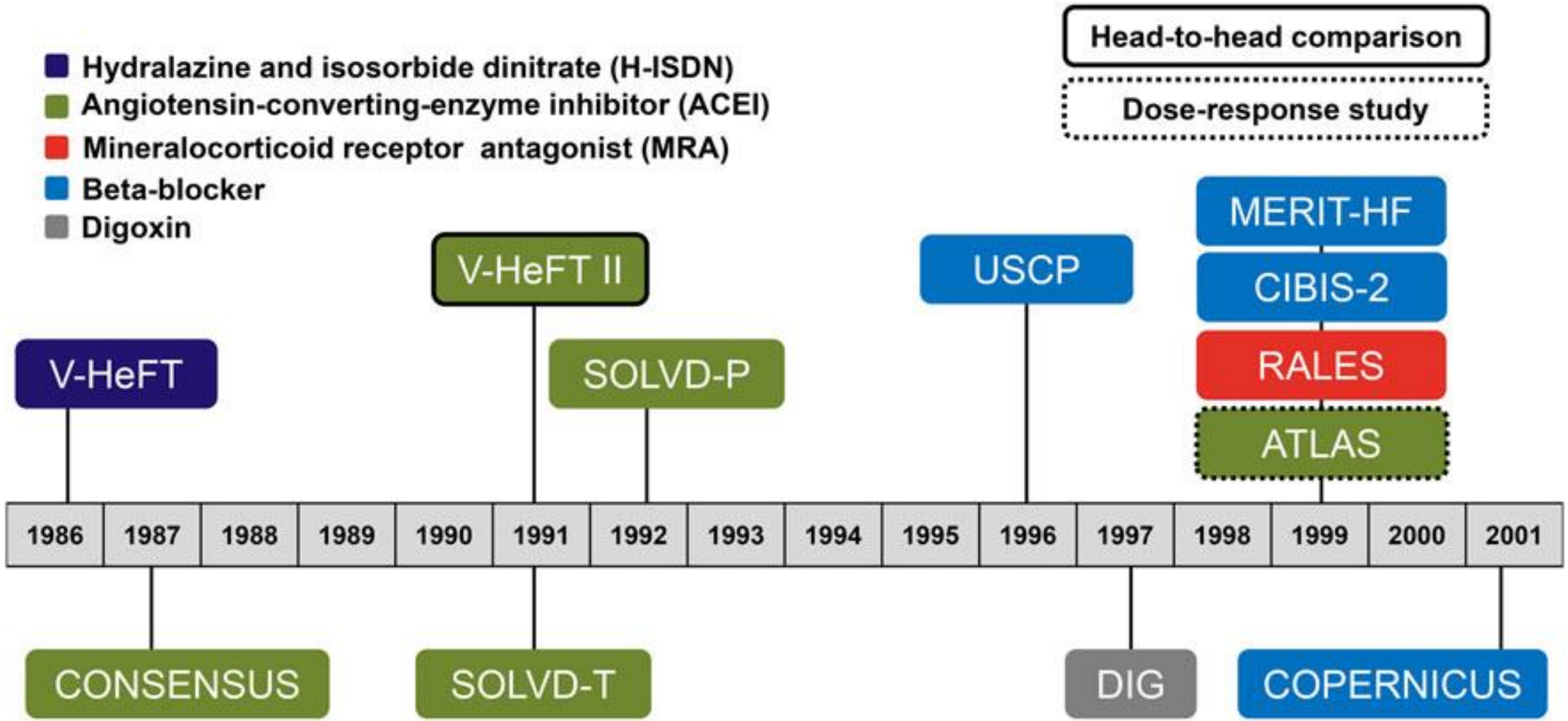
Table 1. Base-Line Clinical Characteristics of Patients in the Two Treatment Groups.

