ECOCARDIOCHIRURGIA®
ECO-RM-TC CHIRURGIA-INTERVENTISTICA

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X CONGRESSO NAZIONALE
ECOCARDIOCHIRURGIA 2018

da un'idea di Antonio Mantero

MILANO, 9-11 APRILE 2018

INSUFFICIENZA CARDIACA

La terapia medica

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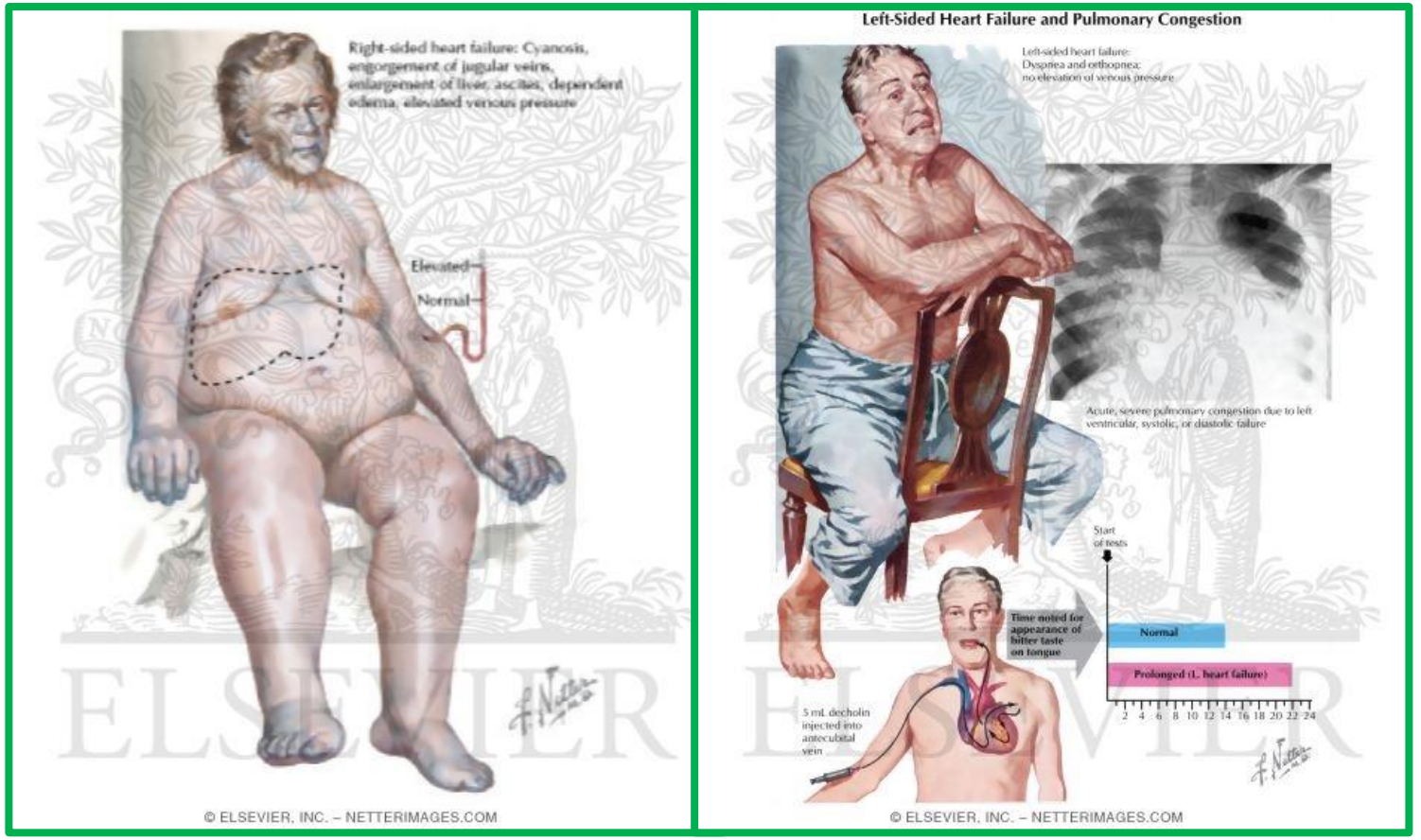
Dr.ssa Rita Belfiore (Pordenone)

