Advanced
Heart Failure
A Swiss
Webinar series

Optimizing Heart Failure Therapy

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2 position papers of the HFA

ELSEVIER

European Journal of Heart Failure 9 (2007) 684–694

The European Journal of Heart Failure

www.elsevier.com/locate/ejheart

Review

Advanced chronic heart failure: A position statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology

Marco Metra [a,*], Piotr Ponikowski [b], Kenneth Dickstein [c], John J.V. McMurray [d], Antonello Gavazzi [e], Claes-Hakan Bergh [f], Alan G. Fraser [g], Tiny Jaarsma [h], Antonis Pitsis [i], Paul Mohacsi [j], Michael Böhm [k], Stefan Anker [l,m], Henry Dargie [n], Dirk Brutsaert [o], Michel Komajda [p]
on behalf of the Heart Failure Association of the European Society of Cardiology

ESC European Society of Cardiology

European Journal of Heart Failure (2018) 20, 1505–1535
doi:10.1002/ejhf.1236

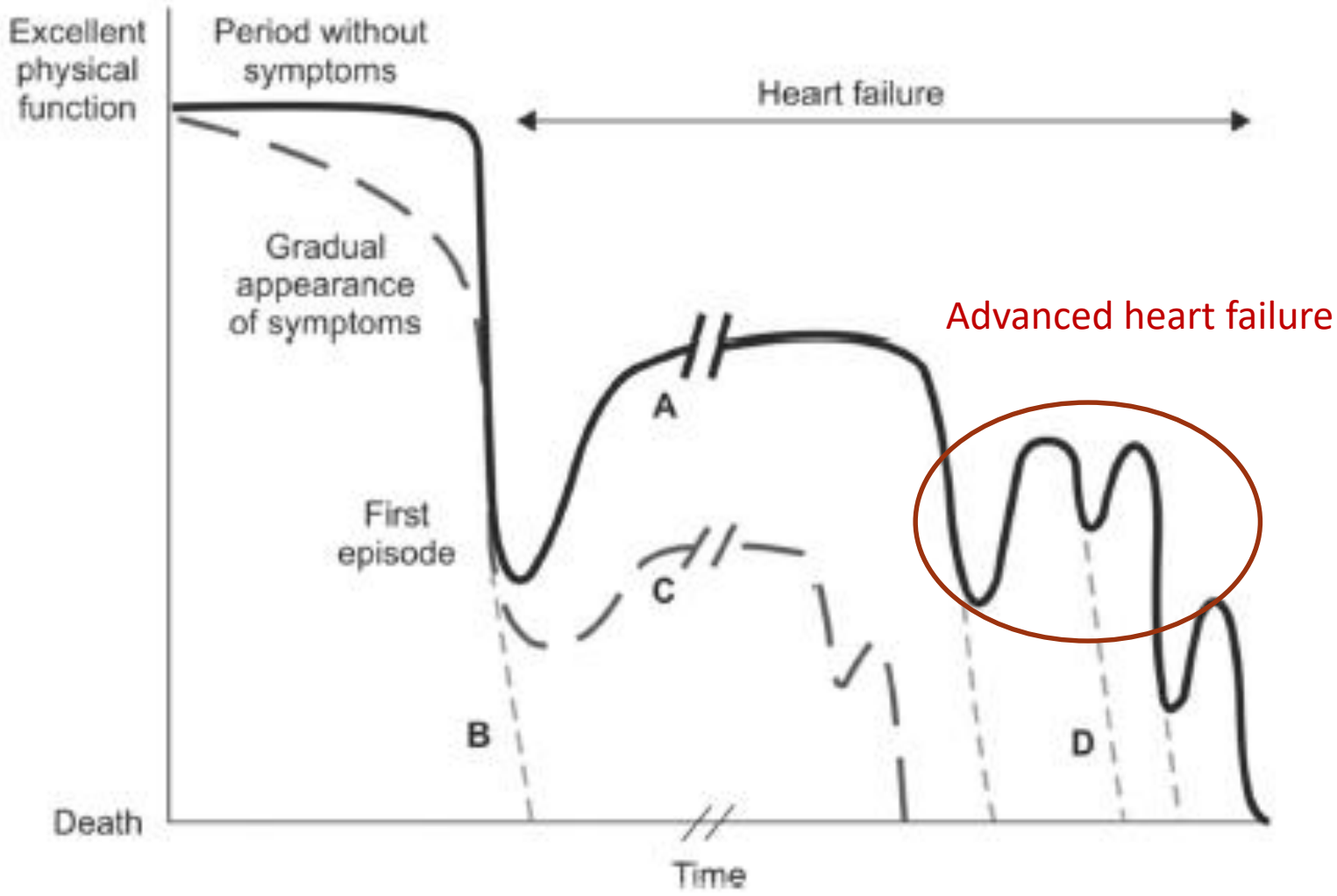
HFA POSITION STATEMENT

Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology

Maria G. Crespo-Leiro[1]*, Marco Metra[2], Lars H. Lund[3], Davor Milicic[4], Maria Rosa Costanzo[5], Gerasimos Filippatos[6], Finn Gustafsson[7], Steven Tsui[8], Eduardo Barge-Caballero[1], Nicolaas De Jonge[9], Maria Frigerio[10], Righab Hamdan[11], Tal Hasin[12], Martin Hülsmann[13], Sanem Nalbantgil[14], Luciano Potena[15], Johann Bauersachs[16], Aggeliki Gkouziouta[17], Arjang Ruhparwar[18], Arsen D. Ristic[19], Ewa Straburzynska-Migaj[20], Theresa McDonagh[21], Petar Seferovic[22], and Frank Ruschitzka[23]

- Clear and up-dated definition of advanced heart failure
- In depth description of therapeutic options
- *≠ Guidelines*
  - No classes of recommandation
  - Level of evidence not provided

Definition of advanced heart failure



Definition of advanced heart failure

4 CRITERIA + 1 CONDITION

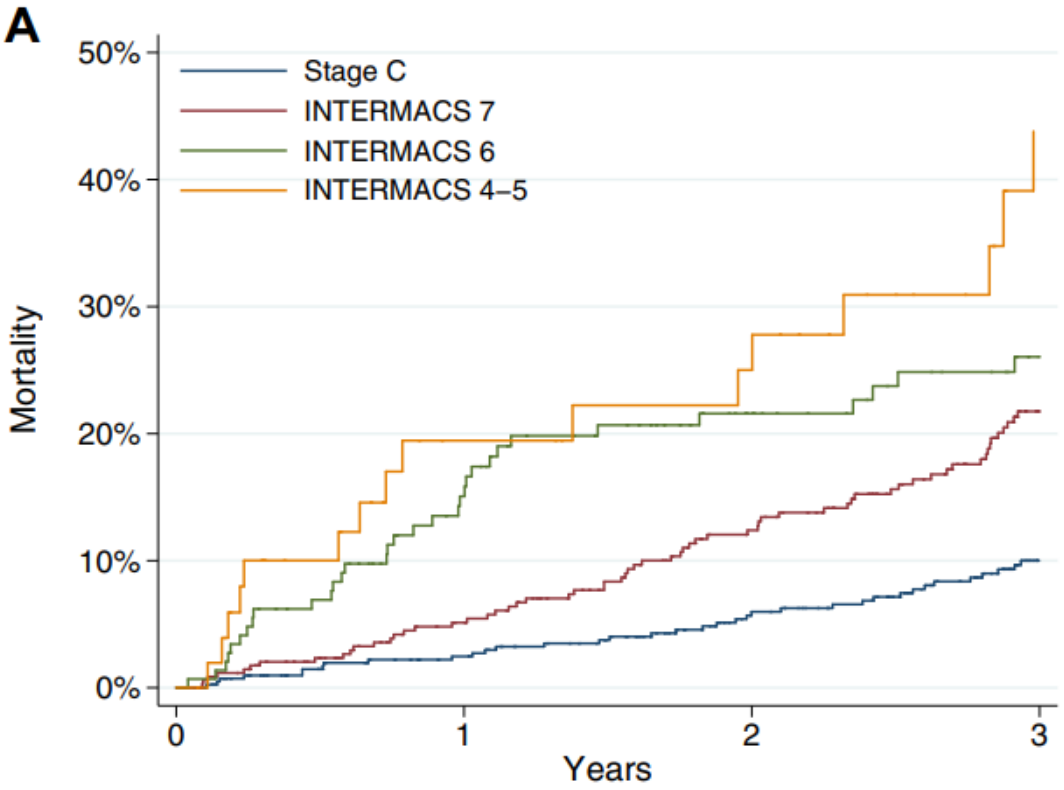
1. Severe and persistent symptoms (dyspnea, fatigue, congestion)
   - NYHA III advanced (minimal exercise) or NYHA IV (rest)
2. Severe heart dysfunction
   - LVEF < 30%
   - Severe diastolic dysfunction or high BNP NTproBNP levels (less clear)
   - Severe isolated RV failure (ARVC)
   - Severe non operable valve diasease
3. Pulmonary or sytemic congestion OR low cardiac output OR malignant arrhythmia
   - High dose IV diuretics or inotropes
   - > 1 episode in last 12 months
4. Severe imparment of functional capacity
   - 6MWD < 300 m
   - pVO2 12-14 ml/kg/min

Despite optimal guideline-directed therapy !

Crespo-Leiro M et al, EJHF 2016

Very poor outcome of AdHF

423 patients stage C (systolic dysfonction + symptoms)
546 patients with advanced HF, categorized according to INTERMACS classification
Censoring at time of transplantation or LVAD implantation



IM 7 = stage 3 (No meaningful exercise possible)

IM 6 = limited to mild exertion

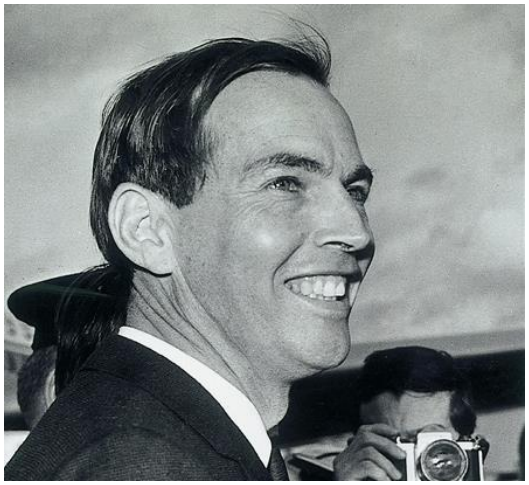
IM 5 = limited to light exercise

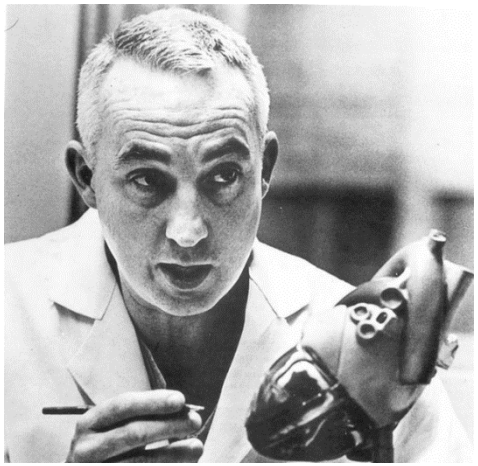
IM 4 = uncomfortable at rest

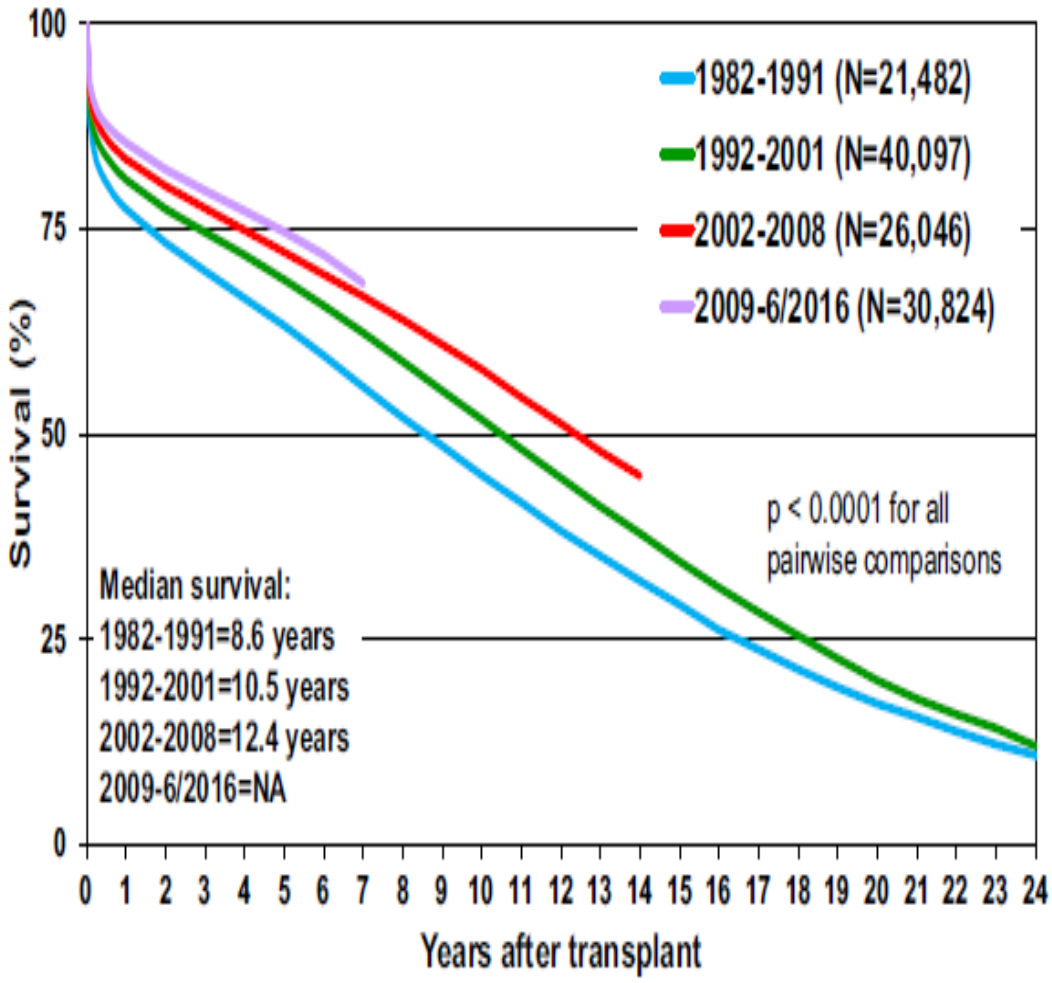
Despite guideline directed therapy !