Characteristic	Treatment Group	
	Placebo (N = 126)	Enalapril (N = 127)
	mean	
Age (yr)	70	71
Sex		
Female	29	30
Male	71	70
Etiologic factors		
Coronary artery disease	74	72
Previous myocardial infarction	48	47
Cardiomyopathy	16	14
Drug therapy		
Digitalis	94	92
Beta-blocker	2	4
Diuretics		
Furosemide (mean dose)	98 (200 mg)	98 (210 mg)
Spironolactone (mean dose)	55 (80 mg)	50 (80 mg)
Any other diuretic	10	14
Vasodilators		
Isosorbide dinitrate	45	47

Enalapril vs placebo

NNT: 5 gedurende 6mnd





McMurray EUH 2015

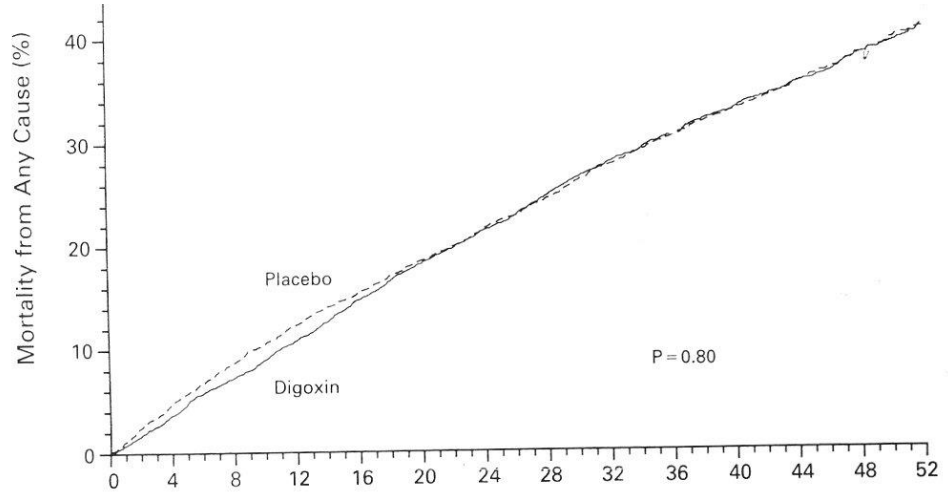
Digoxin?

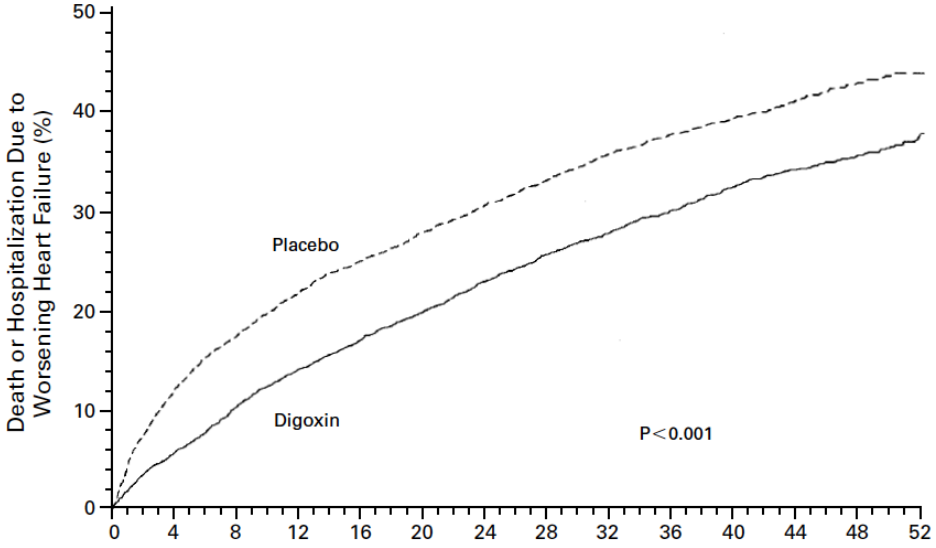
- NEJM 1997
  - Inclusion between 1991-1993
  - N=3403 vs. 3397 patients
  - All patients were in SR
  - LVEF < 45%
  - 87% used ≥ 0.25mg digoxin (high dose)

Characteristic	Digoxin (N=3397)	Placebo (N=3403)
Age (yr) — mean ±SD	63.4±11.0	63.5±10.8
Ejection fraction — mean ±SD	28.6±8.9	28.4±8.9
Median duration of CHF — mo	17	16
Concomitant medications		
Diuretics	81.2	82.2
ACE inhibitors	94.1	94.8
Nitrates	42.1	43.1