Heart Failure: *"…a clinical syndrome characterised by symptoms (such as breathlessness, ankle swelling and fatigue) and signs (eg, raised jugular venous pressure, pulmonary crackles and pheripheral oedema) caused by structural or functional cardiac abnormalities that lead to elevated intracardiac pressure or a reduced cardiac output at rest or during stress…"*

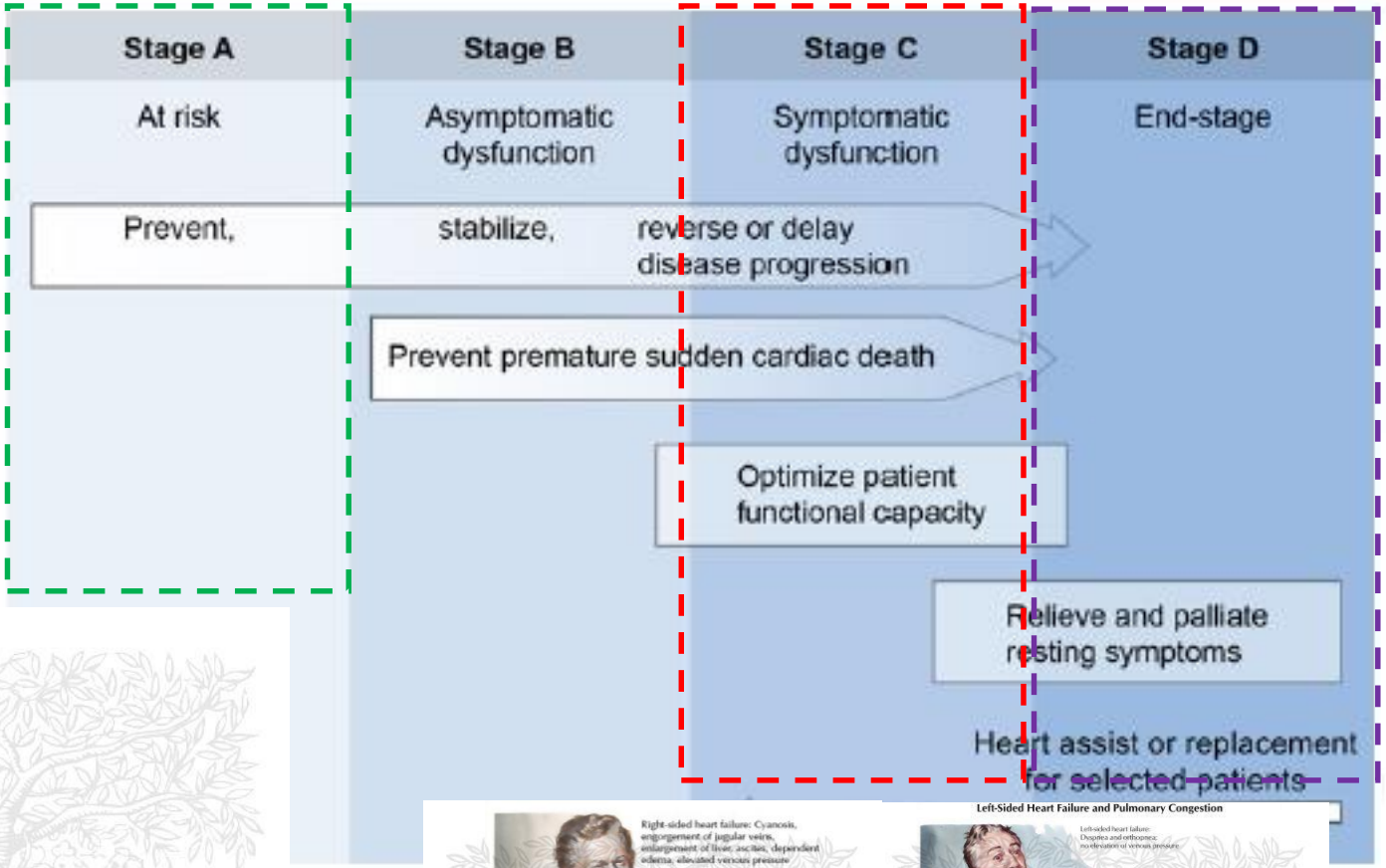


Stage A

Medical therapy

Prevention and treatment of modifiable CV risk factors:

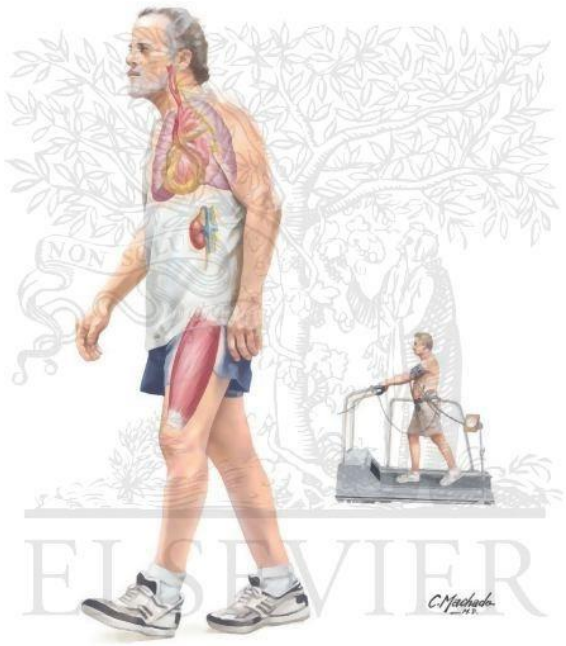
- Liraglutide
- Empagliflozin

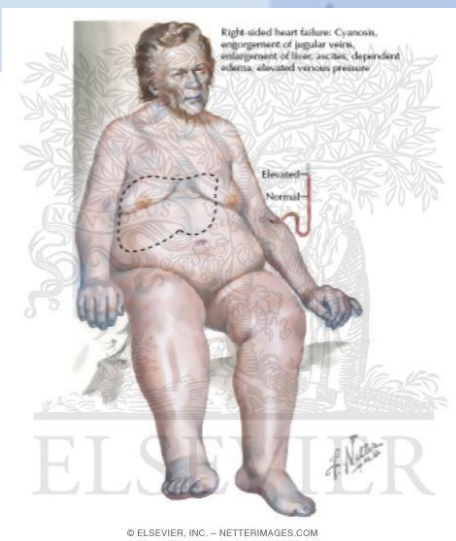


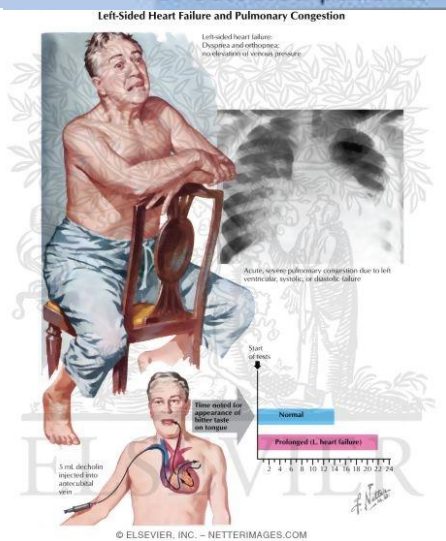
Stage D

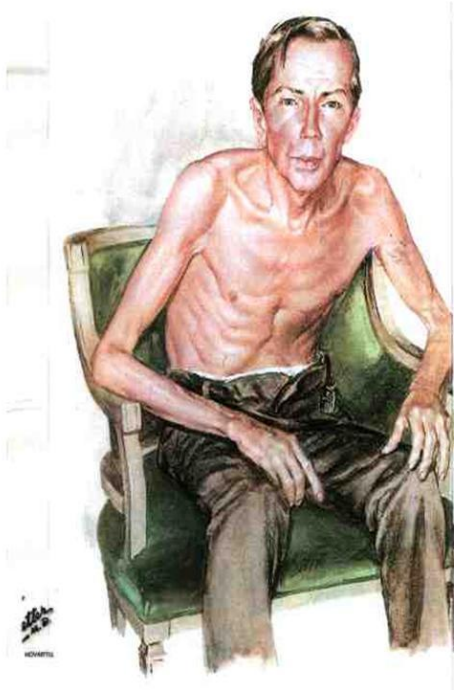
Medical therapy

- Vericiguat
- Omecamtiv mecarbil
- Cardiac regenerative therapy









Circulation. 2016;133:2671-2686

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

Neurohormonal antagonists are the backbone of MT:
ACE-i
ARB
MRA
BB
ARNI

Eur Heart J (2016) ***37****, 2129-2200*

1987 CONSENSUS
NYHA IV
Enalapril vs placebo
↓ all-cause death
↓ NYHA class
↓ CCF progression

1992 SOLVD
EF≤35% asymptomatic
Enalapril vs placebo
↓ HF incidence
↓ HF admission

1999 RALES
NYHA III-IV
Spironolactone vs placebo
↓ all-cause death and SD
↓ all-cause H admission
↑ NYHA class
↓ CCF progression