Samman-Tahan, JACC HF 2018

Therapeutic options N°1: heart transplantation







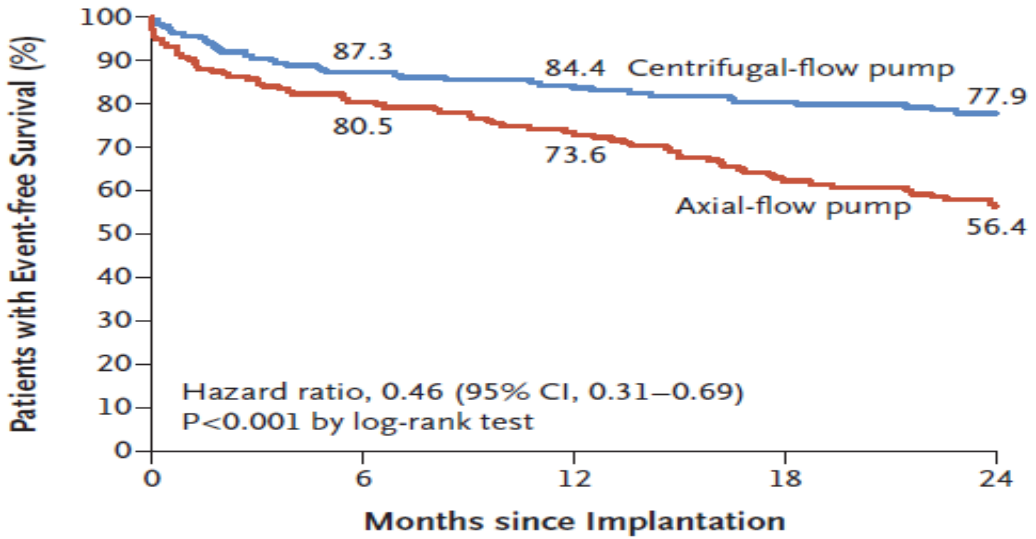
Since 03.12.1967

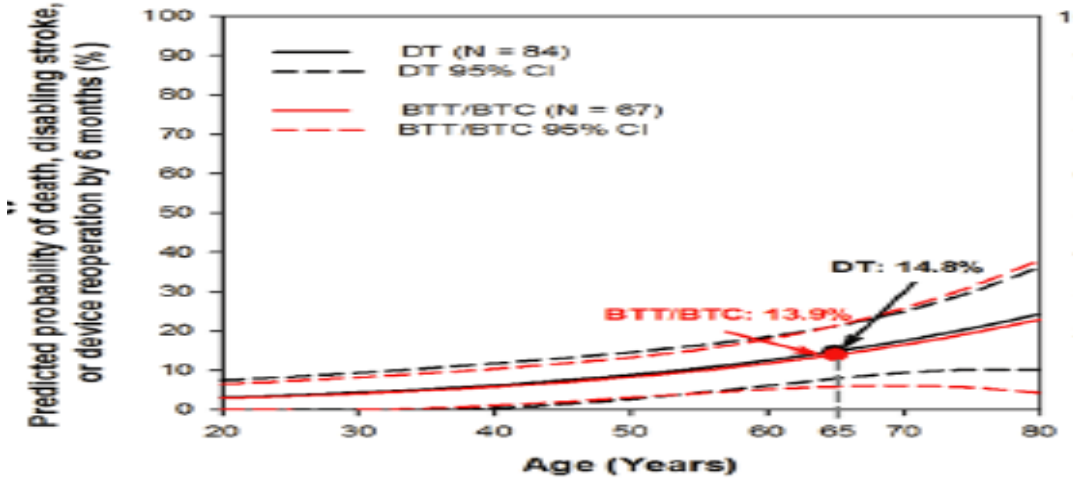
10 years survival > 65%

Khush KK et al, JHLT 2018

Rx N°2 : Destination therapy with LVAD

2y survival without disabling stroke / device malfunction



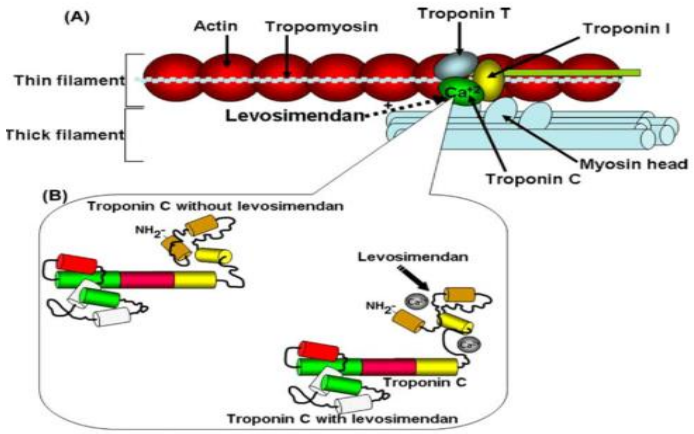


Mehra M et al NEJM 2018 and Goldstein et al JHLT 2018

New inotropes for non HTx – non MCS candidates ?

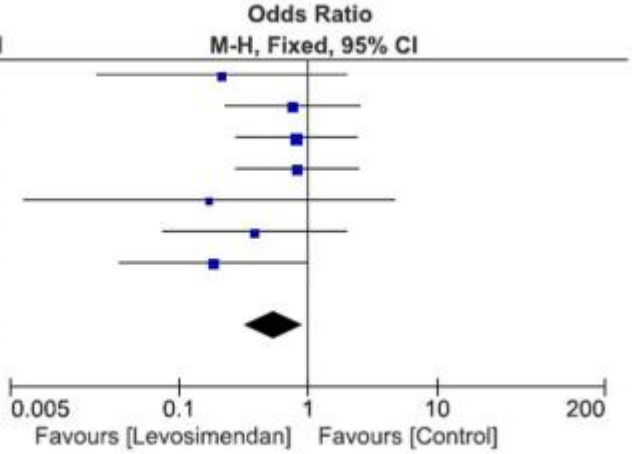
Levosimendan

- Myofilament Calcium sensitizer
- Repeated infusions in AdHF



Study or Subgroup	Levosimendan Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Altenberger J 2014	1	63	4	57	10.9%	0.21 [0.02, 1.97]
Berger R 2007	6	39	7	36	16.3%	0.75 [0.23, 2.50]
Bonios MJ 2012	14	42	8	21	18.8%	0.81 [0.27, 2.42]
Comin-Colét 2015	14	48	7	21	18.2%	0.82 [0.27, 2.47]
Kleber FX 2009	0	18	1	10	4.9%	0.17 [0.01, 4.62]
Malfatto G MD 2012	4	22	4	11	11.5%	0.39 [0.08, 2.00]
Mavrogeni S 2007	2	25	8	25	19.4%	0.18 [0.03, 0.98]
Total (95% CI)		**257**		**181**	**100.0%**	**0.54 [0.32, 0.91]**
Total events	41		39			

Heterogeneity: Chi² = 4.28, df = 6 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)



Silvetti S, IJC 2016

Treatment optimisation….

An example

Mrs I. M; 57 years old in 2016

History :

- Sent from another canton after 2 episodes of acute heart failure with the question of heart transplantation

- Acute myeloid leukemia, 15 years ago, treated with anthacyclins (among other therapies). In remision after medulla transplantation
- Progressive decrease of LVEF already 10 years ago
- Stage NYHA 3 (1 climb of stairs)

Clinical Assessment

- No congestion, IVC 17 mm, inspiratory collapse 40%
- BP : 99 /64 mmhg
- Sinus rythm 72 bpm, narrow QRS (90 ms)

Investigations

- LVEF 29%, no significant MR, no RV dysfunction
- Peak VO2 : 13.9 ml/kg /min, VE/VCO2 slope 36

Mrs I. M; 57 years old in 2016

Labo :

- NTproBNP 2100
- Creatinine 161 umol/l
- K+ 4.9 mmol /L

Treatment

- Candesartan 4 mg x 2
- Carvedilol 6.25 x 2
- Spironolactone 12.5 mg
- Torasemide 20 mg

ICD in primary prevention, no sustained VT

Does this lady have advanced HF ?

4 CRITERIA + 1 CONDITION

1. Severe and persistent symptoms (dyspnea, fatigue, congestion)
   - NYHA III advanced (minimal exercise) or NYHA IV (rest)
2. Severe heart dysfunction
   - LVEF < 30%
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3. Pulmonary or sytemic congestion OR low cardiac output OR malignant arrhythmia
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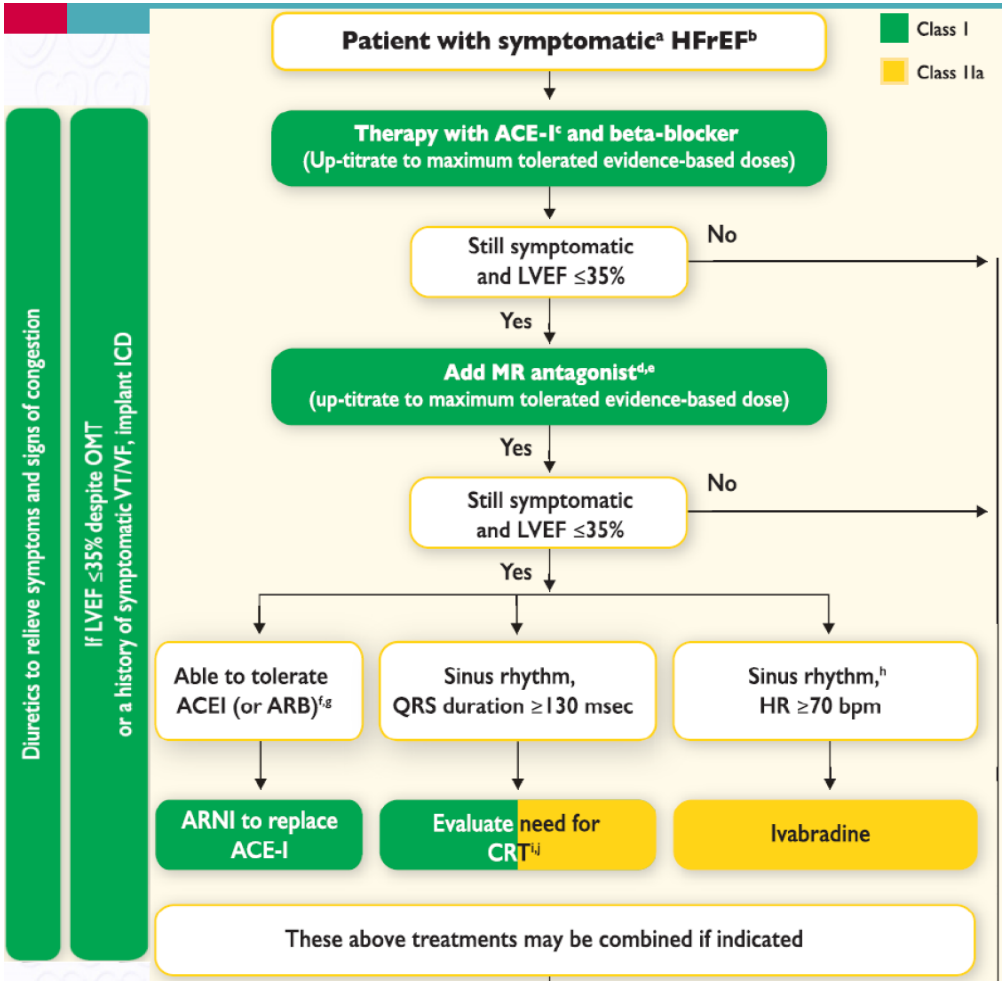
4. Severe imparment of functional capacity
   - 6MWD < 300 m
   - pVO2 12-14 ml/kg/min

Despite optimal guideline-directed therapy !

Crespo-Leiro M et al, EJHF 2016

Does our lady have optimal medical therapy ?



Treatment of Mrs I.M.

- Candesartan 4 mg x 2
- Carvedilol 6.25 x 2
- Spironolactone 12.5 mg
- Torasemide 20 mg

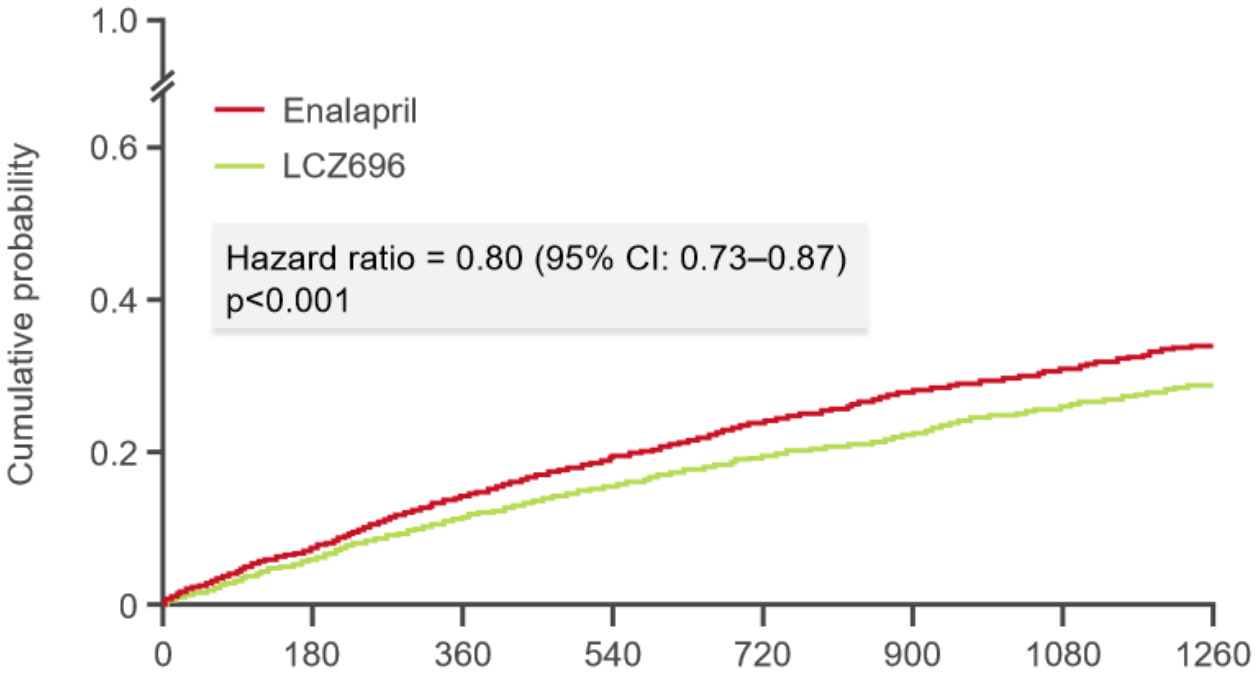
Ponikowski P, EHJ 2016

Should we switch the ARB for Entresto ?

PARADIGM-HF trial
8442 patients randomized for enalapril 2 x 10 mg or Entresto 2 x 200 mg
Almost no patient in NYHA 4 (60 patients only !!!)