THE EFFECT OF DIGOXIN ON MORTALITY AND MORBIDITY IN PATIENTS WITH HEART FAILURE

THE DIGITALIS INVESTIGATION GROUP*

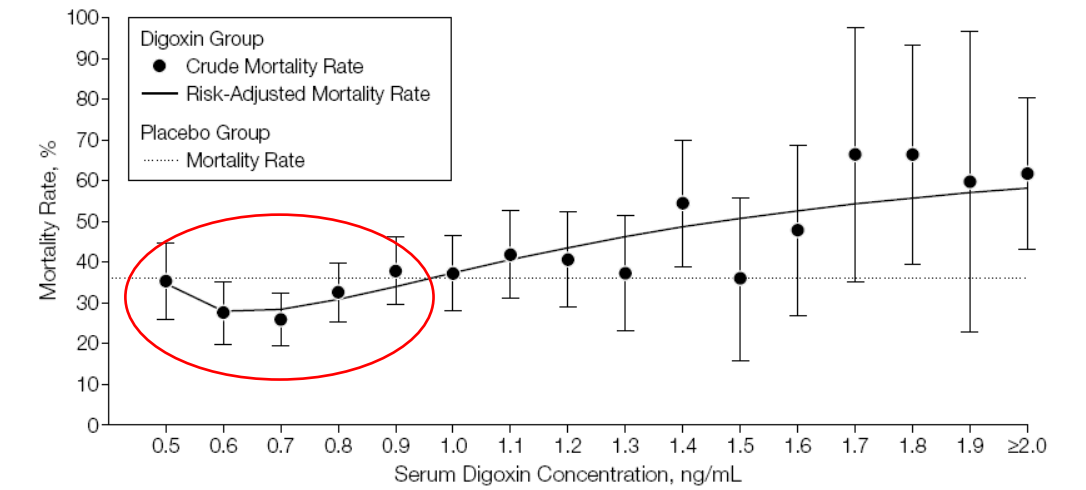




Dutch DECISION STUDY – low dose Dig

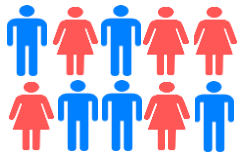
Effect low dose digoxin in heart failure

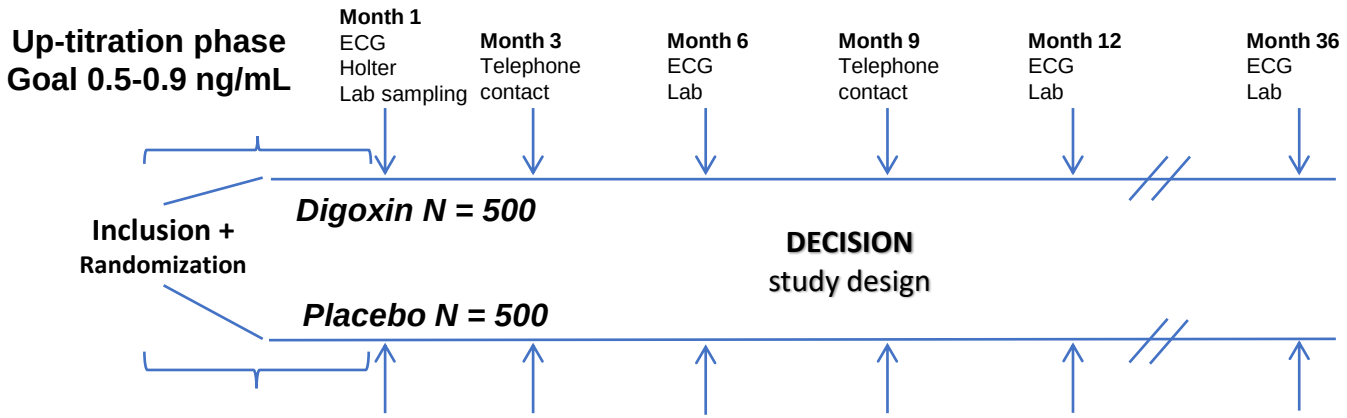
Figure 3. All-Cause Mortality Rates by Serum Digoxin Concentration Groups