1999 MERIT-HF
EF≤40%, NYHA II-IV
Metoprolol vs placebo
↓ all-cause death

1999 CIBIS-II
EF≤35%, NYHA III-IV
Bisoprolol vs placebo
↓ all-cause death and SD
↓ all-cause H admission

2001 COPERNICUS
EF ≤25%, NYHA III-IV
Carvedilol vs placebo
↓ all-cause death
↓ H admission + all cause-death

2001 ValHeFT
EF<40%, NYHA II-IV
Valsartan vs placebo
↓ mortality and morbidity

2003 CHARM
EF ≤40%, NYHA II-IV
Candesartan vs placebo
↓ combined CV death and HF hospitalisation

2003 COMET
EF<35%, NYHA II-IV
Carvedilol vs Metoprolol
↓ all-cause death

2011 EMPHASIS-HF
EF ≤35%, NYHA II
Eplerenone vs placebo
↓ all-cause and CV death

2011 SHIFT
EF ≤ 35% symptomatic, SR
Ivabradine vs placebo
↓ HF admission

2014 PARADIGM-HF
EF ≤ 40%, NYHA II, III, IV
LCZ696 vs enalapril
↓ CV death and HF admission

Timeline of principal RCT for MT in HFrEF

BB
IVABRADINE
ACE-i/ARB
MRA
ARNI

SHIFT

Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial

Setting: HF with EF≤35%, SR, HR ≥70bpm

Ivabradine vs Placebo

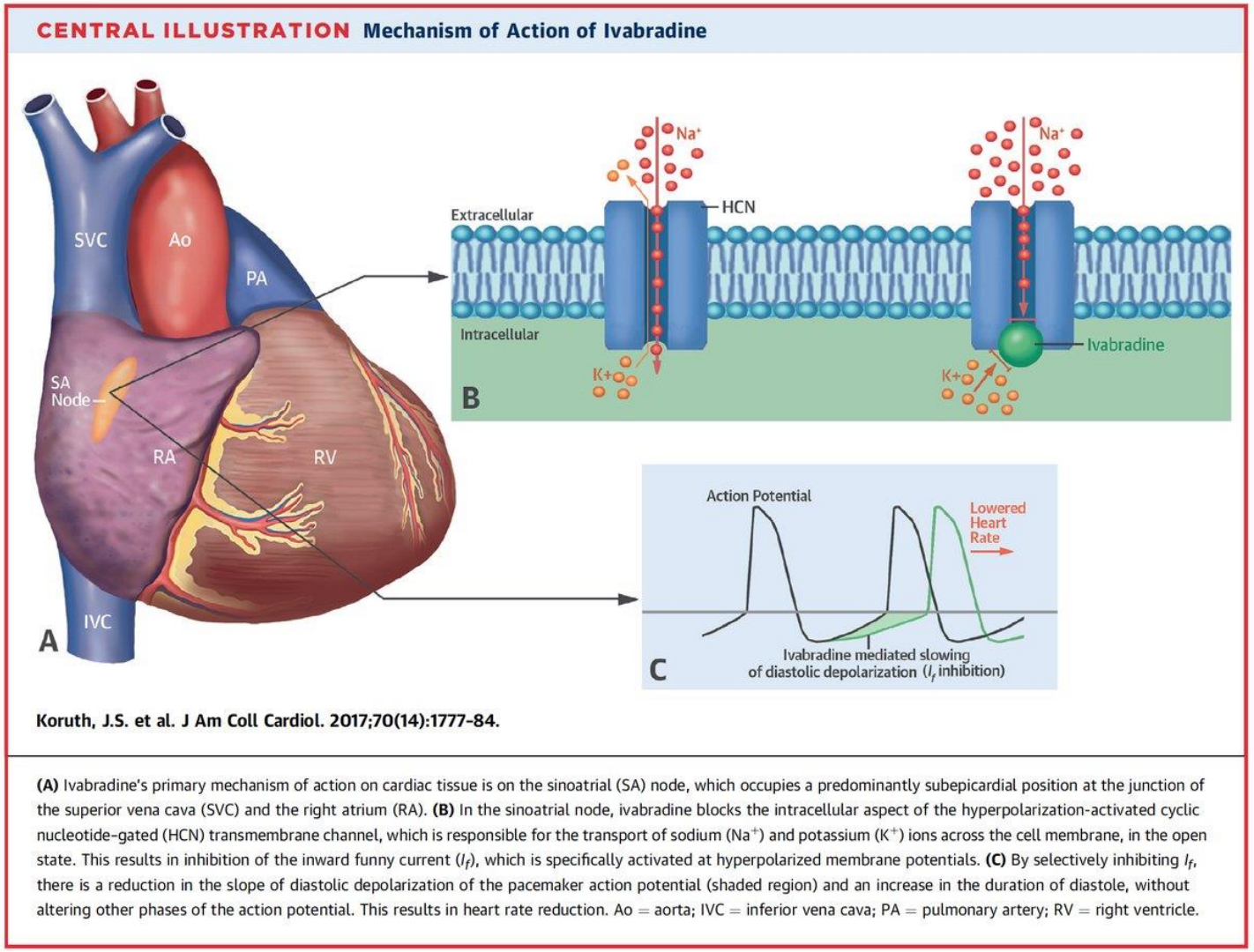
Median f-up: 22.9 months

I endpoint: composite of CV death and HF admission

II endopint: composite of CV death and HF admission in pts at ≥50% of the target daily dose of a BB

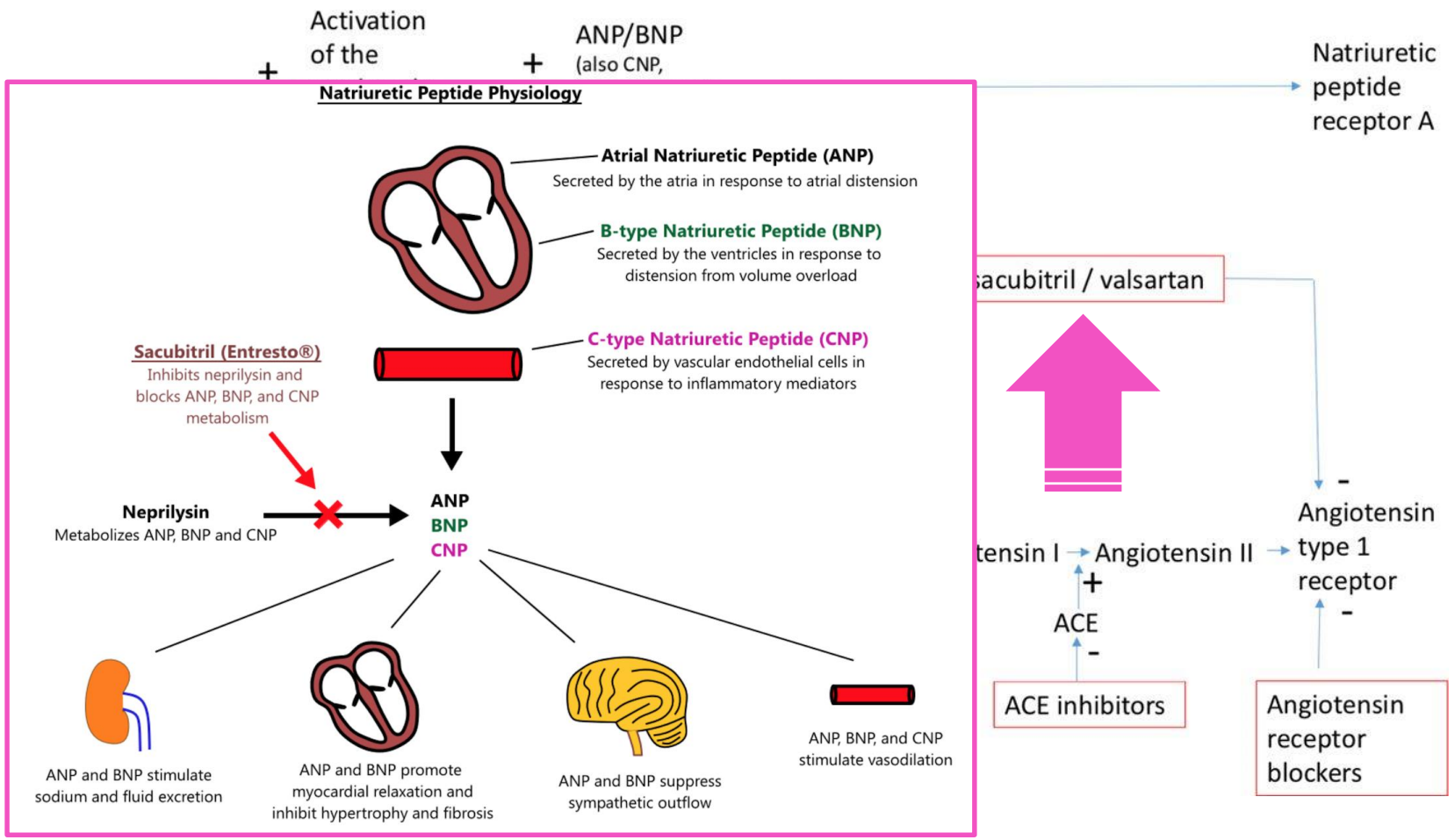
Results:

- Significant ↓ in I endpoint, mainly due to reductions in HF admissions
- In those on ≥50% target daily BB dose→ ↓HF admissions, but NO ↓ in mortality



Lancet. 2010 Sep 11;376(9744):875-85

PATHWAYS BLOCKED BY ACE-I, ARB AND NEPRILYSIN INHIBITORS



N Engl J Med 2014;371:993-1004

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

Setting: EF≤40% (than≤35%), NYHA II-IV, pts taking ACE-i/ARB for at least 4 weeks
Median f-up: 27 months
I endpoint: composite of CV death and HF admission

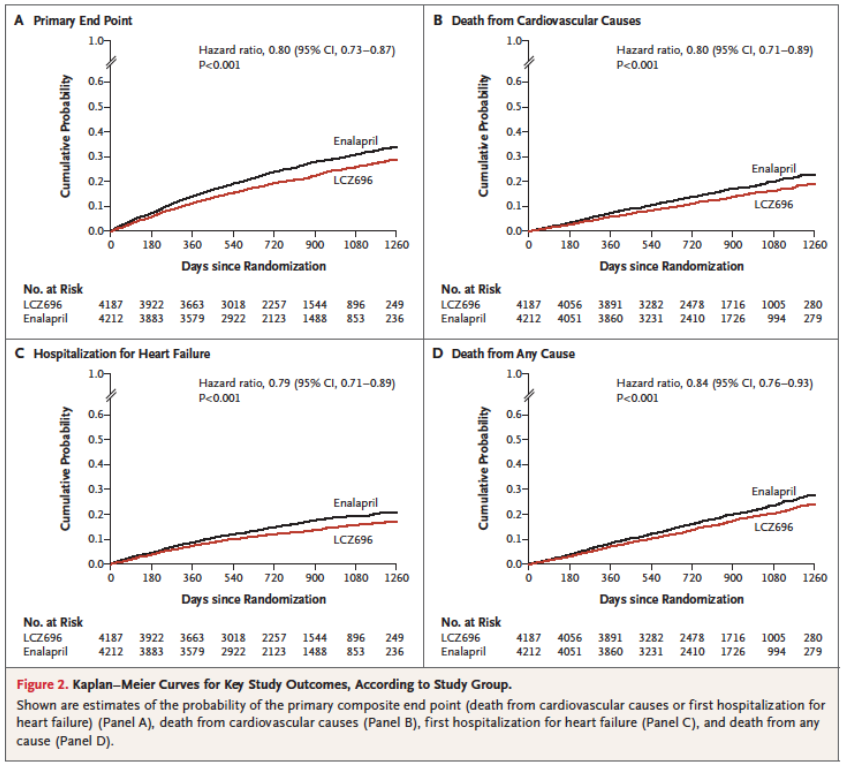
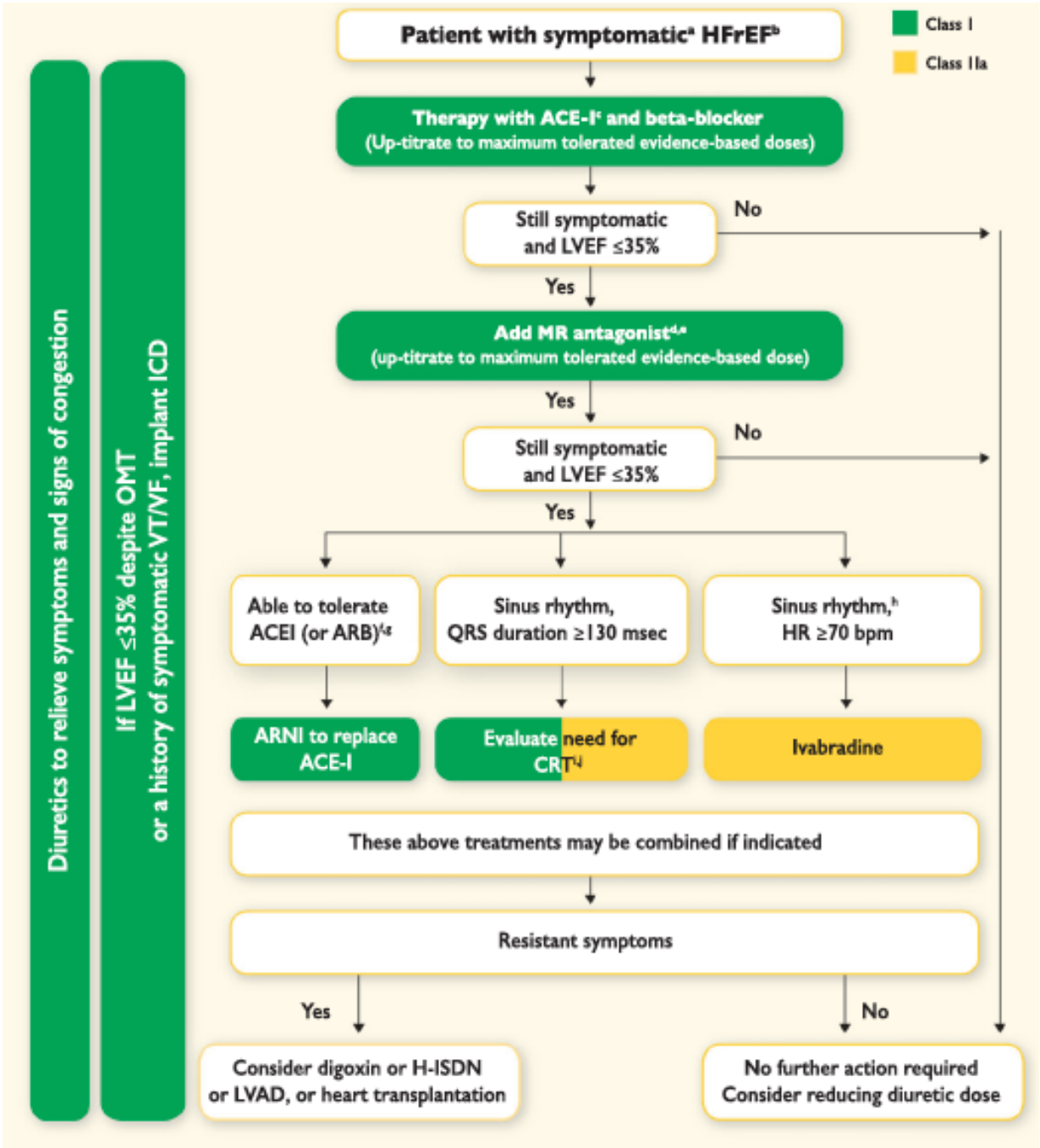


Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.
Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).

HFrEF

Symptoms ± Signs[a]

LVEF <40%



*Eur Heart J (2016) **37**, 2129-2200*

Beta-blockers

	Starting dose	Target dose
Beta Blockers		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily for weight <85 kg and 50 mg twice daily for weight ≥85 kg
Metoprolol succinate	12.5-25 mg/d	200 mg daily

- Adjust dose every 2 weeks

(longer time in frail pts; rapid titration in stable pts)

- Achive target dose in 3-6 months

ACE-i/ARB

ACEI		
Captopril	6.25 mg 3× daily	50 mg 3x daily
Enalapril	2.5 mg twice daily	10-20 mg twice daily
Lisinopril	2.5-5 mg daily	20-40 mg daily
Ramipril	1.25 mg daily	10 mg daily
ARB		
Candesartan	4-8 mg daily	32 mg daily
Losartan	25-50 mg daily	150 mg daily
Valsartan	40 mg twice daily	160 mg twice daily