Primary endpoint:

Death from CV causes or first hospitalization for HF

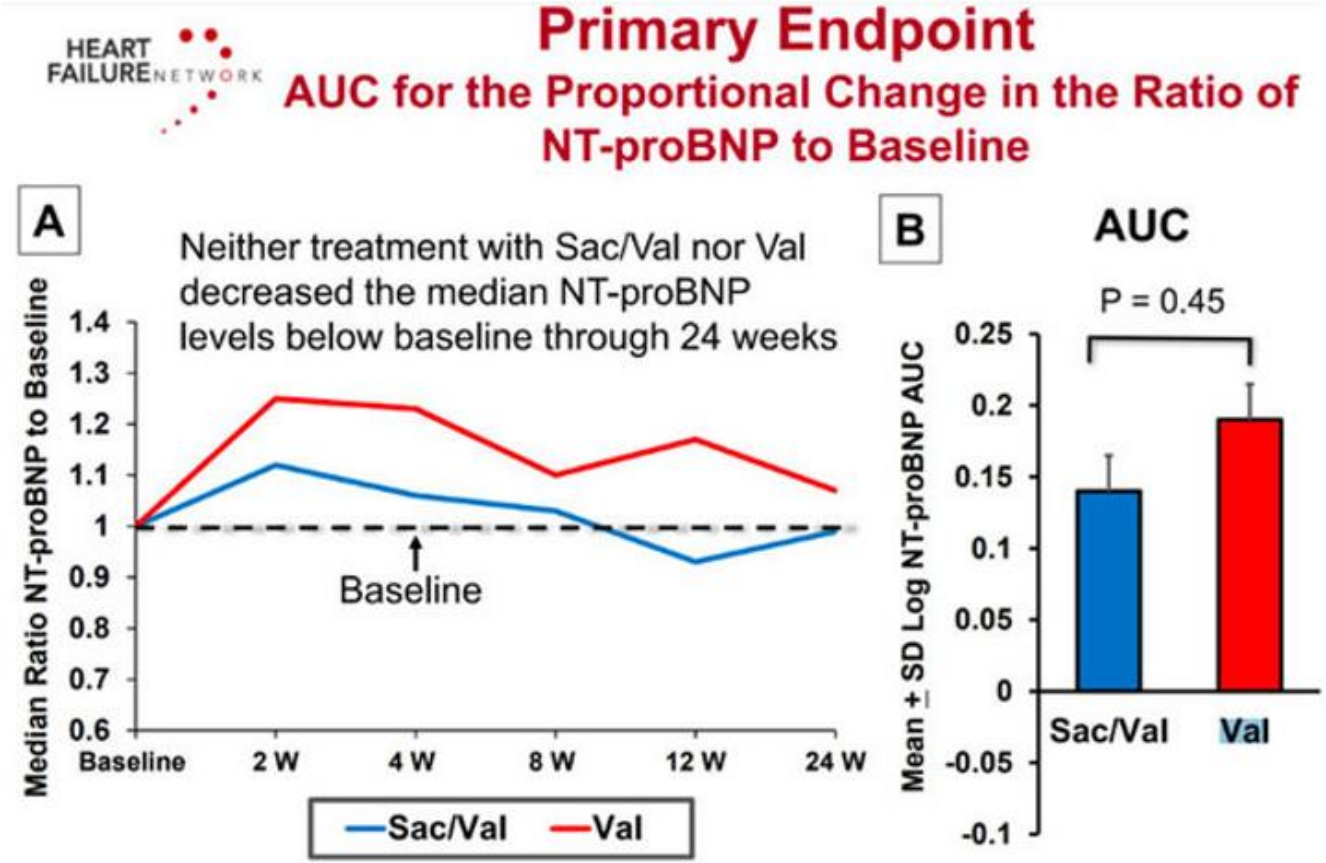


Frequent hypotension !

McMurray J, NEJM 2014

Should we switch the ARB for Entresto ?

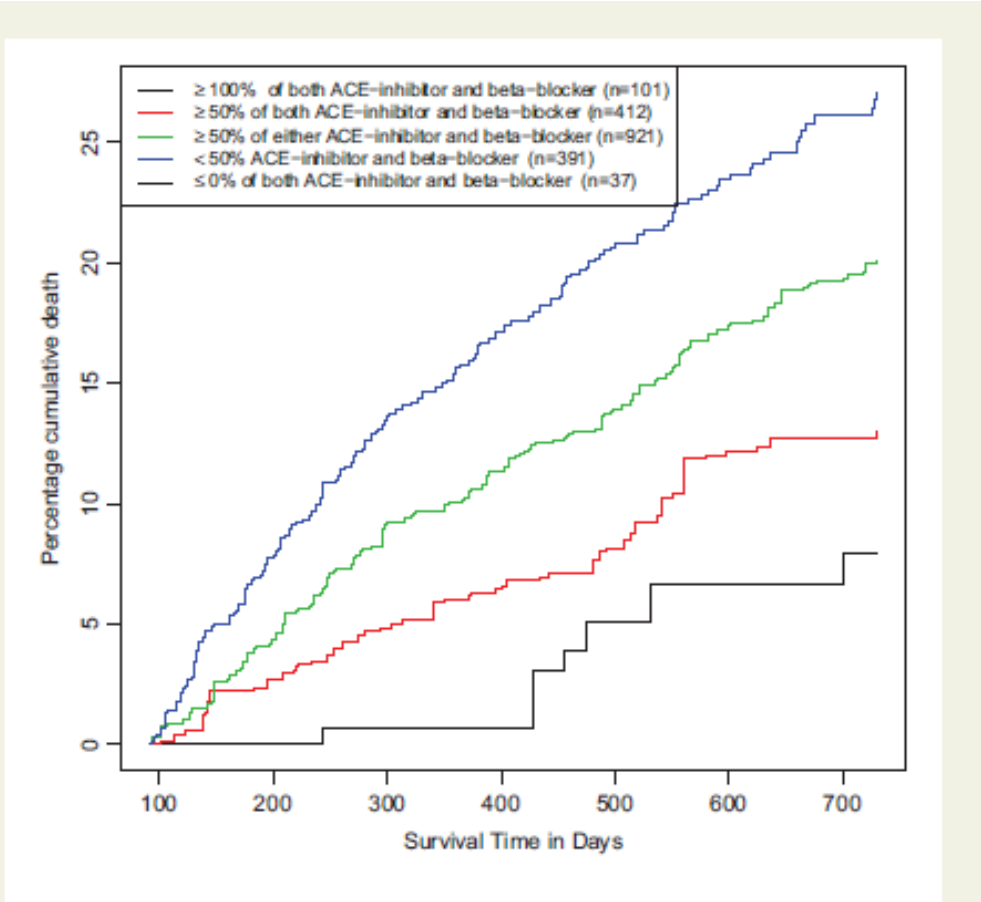
LIFE-HF trial
335 patients with NYHA 4 HF, SBP > 900 mmHg, randomized between entresto and valsartan
Iary endpoint : NTproBNP change after 24 weeks



Mann Douglas, oral presentation, ACC 21, Saint Louis, USA

Should we titrate the existing therapy ?

BIOSTAT-CHF trial
69 centers, 11 European countries
2100 patients with HFrEF inclus, mean follow-up 21 months



<50% ACEi/ARB with <50% BB

>50% ACEi/ARB or BB with <50% of the other

>50% ACEi/ARB + >50% BB

100% ACEi/ARB + 100% BB

Ouwerkerk J et al, EHJ 2017

Should we titrate the existing therapy ?

Frequent barriers to therapy up-titration :

Low blood pressure

Low heart rate

Renal failure

Hyperkalemia

Acute heart failure (BB)

Treatment optimisation

with

Low blood pressure

HF therapy lowers BP, particularly ACEi / ARB / ARNI

Dose dependent reduction of BP

ATLAS trial : 3164 patients, LVEF < 30% randomized to lisinopril low dose (5 mg) vs high dose (35 mg)

Effect oh high dose as compared to low dose :

SBP -4.4+/-0.6 mmHg

DBP -2.3 +/- 0.4 mmHg

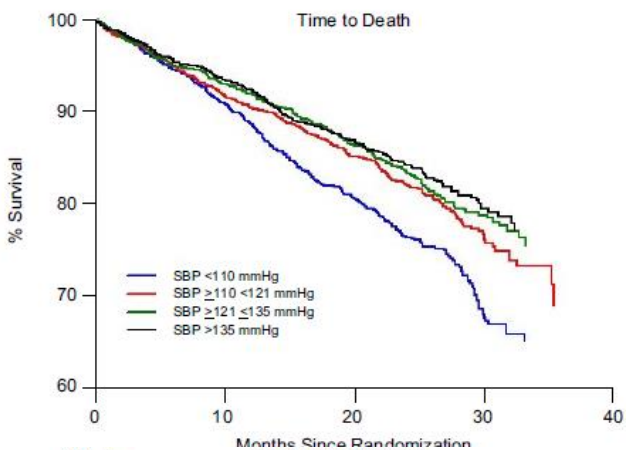
similar for ARB / ARNI / BB…

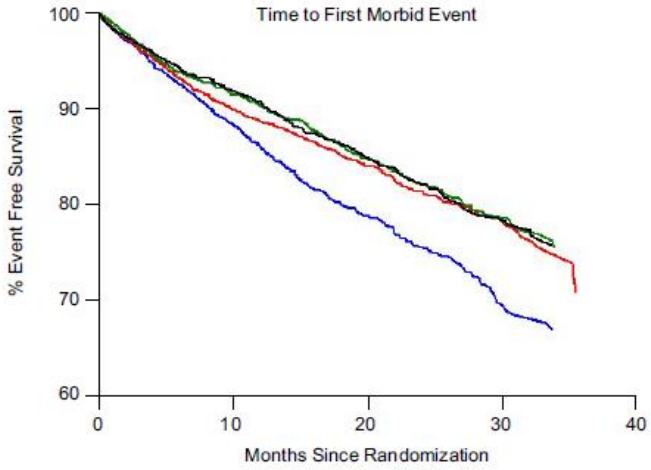
Packer M, Circ 1999

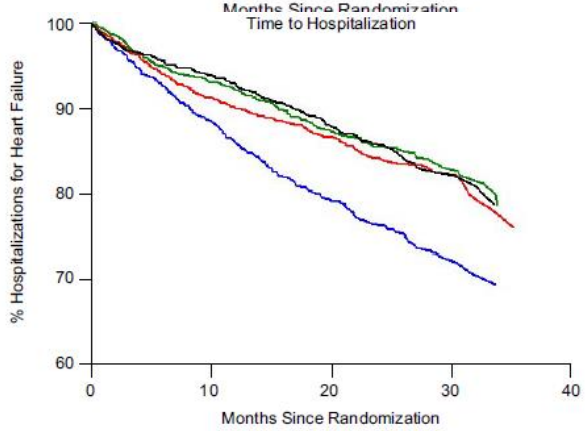
Low blood pressure related to prognosis !

Hypotension related to outcome

VAL-HEFT trial : 5010 patients : outcome according to quartiles of SBP : (Q1: >135 mmHg, Q 2 :121-135 mmhg, Q3 : 110-121 mmHg, Q4 : <110 mmhg)







All outcomes occur earlier in HF patients with lower BP !

Univariate analysis

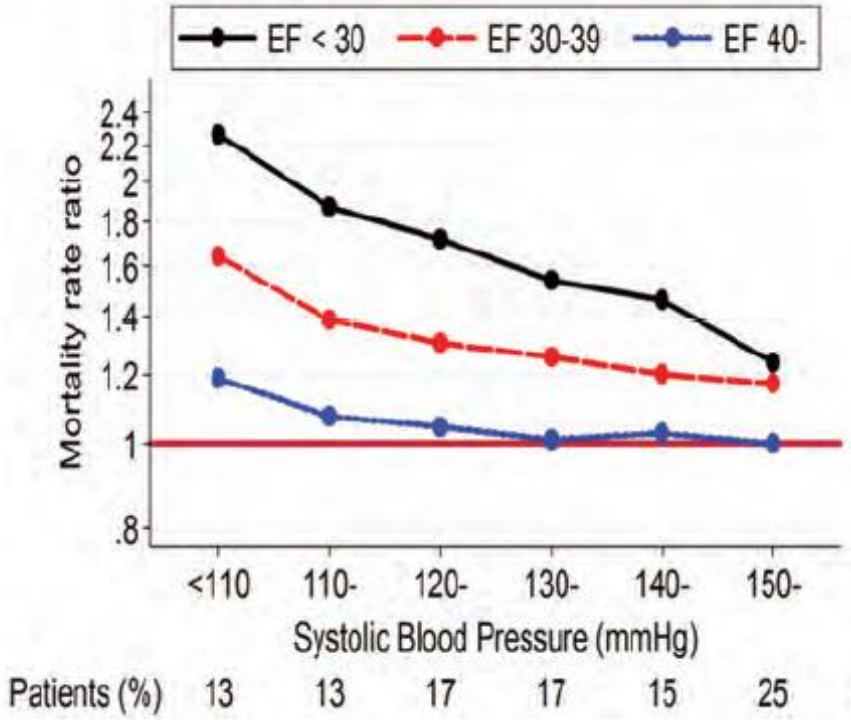
Anand IS M, Circ HF 2008

Attenuated effect in multivariate analysis

MAGICC score

Score based on 39732 patients from 30 studies

In multivariate analysis, rate ratio = 0.882 (95% CI 0.855-0.91) for mortality for each 10 mmHg increase. P<0.0001; significant after adjustment age, sex, NYHA, EF, creatinine…



But effect on outcome largely attenuated by other factors accounting for disease severity, like LVEF especially.

Hypotension is more a marker of SEVERE HF than an independent prognostic variable

Pocock S (MAGGIC), EHJ 2013 ; Cautela J, EJHF 2020

Hypotensive patients benefit from ACEi / ARB !

VAL-HEFT trial : 5010 patients

Effect of Valsartan as compared to placebo according to SBP

Table 3. Effect of Valsartan Versus Placebo on Mortality, First Morbid Event, and Hospitalizations for HF in Patients Grouped by Baseline SBP

	Mean Baseline SBP, mm Hg Mean±SD		No. of Patients		Mortality, HR (95% CI)	First Morbid Event, HR (95% CI)	Hospitalization for HF, HR (95% CI)
	Placebo	Valsartan	Placebo	Valsartan			
Q1	102±5	101±6	474	466	0.82 (0.63 to 1.06)	0.74 (0.60 to 0.91)	0.60 (0.45 to 0.79)
P					0.13	0.005	<0.001
Q2, Q3, and Q4 combined	131±16	130±15	1657	1623	1.04 (0.88 to 1.23)	0.90 (0.79 to 1.02)	0.77 (0.64 to 0.93)
P	...	...	...	...	0.64	0.10	0.006
Interaction *P*	...	...	...	...	0.15	0.29	0.36

As patients with the most severe HF, hypotensive ones benefit MORE from RAASi than normotensive ones.