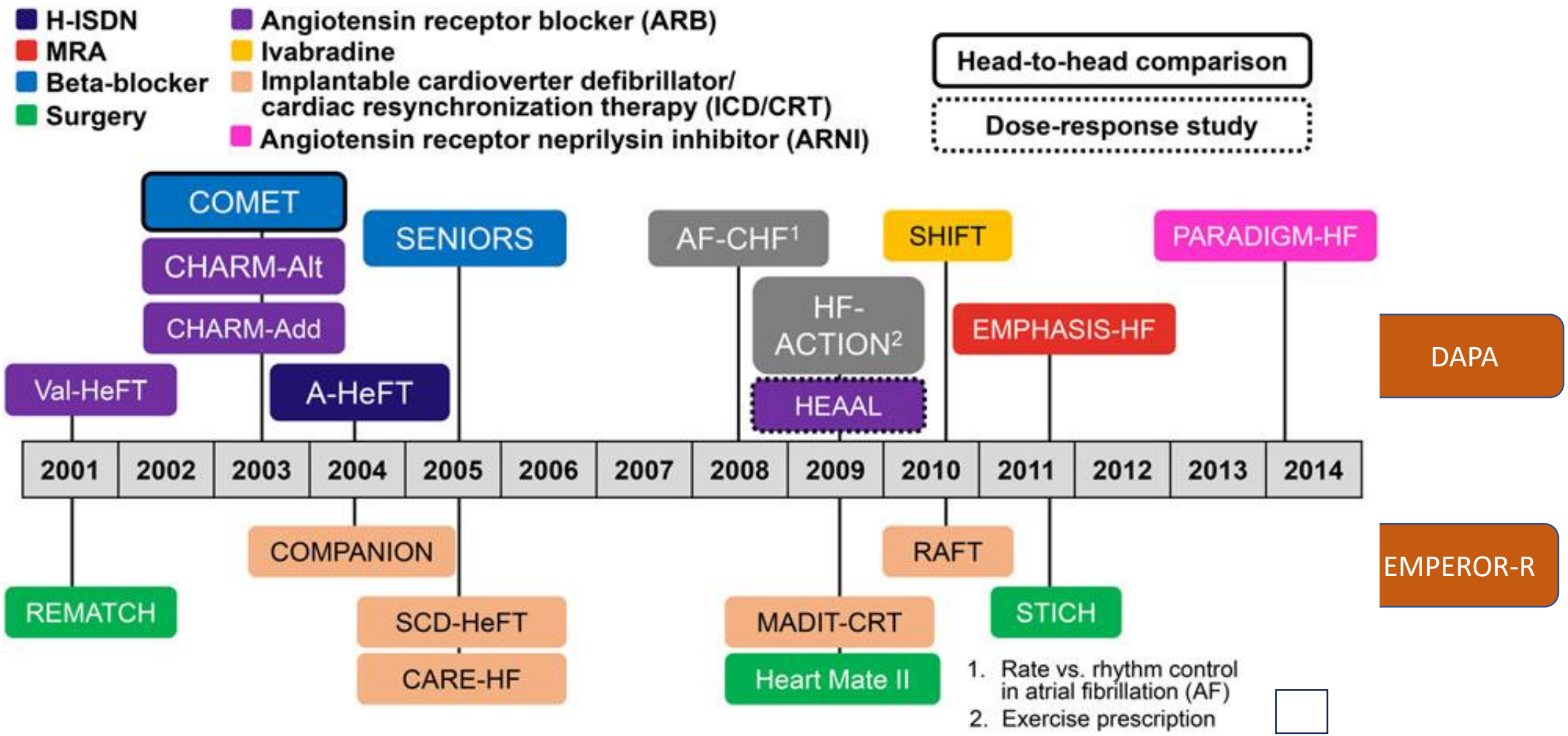
- **Design** Randomized, placebo-controlled, double blind multicenter, national study
- **Treatment:** Low-dose digoxin (0.1 and 0.2 mg) Serum conc: 0.5-0.9 ng/ml *versus* placebo
- **Follow-up:** Median: 3 years
- **Prim. EP:** Cardiovascular mortality and repeated heart failure hospitalizations + urgent HF visits