Anand I et al, Circ Heart Fail 2008

How to deal with hypotension in every day life ?

No evidence in the litterature

Expert opinion only !!

Definition of hypotension

- No definition based on BP !!
- In trials, Hypotension defned by clinical judgement rather than BP threshold
- Hypotension is therfore relevant when *SYMPTOMATIC* (dizziness, light-headedness, especially when getting up from a chair or during the first 3 minutes of walking, fatigue, syncope in severe cases)
- Symptoms should guide management rather than BP values
- (Low BP ususally also considered when SPB < 90 mmHg asymptomatic)

Cautela J, EJHF 2020

How to deal with hypotension in every day life ?

TAS 90-100 mmHg
TAS ≤ 90 mmHg (asy)

↓

Monitor GFR, K+
And heart rate

↓

GFR > 25, K<5, HR>60-65 → NO → Reduce ACEi/ARB/ARNI or BB accordingly

↓

YES

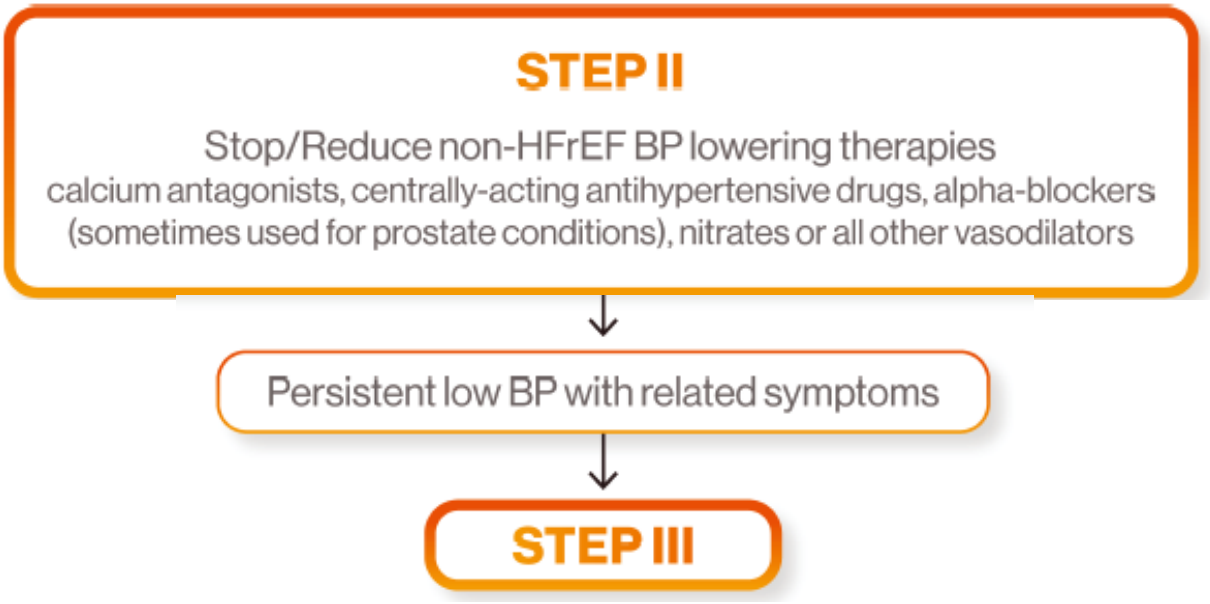
↓

Continue titration
Slowly
Small steps

Cautela J, EJHF 2020

How to deal with hypotension in every day life ?

TAS 90-100 mmHg with symptoms
TAS ≤ 90 mmHg with symptoms



Cautela J, EJHF 2020

How to deal with hypotension in every day life ?

STEP III

Lower diuretics dose in non-congestive patients

Clinical evaluation, BNP/NT pro BNP, lung ultrasound, echocardiography, congestion score

Diuretics absolutely necessary in acute heart failure when congestion threaten patient's organ function

Diuretic = barrier to guideline therapy uptitration once the patient decongested !

1°) Assess congestion clinically (jugular vein,. Hepatojugular reflux, peripheral edema, inspiratory fine crackles)

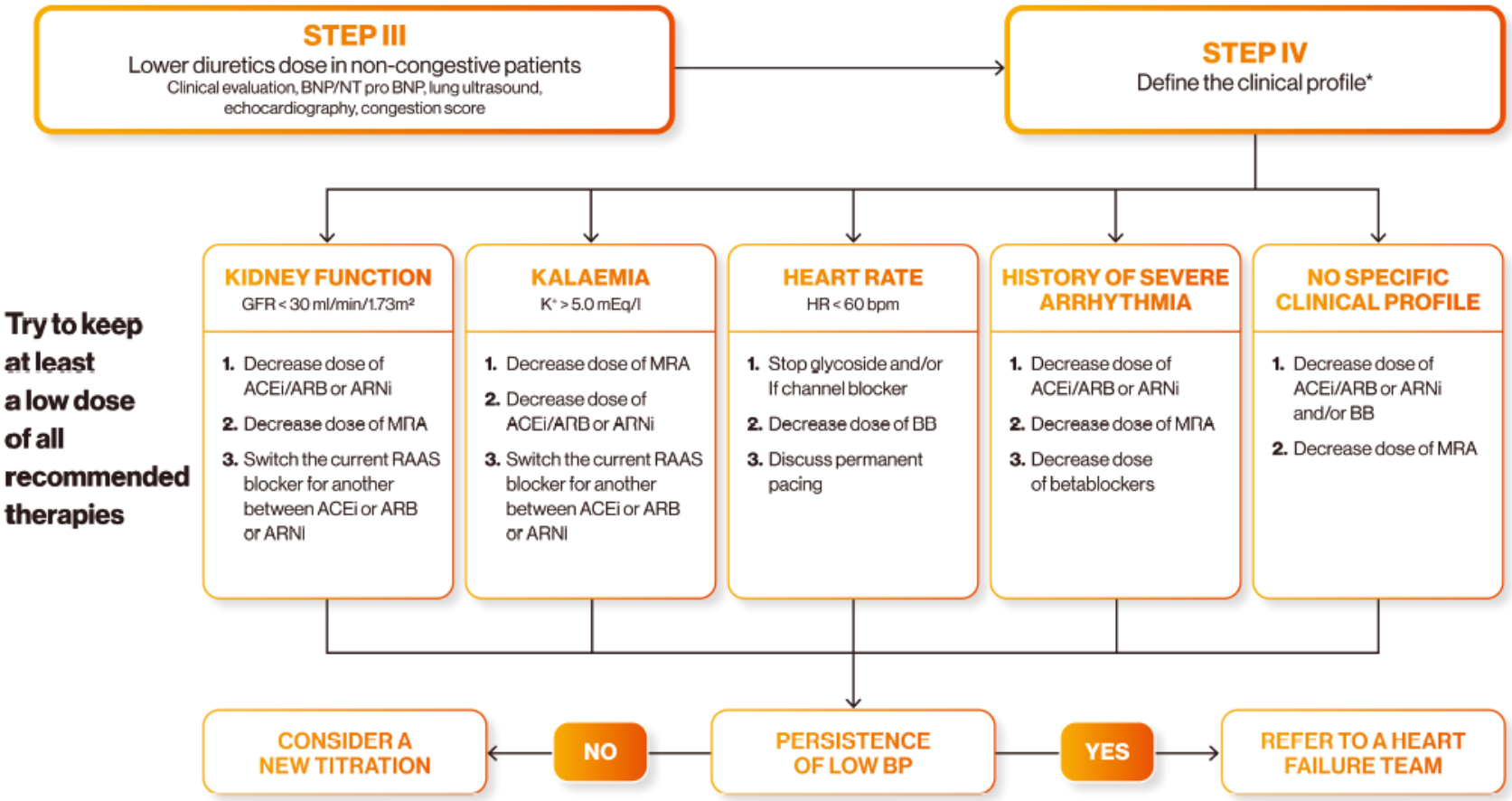
2°) If difficult (obesity, post-thrombotic syndrome, varicose veins), assess inferior vena cava by echocardiography (should be < 2 cm)

3°) If no congestion, decrease diuretics carefully

4°) if still non congestion, withdraw diuretics

Cautela J, EJHF 2020

How to deal with hypotension in every day life ?



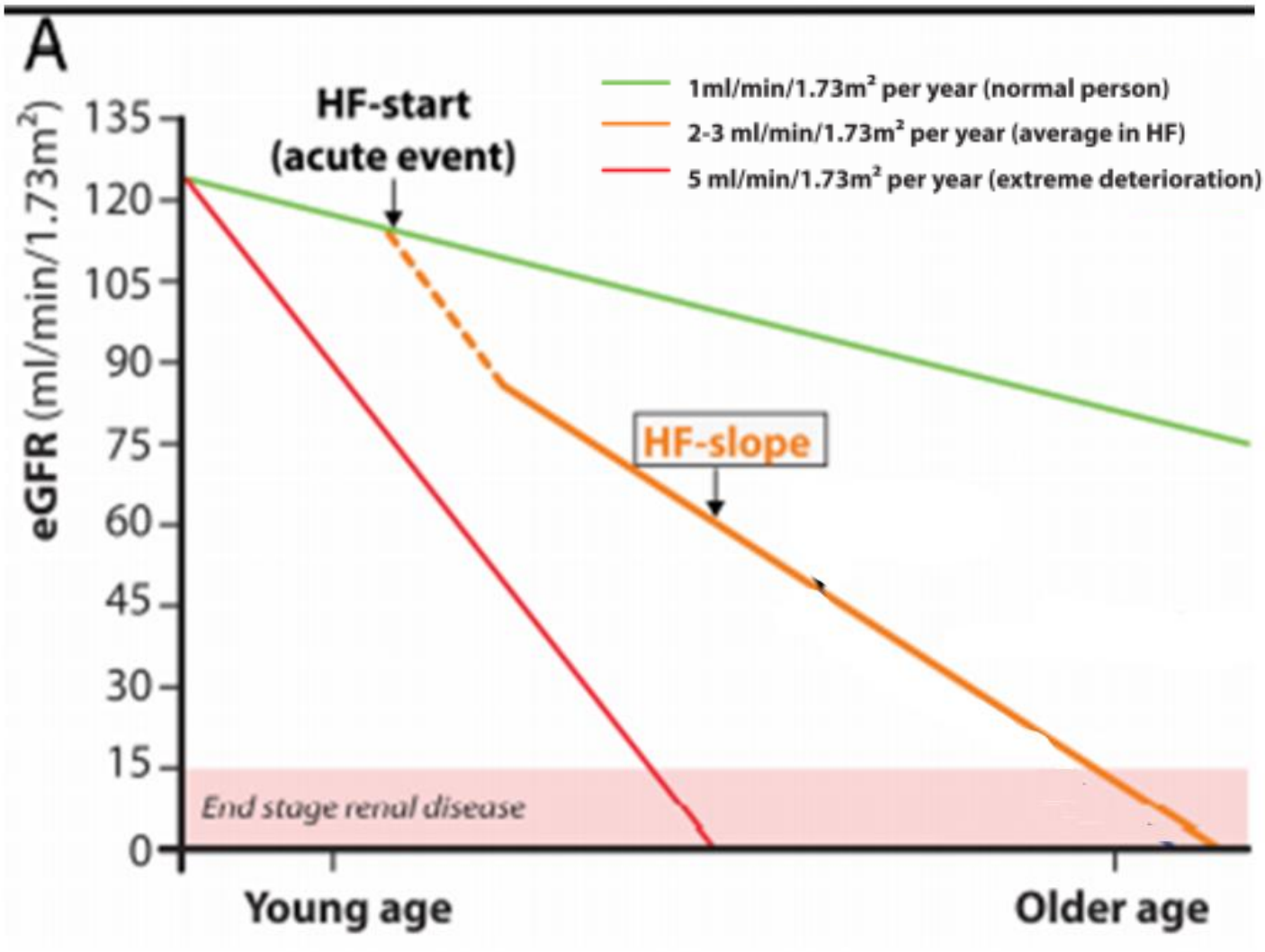
Cautela J, EJHF 2020

Treatment optimisation

with

Renal failure

How to deal with HF therapy in case of renal failure ?

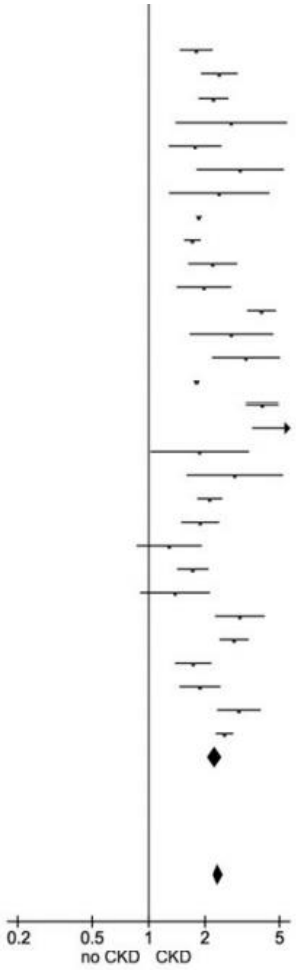


Mullens W, EJHF 2020

Baseline kidney function associated with outcome in chronic HF

Meta-analysis, 57 studies, 1'076'104 patients

Chronic Heart Failure							
Dries (SOLVD Prevention)	167	757	397	2916	2.5%	1.80 [1.47, 2.20]	2000
Hillege (PRIME II)	286	933	146	933	2.4%	2.38 [1.90, 2.98]	2000
Dries (SOLVD Treatment)	363	772	397	1389	2.7%	2.22 [1.85, 2.66]	2000
Marenzi	34	56	33	92	0.7%	2.76 [1.39, 5.48]	2001
McLellan	113	252	130	413	1.8%	1.77 [1.28, 2.45]	2002
Muntwyler	34	118	34	293	1.0%	3.08 [1.81, 5.27]	2002
Pulignano (IN-CHF)	16	47	292	1638	0.8%	2.38 [1.28, 4.41]	2002
Herzog	7083	16633	38104	133367	3.4%	1.85 [1.79, 1.92]	2004
Shlipak (DIG)	1309	3157	1066	3643	3.2%	1.71 [1.55, 1.89]	2004
McAllister	207	419	103	335	1.9%	2.20 [1.63, 2.97]	2004
Bibbins-Domingo (HERS)	159	425	69	297	1.7%	1.98 [1.42, 2.76]	2004
Ezekowitz (APPROACH)	438	2513	196	3914	2.7%	4.00 [3.36, 4.78]	2004
Shlipak (CHS)	107	140	75	139	1.0%	2.77 [1.66, 4.62]	2005
Roik	67	148	70	350	1.4%	3.31 [2.18, 5.02]	2006
Go (ANCHOR)	11700	24473	10676	31694	3.4%	1.80 [1.74, 1.87]	2006
Hillege (CHARM)	330	966	195	1714	2.5%	4.04 [3.31, 4.94]	2006
Bruch	66	135	17	134	0.8%	6.58 [3.58, 12.12]	2007
Shalaby	49	209	17	121	0.8%	1.87 [1.02, 3.43]	2008
Scrutinio	48	138	20	128	0.8%	2.88 [1.59, 5.21]	2009
Anand (VALHEFT)	703	2916	273	2094	2.8%	2.12 [1.82, 2.47]	2009
Cohen-Solal (SENIORS)	163	704	194	1408	2.3%	1.89 [1.50, 2.38]	2009
Alehagen	76	235	62	229	1.4%	1.29 [0.86, 1.92]	2009
Wali	414	2566	166	1651	2.6%	1.72 [1.42, 2.08]	2010
Hebert	34	338	72	963	1.3%	1.38 [0.90, 2.12]	2010
Damman (COACH)	229	619	69	430	1.9%	3.07 [2.26, 4.17]	2010
Waldum	547	1080	305	1155	2.7%	2.86 [2.40, 3.41]	2010
Damman (CIBIS II)	162	833	220	1797	2.4%	1.73 [1.39, 2.16]	2010
Filippatos (BEST)	160	397	228	863	2.2%	1.88 [1.46, 2.42]	2011
Scrutinio (2011)	237	422	157	529	2.1%	3.04 [2.32, 3.97]	2011
Masson (GISSI-HF)	1035	2566	918	4369	3.1%	2.54 [2.28, 2.83]	2011
Subtotal (95% CI)		**64967**		**198998**	**60.5%**	**2.26 [2.08, 2.47]**	
Total events	26336		54701				
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 255.62$, df = 29 ($P < 0.00001$); $I^2 = 89\%$							
Test for overall effect: $Z = 18.68$ ($P < 0.00001$)							
Total (95% CI)		**342466**		**733638**	**100.0%**	**2.34 [2.20, 2.50]**	
Total events	54334		83184				
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 530.74$, df = 56 ($P < 0.00001$); $I^2 = 89\%$							
Test for overall effect: $Z = 26.65$ ($P < 0.00001$)							
Test for subgroup differences: $Chi^2 = 1.00$, df = 1 ($P = 0.32$), $I^2 = 0.0\%$							



- Subgroup chronic heart failure
- CKD as defined in individualized studies
- Mean FUP : 942±802 d
- OR for all-cause mortality : 2.26

Damman K, EHJ 2014

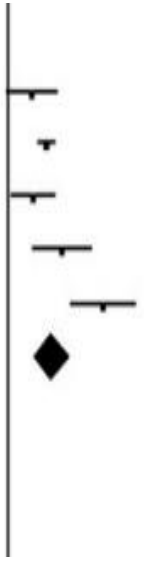
Worsening renal failure associated with outcome in chronic HF

Meta-analysis, 57 studies, 1’076’104 patients

Chronic Heart Failure							
De Silva	44	161	219	1055	4.6%	1.44 [0.98, 2.09]	2005
Khan	628	2060	879	4475	6.0%	1.79 [1.59, 2.02]	2006
Jose	58	223	316	1631	4.9%	1.46 [1.06, 2.02]	2006
Iglesias	47	221	49	461	4.2%	2.27 [1.47, 3.52]	2008
Damman	30	106	76	894	3.9%	4.25 [2.62, 6.89]	2010
Subtotal (95% CI)		**2771**		**8516**	**23.6%**	**1.96 [1.48, 2.61]**	
Total events	807		1539				

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 16.14$, df = 4 ($P = 0.003$); $I^2 = 75\%$

Test for overall effect: $Z = 4.66$ ($P < 0.00001$)



- Subgroup chronic heart failure
- WRF as defined in individualized studies (absolute / relative increase in serm creatinine, cystatin C or eGFR)
- OR for all-cause mortality : 1.96

Damman K, EHJ 2014

Effects of HF and RAASi on GFR

Heart failure

↓

Low CO / low BP

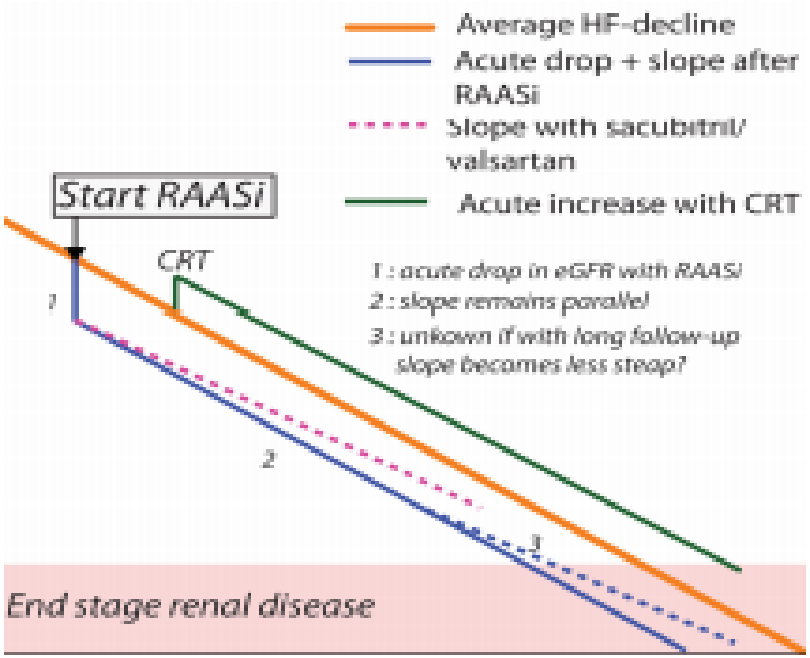
↓

Triggers renal auto-regulation of blood flow to preserve GFR

↓	↓
A. Afferens	A. Efferens
↓	↓
Dilation	Constriction
↓	↓
1. Through direct Myogenic reflex	Through AgII via
2. Through NO > Macula densa (low NaCl sensing)	1. sympathetic stimulation of juxtaglomerular cells
	2. Through PGE2 > Macula densa (low NaCl sensing)

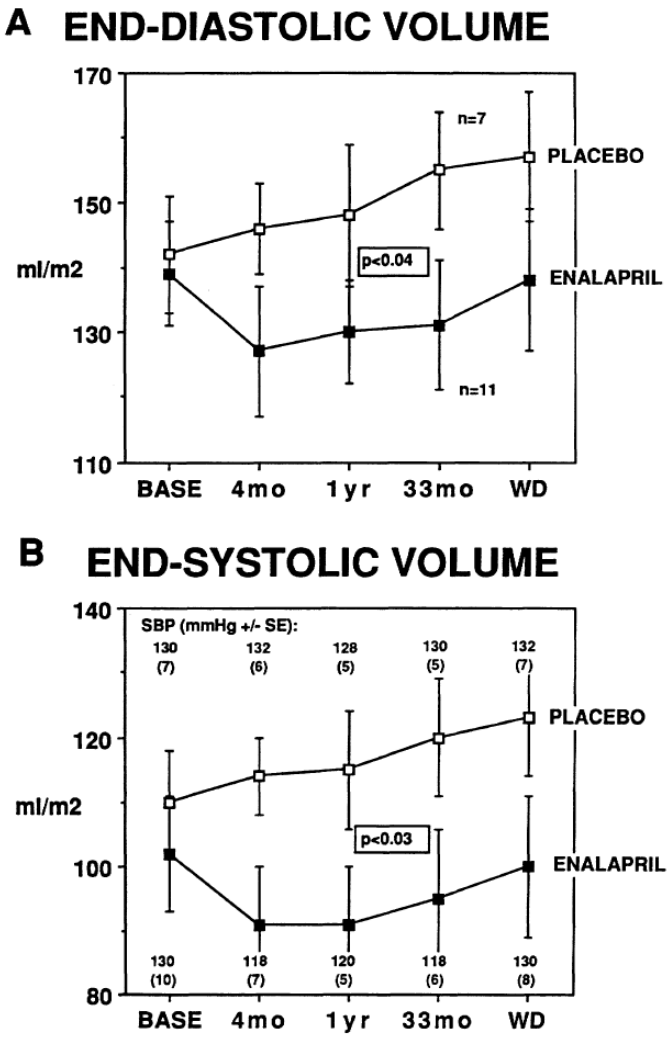
RAAS inhibition

↓ GFR about 15-20%



- Intraglomerular HD change
- ≠ kidney injury
- Usually reversible
- As opposed to DM or CKD, no data showing long term decrease of loss pace

Effects of RAASi on heart failure and prognosis



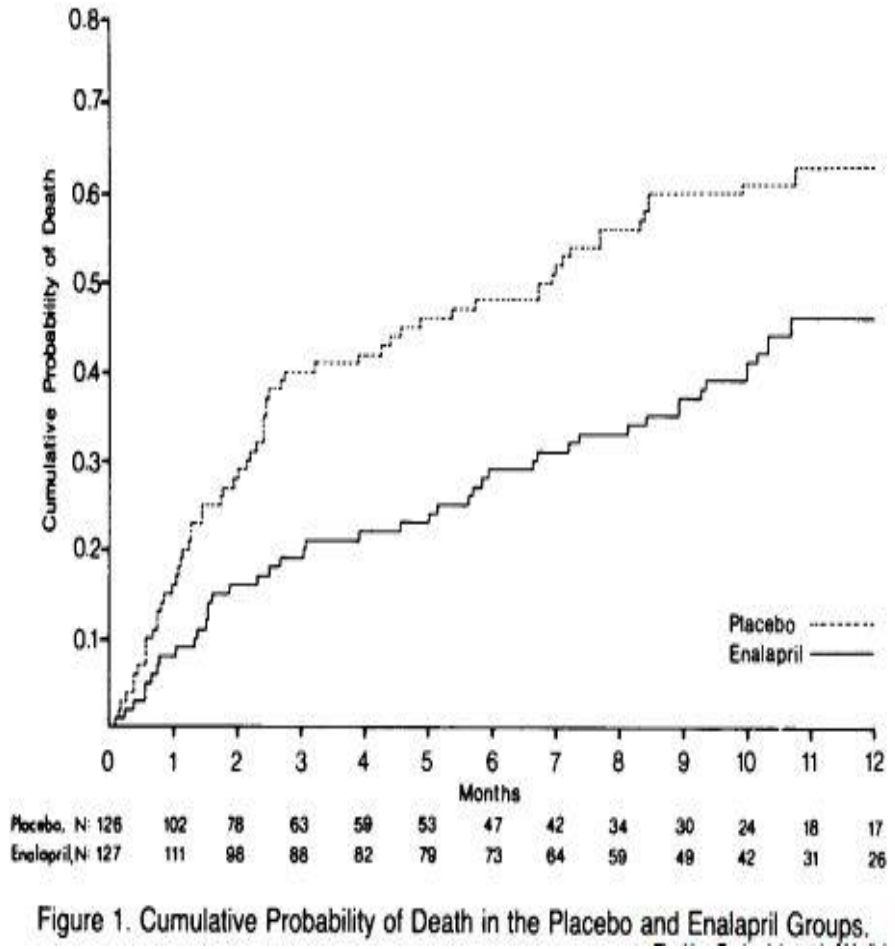


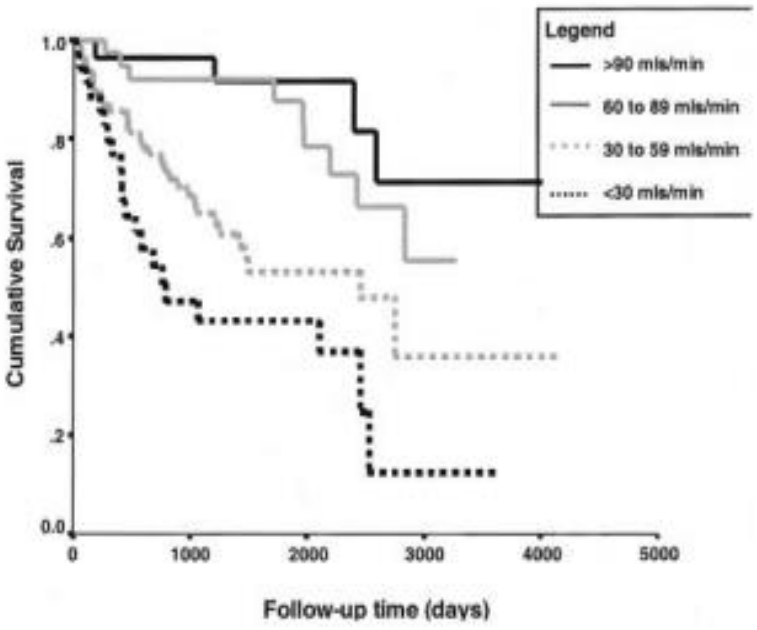
Figure 1. Cumulative Probability of Death in the Placebo and Enalapril Groups.

Konstam et al , SOLVD trial, Circulation 1992

CONSENSUS trial, NEJM 1992

Benefit of RAASi…. Also in CKD patients !