HF patients
(SR/AF)





Hartstichting


H-ISDN
MRA
Beta-blocker
Surgery
Angiotensin receptor blocker (ARB)
Ivabradine
Implantable cardioverter defibrillator/ cardiac resynchronization therapy (ICD/CRT)
Angiotensin receptor neprilysin inhibitor (ARNI)
Head-to-head comparison
Dose-response study
COMET
CHARM-Alt
CHARM-Add
Val-HeFT
A-HeFT
SENIORS
AF-CHF1
HF-ACTION2
HEAAL
SHIFT
EMPHASIS-HF
PARADIGM-HF
DAPA
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
REMATCH
COMPANION
SCD-HeFT
CARE-HF
MADIT-CRT
Heart Mate II
RAFT
STICH
EMPEROR-R
1. Rate vs. rhythm control in atrial fibrillation (AF)
2. Exercise prescription

Management of HFrEF

To reduce mortality - for all patients

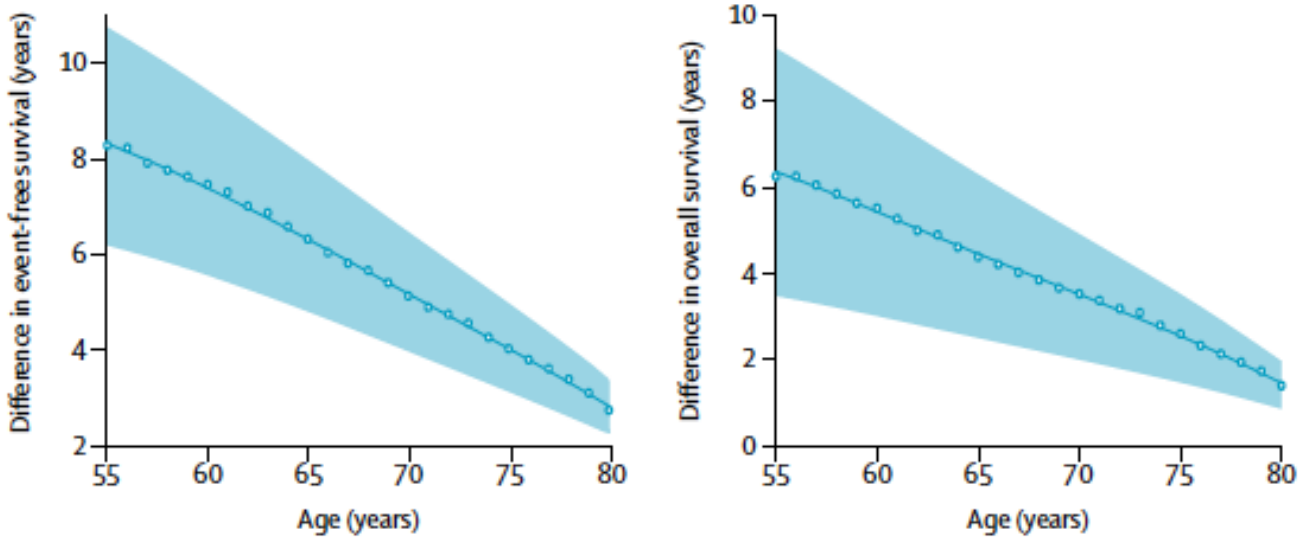
ACE-I/ARNI | BB | MRA | SGLT2i

To reduce HF hospitalization/mortality - for selected patients

Volume overload

Diuretics

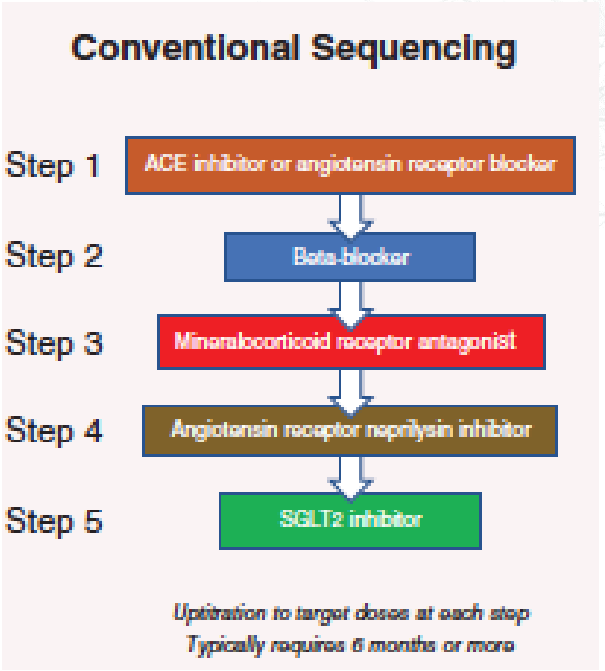
ARNI + BB +
SGLT2i + MRA
vs.
ACEi +BB

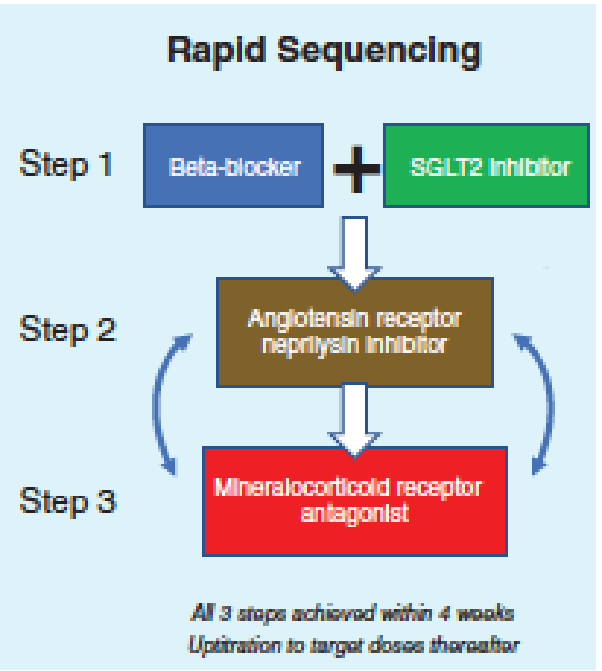


Optitratie van HF medicatie?