Cohort of 1042 HF patients, 69 years old
17% GFR >90ml/'; 26% GFR 60-90 ml/'; 41% GFR 30-60 ml/'; 16% GFR<30 ml/'



OR for global mortality at 1 year with GFR<30 : 2.48

1% increase mortality for each 1 ml/' GFR loss

ACEi / ARB lower 1 y mortality (OR = 0.4 (65% CI 0.24-0.66) in the whole cohort

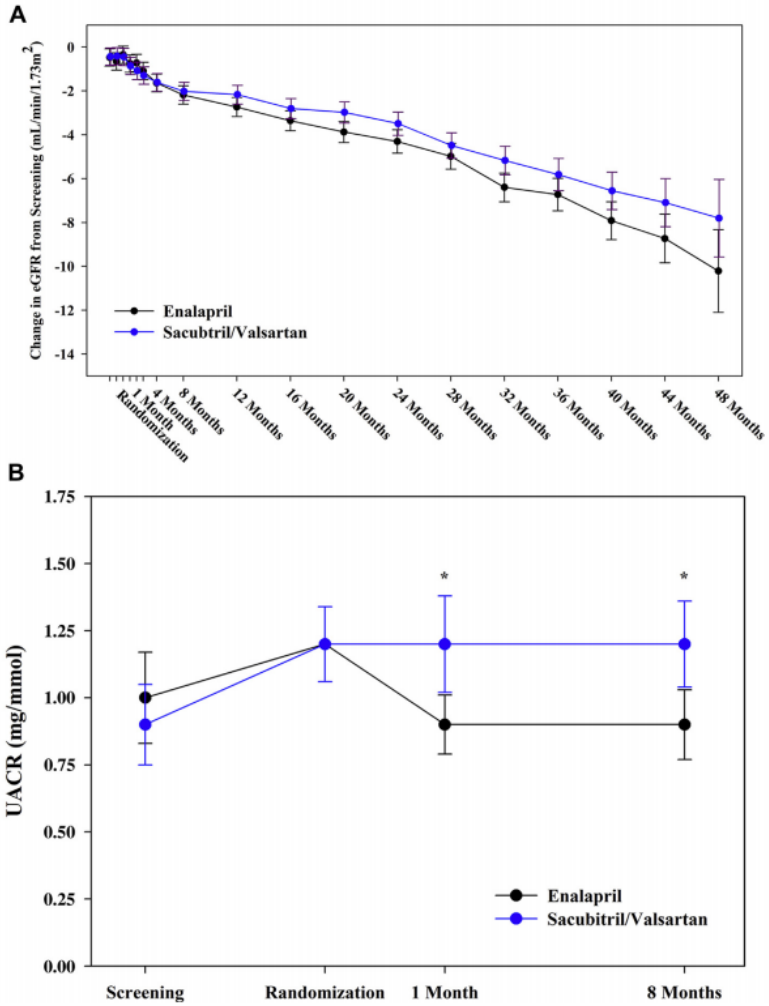
ACEi / ARB effect on mortality similar :

- In patients with GFR >60ml/' (OR=0.28; 95% CI 0.11-0.7)
- In patients with GFR <60 ml/' (OR=0.46; 95% CI 0.26-0.82)

Mc Alistair, Circulation 2004

Benefit of ARNi as compared to ACEi on GFR loss

Sub-analysis of the PARADIGM-HF trial, 8399 patients
GFR 70 +/- 20 ml/' at screening; 33% with CKD (<60 ml/')



GFR loss less important on Entresto than on enalapril (-1.61 ml/year)

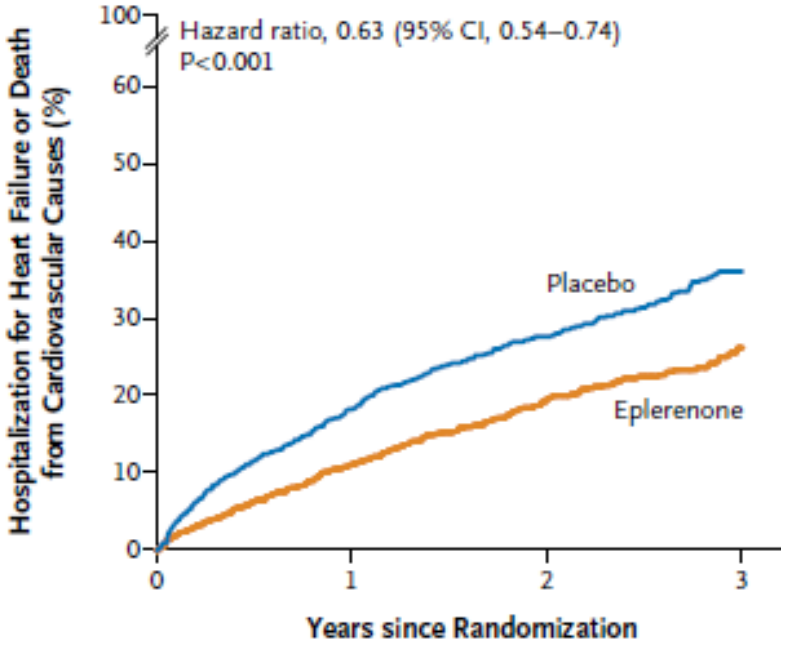
Despite increased albuminuria

- Transient after ARNi cessation
- Generally associated with true renal injury (diabetes) leading to true WRF
- Transient effect of natri-uretic peptides on mesangiual cells and podoctytes ?

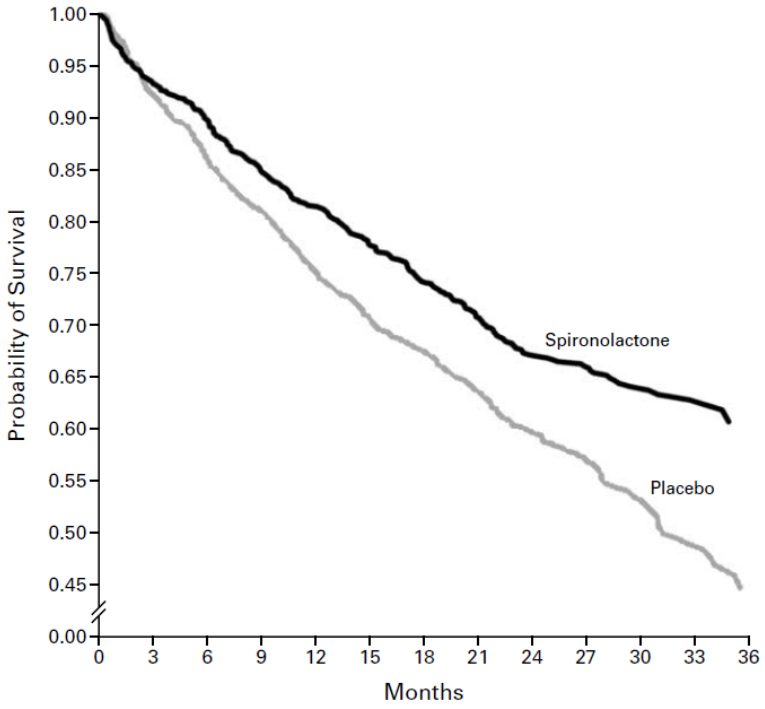
Damman K. JACC HF 2018

What about MRAs and renal failure ?

Heart failure patients benefit form MRA
Including with advanced symptoms (RALES trial with spironolactone)



No. at Risk				
Placebo	1373	848	512	199
Eplerenone	1364	925	562	232



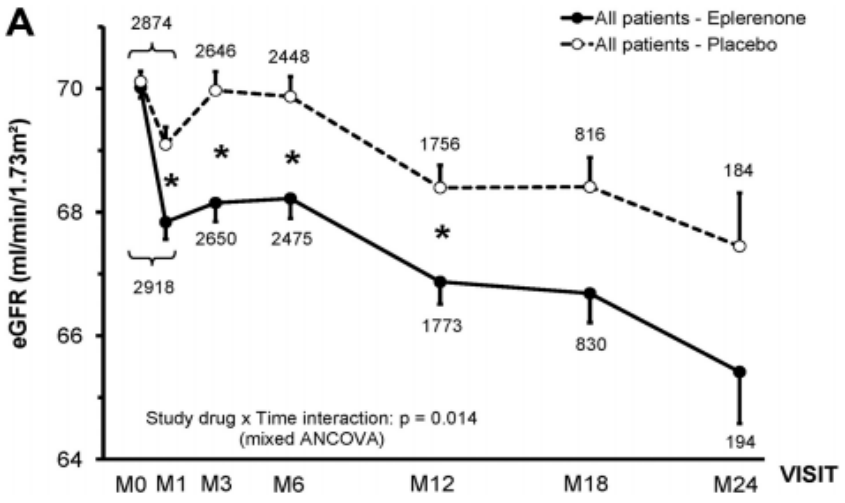
No. at Risk													
Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

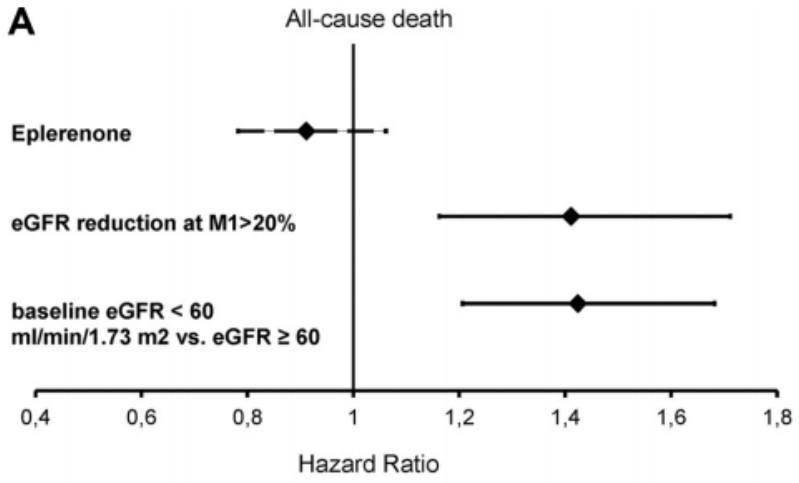
Zannad F, NEJM 2011

Pitt B, NEJM 1999

Effect of MRAs on GFR and prognosis with CKD

Ephesus trial. Post MI. LVEF <40%.





Small placebo-adjusted effect of eplerenone on GFR : -1.4 ml/' / year

Patients with deteriorated renal function after MI had worse prognosis

But eplerenone is of equal benefit with or without CKD

HR for death and hospitalization without eplerenone according to GFR

- **>60 ml/' : 1.4 (95% CI 1.23-1.6)**
- **<60 ml/': 1.23 (95% CI 1.01-1.5)**

Rossignol. Circulation 2012

Practical management of RAASi in «advanced» HF and CKD

« Advanced » Heart failure patient with CKD and low-dose RAASi

↓

(S creatinine > 50% baseline)
S creatinine > 265 µmol/L
eGFR < 25 ml/min

↓

No potential to titrate RAASi

↓

Assess congestion

No

↓

Assess
Hypotension/
Hypoperfusion

No

↓

Severe worsening
renal function
Intrinsinc renal disease

↓

Nephrologist

Yes

↓

Treat congestion
Re-assess renal function

Yes

↓

Reduce (stop?) RAASi
Consider inotropic support, heart transplantation, MCS
as appropriate

(S creatinine < 50% baseline)
S creatinine < 265 µmol/L
eGFR > 25 ml/min

↓

RAASi must be titrated
(unless other contra-indication)
Until maximal dose
Until thresholds reached
(assess K+ and Screat every 2 wks)

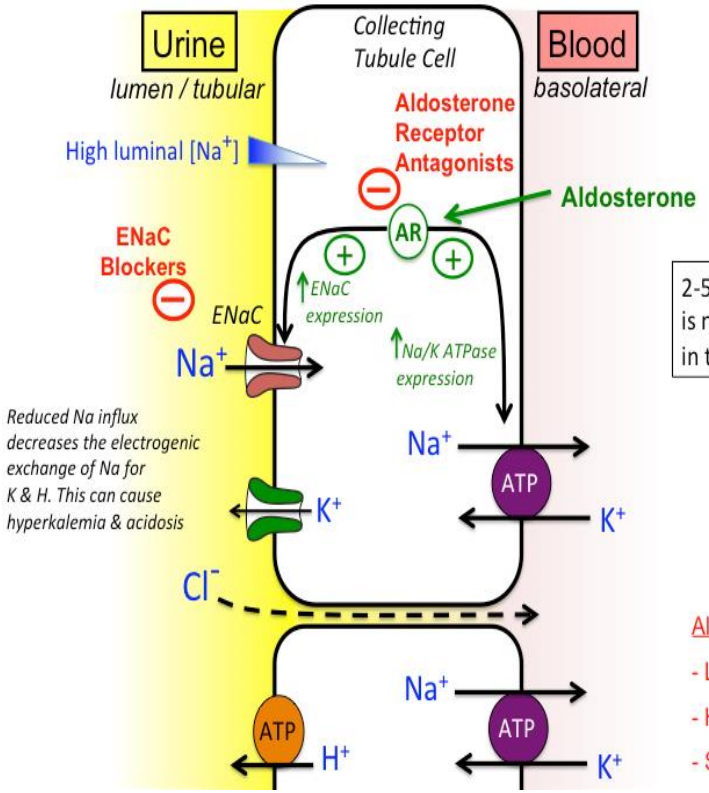
After Mullens W, EJHF 2020 and Ponikowski P, EHJ 2016

Treatment optimisation

with

Hyperkalemia

RAASi increase serum K+ level, especially MRAs



2-5% of filtered Na is normally reabsorbed in the collecting duct

Aldosterone antagonists

- Loss of Na & Water
- Hyperkalemia
- Some risk for acidosis

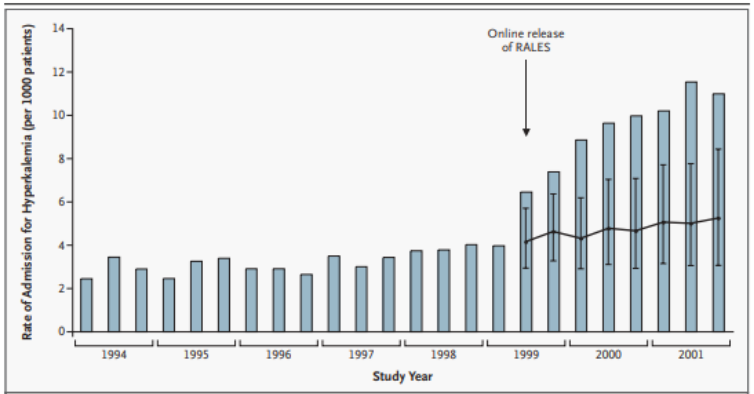


Figure 2. Rate of Hospital Admission for Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.

Each bar shows the rate of hospital admission for hyperkalemia per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected admission rates for hyperkalemia derived from interventional ARIMA models, with I bars representing the 95 percent confidence intervals.

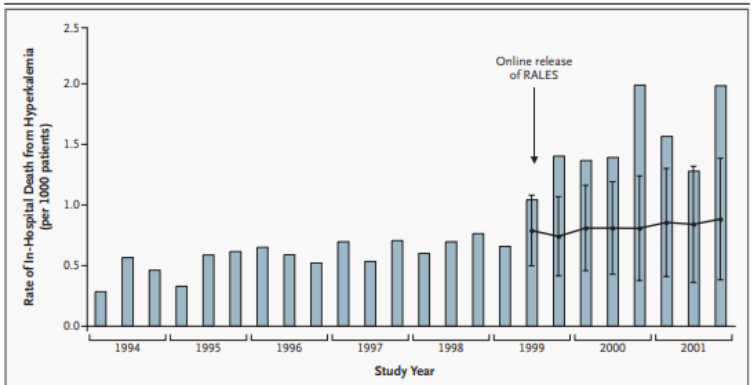


Figure 3. Rate of In-Hospital Death Associated with Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.

Each bar shows the rate of in-hospital death associated with hyperkalemia per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected death rates derived from interventional ARIMA models, with I bars representing the 95 percent confidence intervals.

Juurlink, NEJM 2004

Management of hyperkalemia

Mild hyperkalemia : 5.1-5.5 mmol/L
Moderate hyperkalemia : 5.6-6.0 mmol/L
Severe hyperkalemia : ≥ 6.1 mmol/L

Associated with increased mortality

HyperK > 2 times per year in 50% HF patients with DM and / or CKD

2 novel agents available :

- Sodium zirconium cyclosilicate, not (yet?) reimbursed in CH
- Patiromer, approved for re-imbursment in CH, K+/Ca++ exchange in the colon.
  - Rapid K+ normalisation
  - Low incidence of hypokalemia
  - RAASi titration enablement
  - No data on hard endpoints yet (DIAMOND trial on track)
  - Well tolerated, but watch hypomagnesemia and drug interactions

Practical management of hyperkalemia

	Normokalemia	Chronic hyperkalemia			
1. Serum K^+	Column A **4–5 mEq/L[1]**	Column B **Mild** **5.1–5.5 mEq/L**		Column C **Moderate** **5.6–6 mEq/L**	Column D **Severe** **> 6 mEq/L**
2. Patients undergoing RAASi optimization	Not on maximal tolerated RAASi dose	Not on maximal tolerated RAASi dose	Not on maximal tolerated RAASi dose *but* **previous hyperkalemia when up-titrating RAASi** *or* **HF and/or CKD 3b–4[a] and/or DM**	Whether on or not on maximal tolerated RAASi dose	Whether or not on maximal tolerated RAASi dose
3. Actions	Initiate/up-titrate RAASi	Initiate/up-titrate RAASi	**Initiate/up-titrate novel potassium binders/patiromer[b] until serum $K^+ \leq 5.0$ mEq/L[4]**	**Initiate/up-titrate novel potassium binders/patiromer[b] until serum $K^+ \leq 5.0$ mEq/L[4]**	**Discontinue/Reduce RAASi** and **Initiate/up-titrate novel potassium binders/patiromer[b] until serum $K^+ \leq 5.0$ mEq/L[4]**
	Monitor K^+[2]	Monitor K^+[2]	Monitor K^+[3]	Monitor K^+[3]	
	$K^+ \leq 5$	$K^+ \leq 5.5$	If $K^+ \leq 5.0$ up-titrate RAASi and maintain novel potassium binders/patiromer[b][4]	If $K^+ \leq 5.0$ up-titrate RAASi and maintain novel potassium binders/patiromer[b][4]	
	$K^+ > 5$ **see columns B, C, or D**	$K^+ > 5.5$ **see columns C or D**			
4. Follow-up	**Maintain RAASi on maximal tolerated doses, monitor K^+ and renal function, and check for additional causes of hyperkalemia** (K^+ diet content, salt substitutes, drugs impairing renal function and K^+ excretion)				

Silva Cardoso et al , HF rev 2021

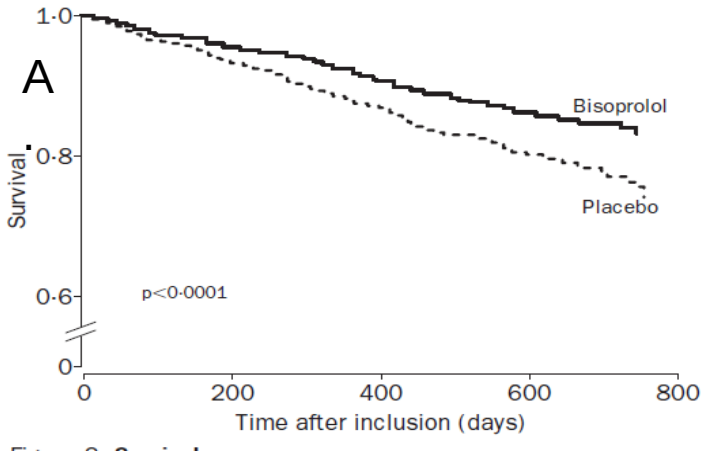
Optimalising

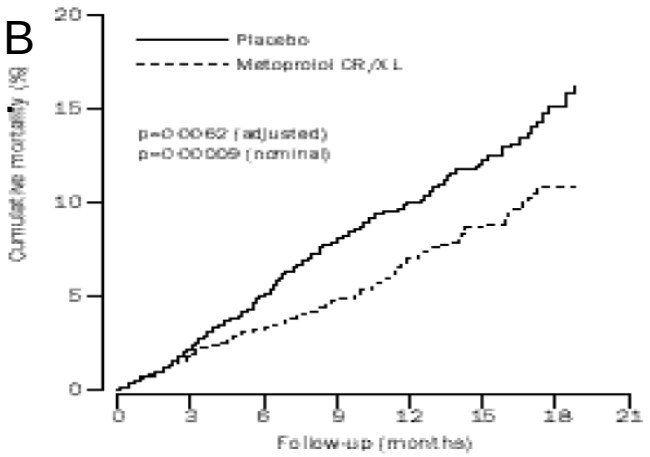
Beta blockers

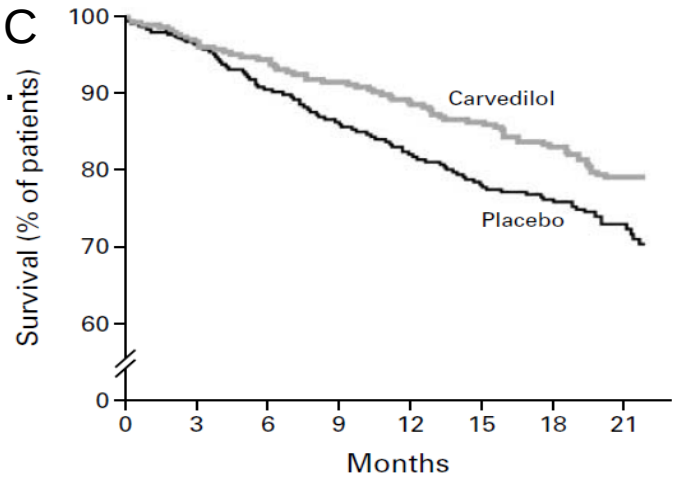
And

Heart rate

Practical management of hyperkalemia





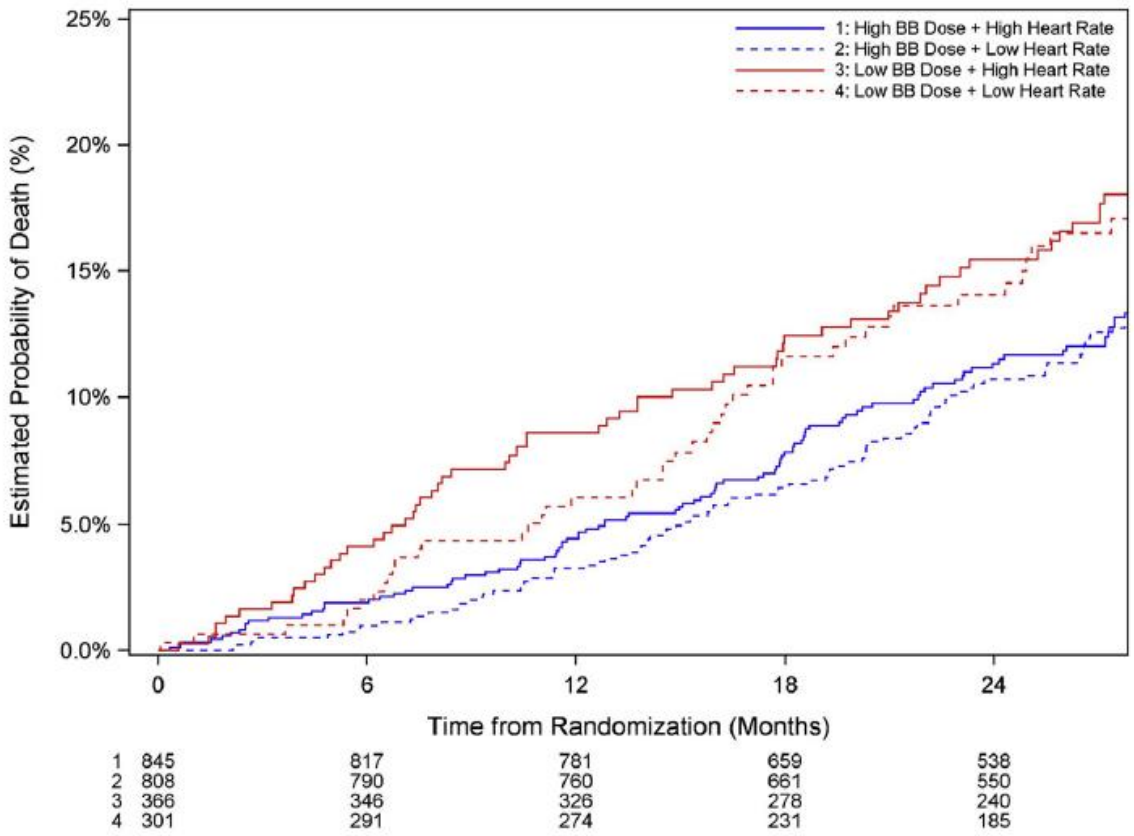


Beta-blockers		
Bisoprolol	1.25 *o.d.*	10 *o.d.*
Carvedilol	3.125 *b.i.d.*	25 *b.i.d.*[d]
Metoprolol succinate (CR/XL)	12.5–25 *o.d.*	200 o.d.
Nebivolol[c]	1.25 *o.d.*	10 *o.d.*

Should we aim at maximal dosing or at specific heart rate (in SR) ?

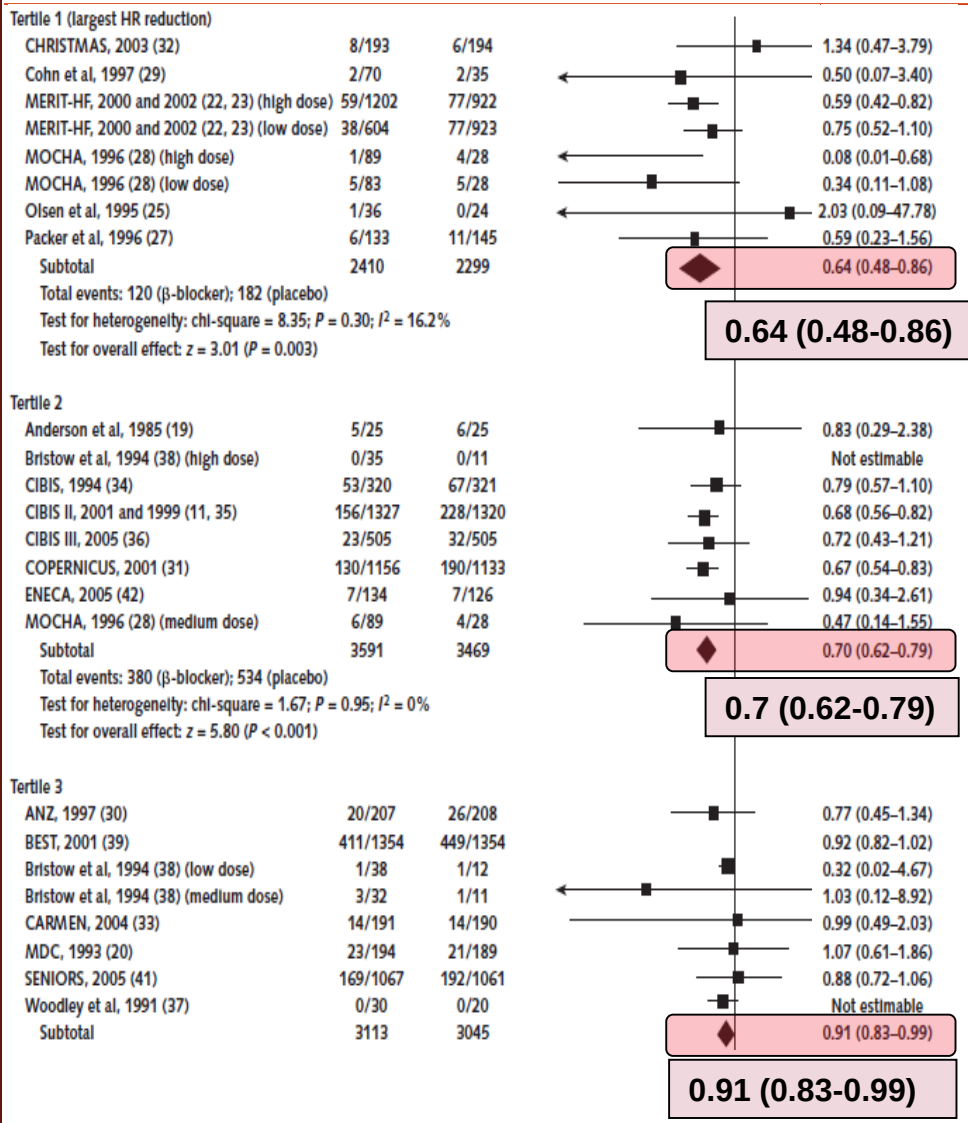
HF-Action trial, 2331 patients, all ambulatory, LVEF < 0.35

FIGURE 1 All-Cause Death or Hospitalization by BB Dose (High/Low) and HR (High/Low) at Baseline



Fiuzat M et al, JACC HF 2016

Should we aim at maximal dosing or at specific heart rate (in SR) ?