- EJHF 2021

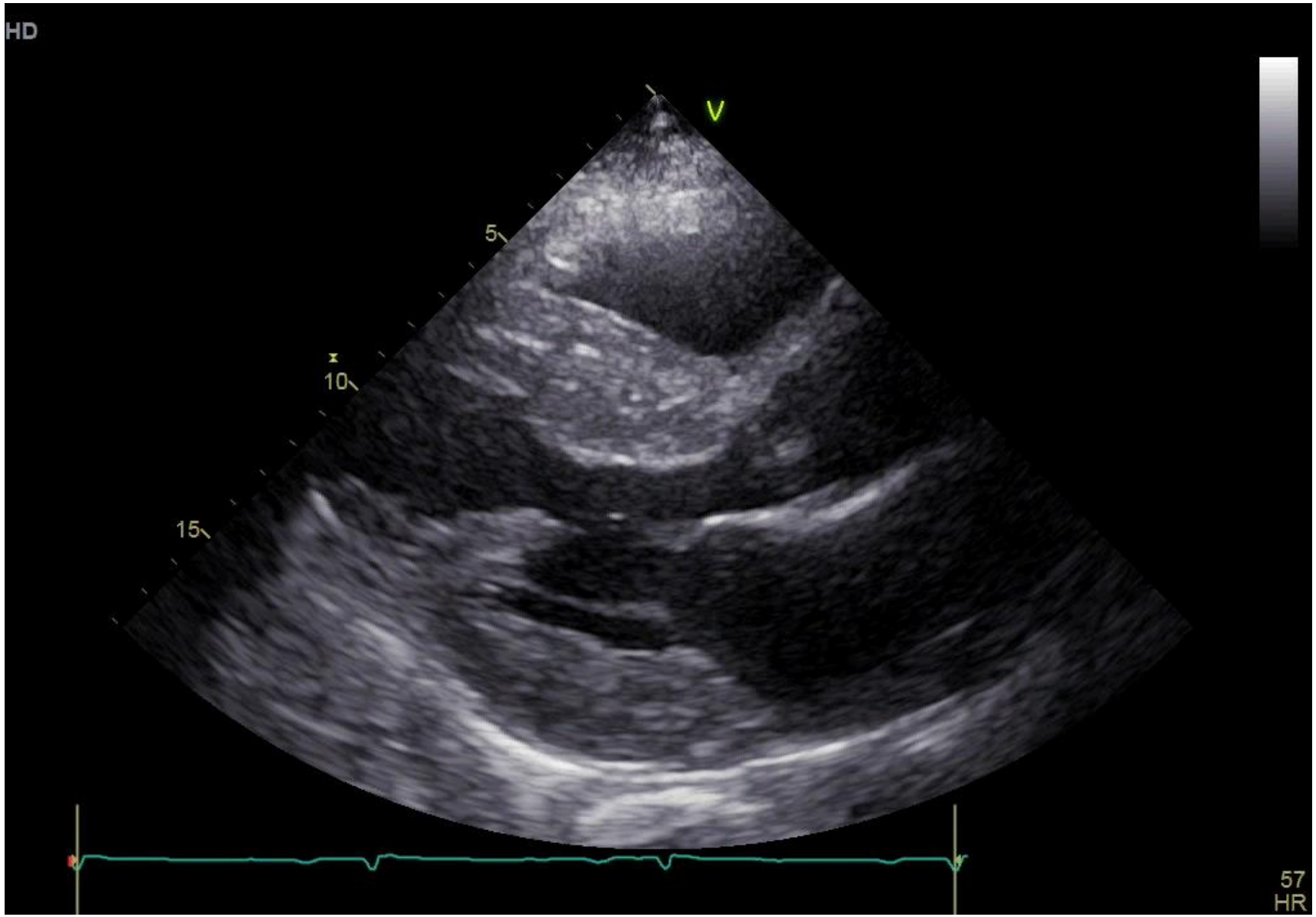
Trial	Drug	Endpoint			HR
EPHESUS	**Eplerenone** Starting dose: 25 mg QD Target dose: 50 mg QD	All-cause mortality	Effect at 30 days	25 mg QD by study design	0.69 (0.54, 0.89)
			Overall effect (mean follow-up, 16 months)	42.6 mg QD overall	0.85 (0.75, 0.96)
		Sudden cardiac death	Effect at 30 days	25 mg QD by study design	0.63 (0.40, 1.00)
			Overall effect (mean follow-up, 16 months)	42.6 mg QD overall	0.79 (0.64, 0.97)
PARADIGM-HF	**Sacubitril/valsartan** 97/103 mg BID (randomized at target dose)	Cardiovascular death or hospitalization for heart failure	Effect at 30 days	Most patients maintained at target dose	0.65 (0.45-0.93)
			Effect in overall trial (median follow-up, 27 months)		0.80 (0.73, 0.87)
EMPEROR-Reduced	**Empagliflozin** Starting dose: 10 mg QD Target dose: 10 mg QD	Cardiovascular death and hospitalization or urgent visit for worsening heart failure	Effect at 12 days	10 mg QD	0.42 (0.19-0.92)
			Effect at 28 days	10 mg QD	0.67 (0.44-1.00)
			Effect in overall trial (median follow-up, 16 months)	10 mg QD	0.76 (0.67-0.87)





One size fits all?