Mortaliy

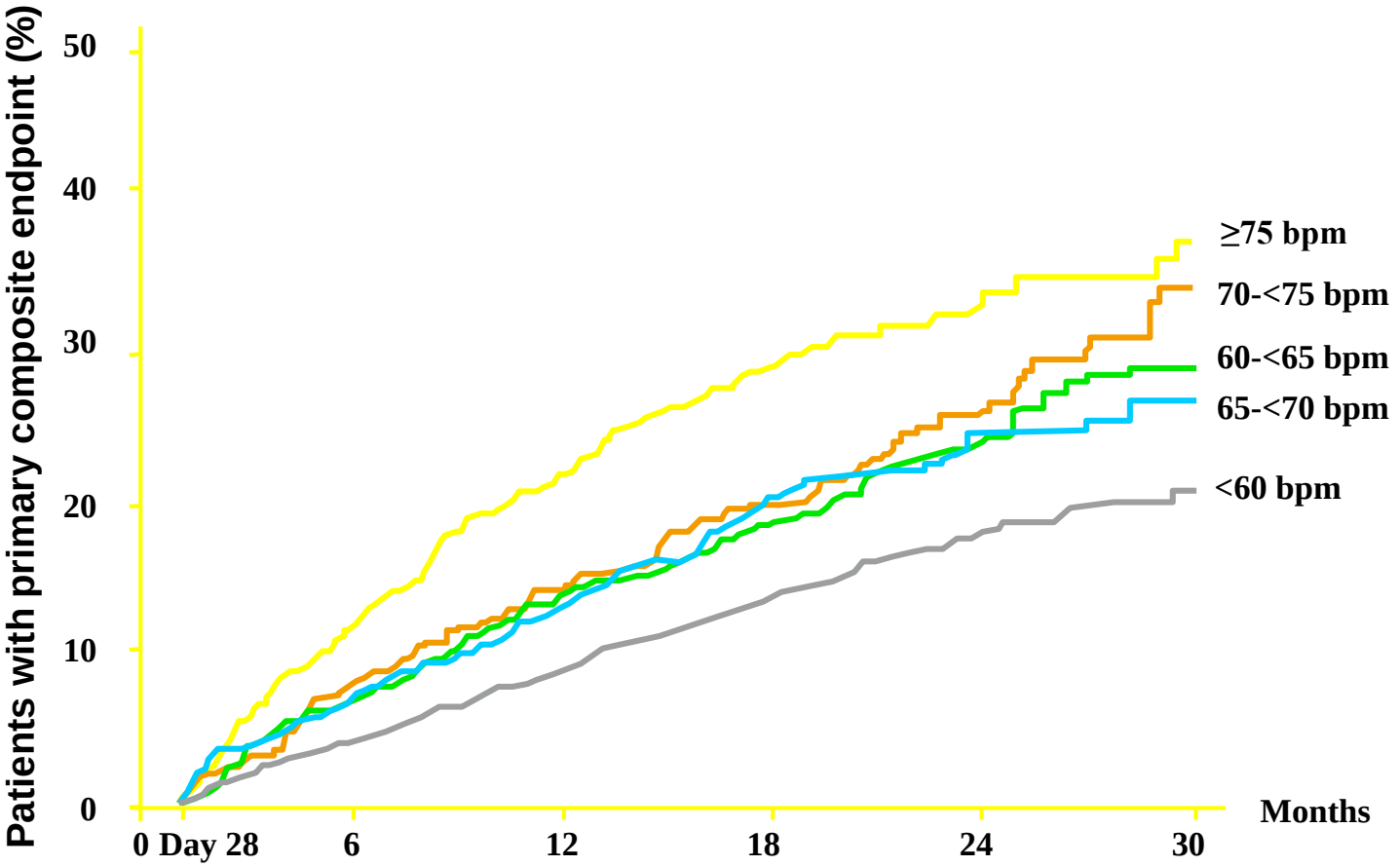
- dépends HR lowering (tertiles)
- ↓18% RR by 5 bpm HR decrease
- Not related to the dose !
  - Dose > 50% target dose

    RR = 0.74
  - Dose < 50% target dose

    RR = 0.78

Mc Alister et al, Annals Int Med 2009

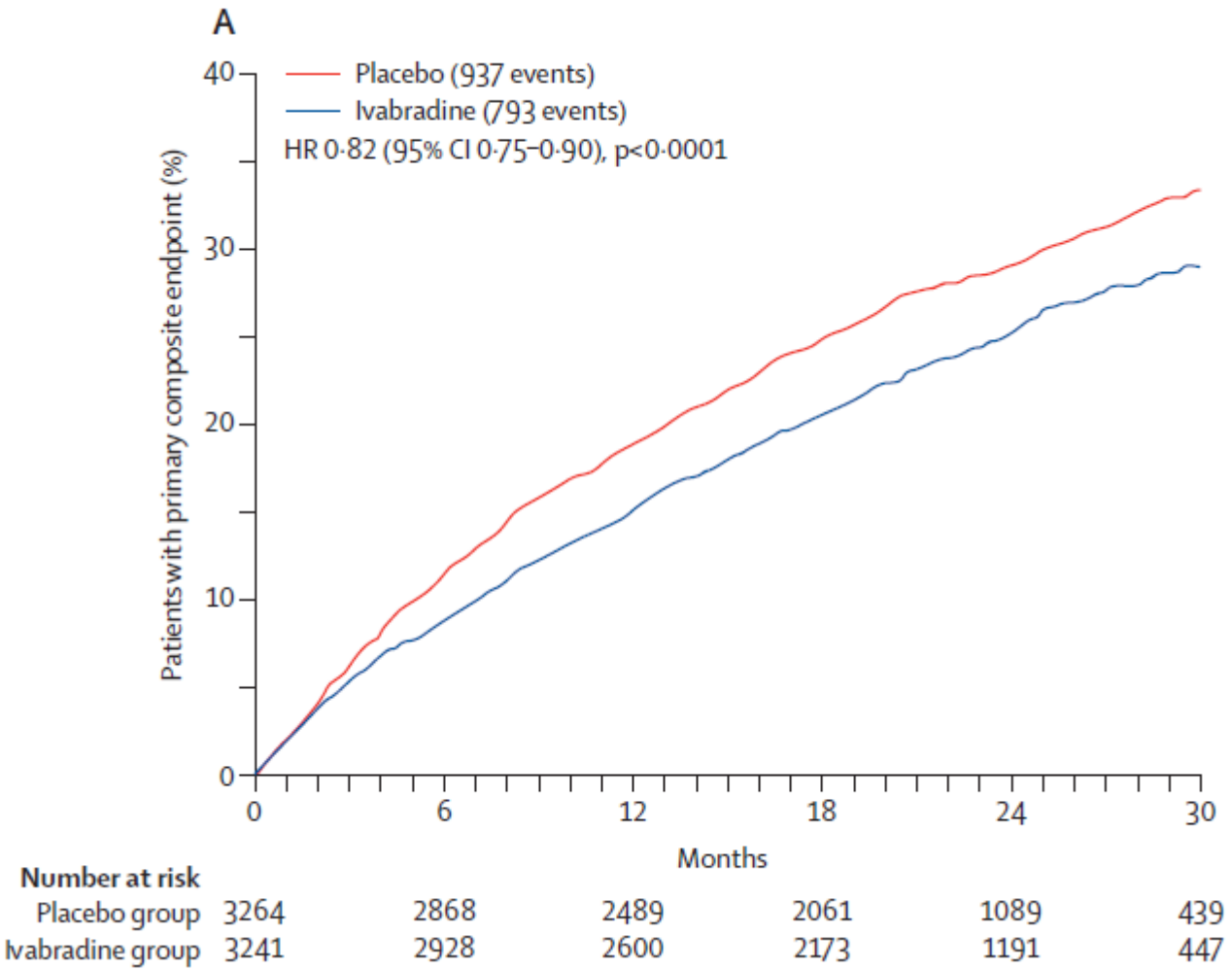
Should we aim at maximal dosing or at specific heart rate (in SR) ?



Swedberg et al, the SHIFT Trial, Lancet 2010

Should we aim at maximal dosing or at specific heart rate (in SR) ?

HR ≥70 bpm insinus rythm, Ivabradine vs placebo



Swedberg et al, the SHIFT Trial, Lancet 2010

Optimizing heart failure therapy

in advanced heart failure :

Other therapies

Other therapies to optimize HF treatment in AdHF

CRT

Of benefit in ambulatory stage IV patients

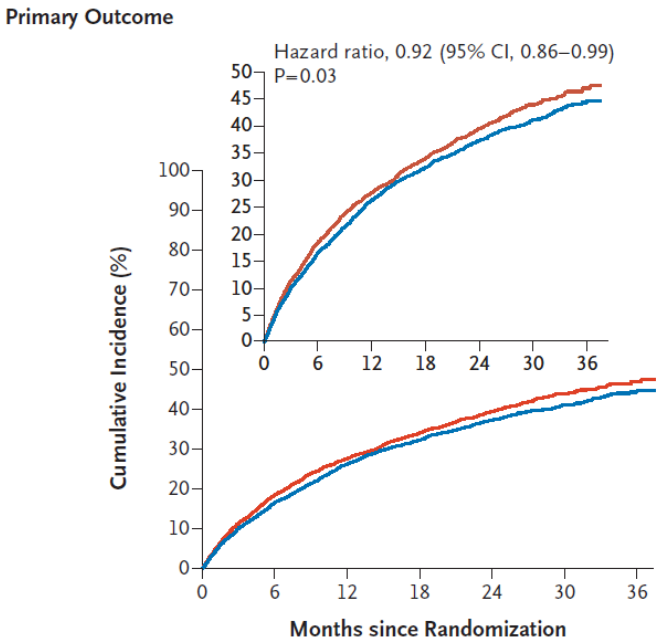
Probably of benefit in inotrope dempendent patients

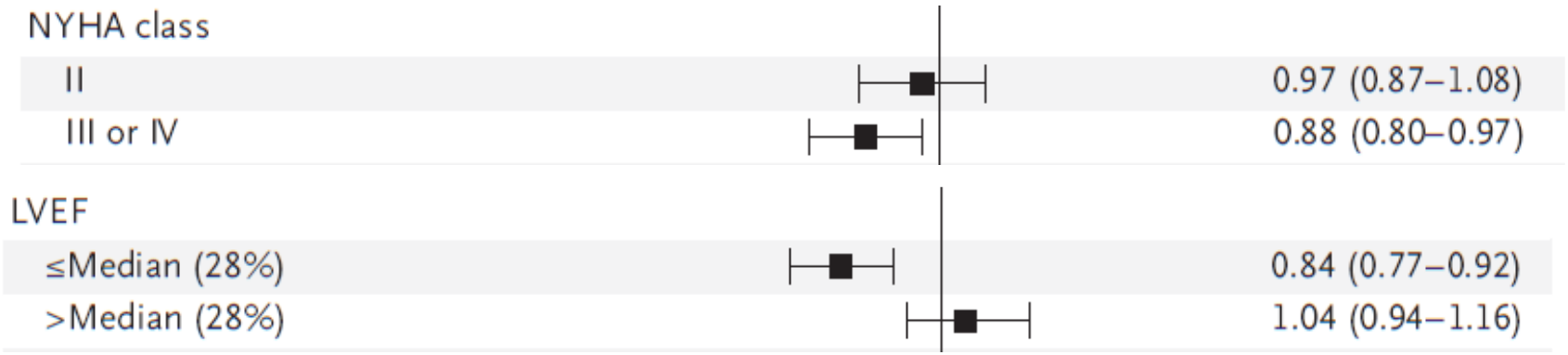
SGLT2i

Not enough data instege IV patients, not enough data in AdHF

Other therapies to optimize HF treatment in AdHF

Omecantiv mercabile





Teerlink J, the GALACTIC-HF trial, NEJM 2020

Mrs I. M; 58 years old in 2017

After 1 year

Clinical Assessment

- No congestion, IVC 17 mm, inspiratory collapse 40%
- BP : 94 /60 mmhg
- Sinus rythm 64 bpm, narrow QRS (90 ms)

Investigations

- LVEF 35%, no significant MR, no RV dysfunction
- Peak VO2 : 15.4 ml/kg /min, VE/VCO2 slope 32.5

Mrs I. M; 57 years old in 2017

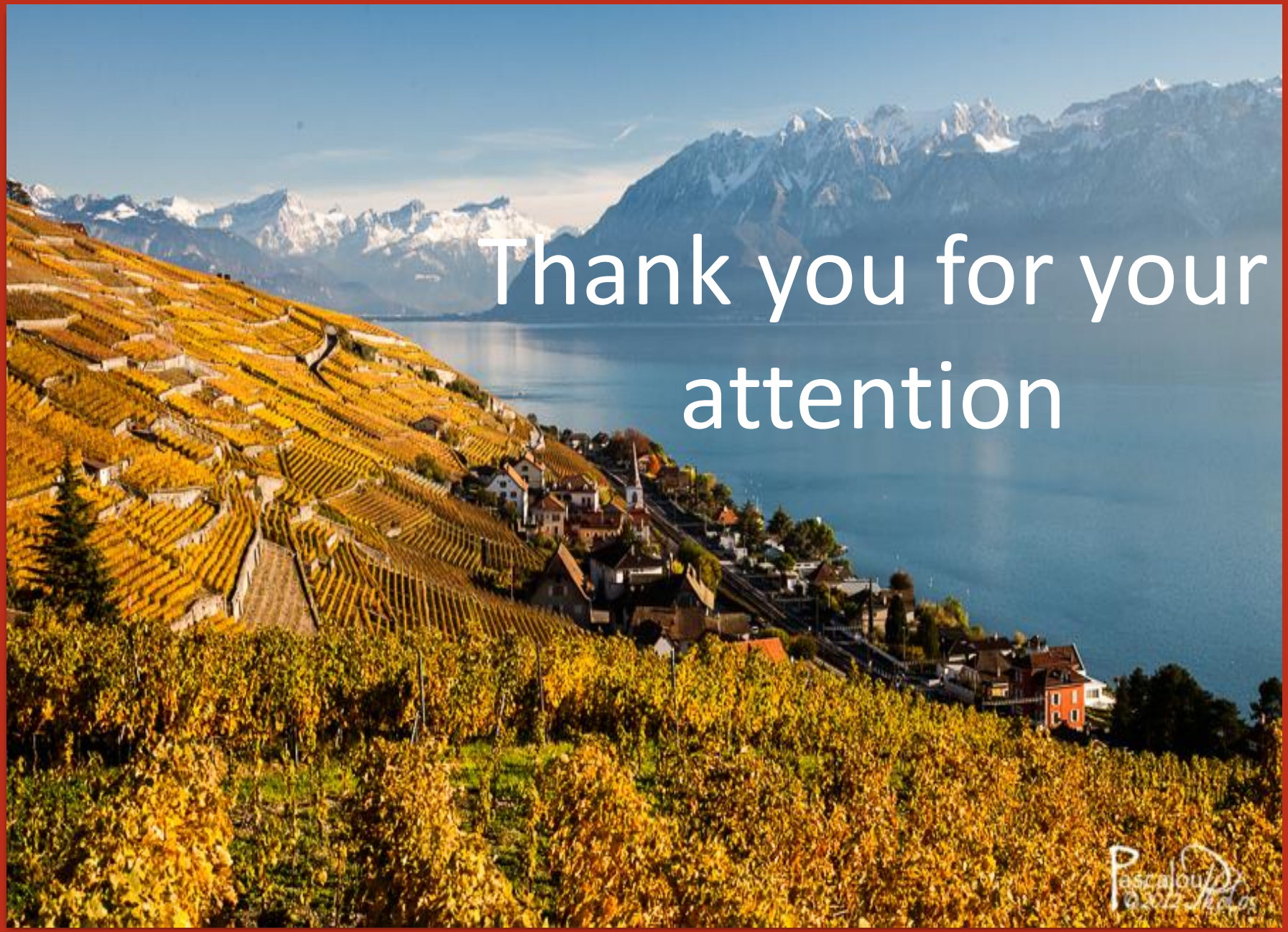
Labo :

- NTproBNP 1600
- Creatinine 196 umol/l
- K+ 4.9 mmol /L

Treatment

- Candesartan 8 mg x 2
- Carvedilol 12.5 x 2
- Spironolactone 25 mg
- Torasemide 5 mg

ICD in primary prevention, no sustained VT


Thank you for your attention