ATTR – amyloïdose



Nederlandse data - prevalentie

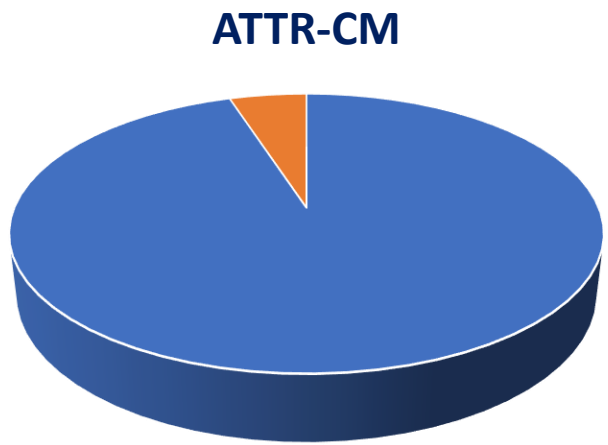
	$HF^{ATTRwt-}$ (n=98)	$HF^{ATTRwt+}$ (n=5)	p-value	
Age at diagnosis, years ± SD	72.7 ± 7.8	73.9 ± 12.6	.720	
Men	49.0%	80.0%	.060	
Hypertension	79.2%	28.6%	.003	
Diabetes Mellitus type II	39.6%	42.9%	.860	
Myocardial Infarction	21.9%	14.3%	.640	
Rhythm			.830	
Sinus rhythm	62.5%	71.4%		
Atrial fibrillation	34.4%	28.6%		
Atrial flutter	3.1%	0.0%		
Clinical				
Systolic blood pressure (mmHg)	139.0 (125.0, 154.0)	139.0 (129.0, 160.0)	.610	
Diastolic blood pressure (mmHg)	73.0 (62.0, 82.0)	66.0 (62.0, 77.0)	.480	
IVSD (mm)	10.0 (9.0, 12.0)	12.5 (11.0, 13.0)	.032	
LVMi	95.0 (77.0, 121.0)	118.0 (108.0, 144.0)	.053	
LVEF (%)	55.0 (50.0, 58.0)	55.0 (55.0, 55.0)	.980	
Laboratory				
NTproBNP (ng/L)	1490.0 (687.0, 2490.5)	1275.0 (962.0, 1594.0)	.900	
eGFR (ml/min * 1.73 m2)	48.5 (37.0, 72.0)	52.0 (43.0, 58.0)	.930	
Creatinine (µmol)	106.0 (85.0, 143.0)	116.0 (104.0, 137.0)	.460	
ALAT (IU/L)	19.5 (14.0, 25.0)	22.0 (15.0, 29.0)	.380	

Prospective screening study

LVEF > 40%

Elevated NTproBNP

NYHA II-III + diuretics



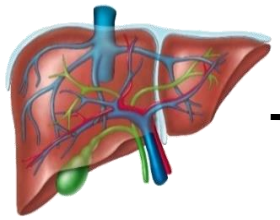
Tubben, … Van der Meer, EJHF 2024

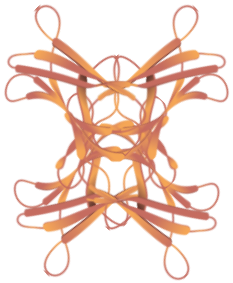
Behandelopties voor ATTR-CM

Liver transplant, patisiran*, inotersen*, vutrisiran*

tafamidis, diflunisal*, AG-10*

NNC6019-0001*, NI006*

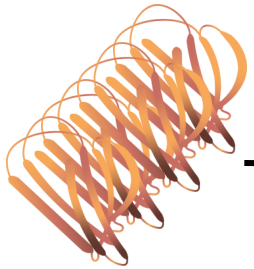




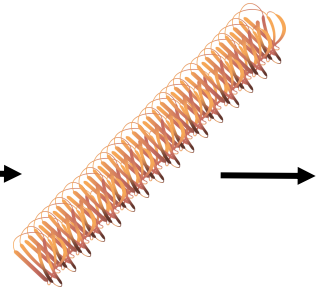
Folded TTR tetramers

Folded monomers

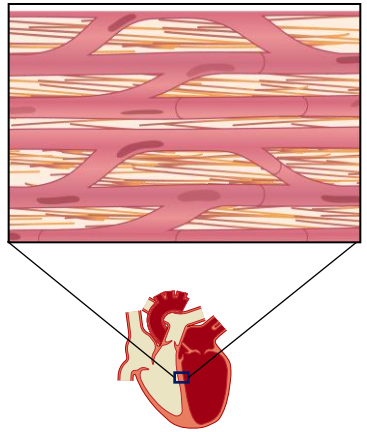
Misfolded monomers



Oligomers



Amyloid fibrils



Deposition of amyloid fibrils in the myocardium

Inhibit production of TTR (RNAi)

TTR tetramer stabilisers

Amyloid breakdown