- Adjust dose every 2 weeks

(rapid titration in stable pts)

- Achive target dose in 3-6 months
- Assess renal function and K^+ within 1-2 weeks of the initiation or dose increase of ACE-I/ARB

MRA

Aldosterone antagonists		
Eplerenone	25 mg daily	50 mg daily
Spironolactone	12.5-25 mg daily	25-50 mg daily

- Not necessary to achieve target or maximally tolerated doses of other drugs before adding MRA
- Contraindicated if eGFR<30mL/min or K^+>5mEq/dL

IVABRADINE

Ivabradine		
Ivabradine	2.5-5 mg twice daily	Titrate to heart rate 50-60 bpm. Maximum dose 7.5 mg twice daily

- Adjust dose every 2 weeks in pts with HR≥70bpm already on target or maximally tolerated dose of BB
- NO Hypotension

Agents that affect renal function:
If decrease in eGFR of >30% or hyperkalemia are noted→reduce dose

JACC (2017) article in press

ARNI

ARNI		
Sacubitril/valsartan	24/26 mg–49/51 mg twice daily	97/103 mg twice daily

Who should be prescribed?

- Outpatient with EF≤ 40%; NYHA II-IV; SBP>100mmHg
- NOT recommended in pt with severe liver disease

How should be prescribed?

- 36 hrs wash out from ACE-i before starting ARNI
- Standard dose: 49/51 mf bid; lower dose in certain groups

How should be titrated?

- Increase dose every 2-4 weeks to allow time for adjustment to the vasodilatory effects
- Monitor BP, renal function, K+; BNP monitoring is useless

Population	Initial Dose
Moderate- or high-dose ACEI *Equivalent of enalapril ≥10 mg twice daily*	**49/51 mg twice daily**
Moderate- or high-dose ARB *Equivalent of valsartan ≥80 mg twice daily*	
Low dose ACEI *Equivalent of <10 mg of enalapril twice daily*	**24/26 mg twice daily**
Low dose ARB *Equivalent of valsartan ≤80 mg twice daily*	
ACEI/ARB naïve*	
Severe renal impairment† (eGFR <30 mL/min/1.73 m^2)	
Moderate hepatic impairment (Child-Pugh Class B)	
Elderly (age ≥75 years)	

JACC (2017) article in press

- No targeted therapy→we treat all HFrEF pts with the same therapies, titrated to the same target doses

- Existing **therapies are underutilised** in the real word:

	MADIT ('96)		MADIT II ('02)		CAT ('02)		AMIOVIRT ('03)		DEFINITE ('04)		SCD-HeFT ('05)		
	OMT	ICD	OMT	ICD	OMT	ICD	Amio	ICD	OMT	ICD	Amio	Placebo	ICD
ACE-i ARB	51%	57%	68%	72%	98.1%	94%	81%	90%	87.3% 8.7%	83.8% 13.5%	85%	88%	86%
BB	14%	31%	70%	70%	3.7%	4%	50%	53%	84.3%	85.6%	72%	79%	82%
MRA							19%	20%			28%	33%	32%

n	305	686	639	470	200	1062	581	257
Mortality rate, % (n)	29% (89)	25% (172)	14% (92)	15% (70)	27% (53)	22% (233)	16% (93)	17% (44)
Mortality and/or HF-hospitalization rate, % (n)	50% (152)	39% (267)	29% (185)	29% (137)	41% (82)	36% (286)	31% (182)	35% (91)
HR Mortality	1.76 (1.54–1.98)	1.50 (1.33–1.67)	0.82 (0.61–1.02)	–	2.41 (2.13–2.68)	1.91 (1.74–2.08)	1.29 (1.07–1.51)	–
HR Mortality and/or HF-hospitalization	1.77 (1.61–1.94)	1.23 (1.09–1.36)	0.86 (0.71–1.00)	–	1.51 (1.29–1.72)	1.27 (1.15–1.39)	1.04 (0.89–1.20)	–

-lower HR
-lower DBP
-more signs of congestion

MRA:
-lower eGFR
-Hyperkalaemia

2)Clinician inertia

European Heart Journal (2017) 38, 1883–1890

HOW TO GUIDE OMT

- Remember: target doses are associated with better outcomes; **titration should occur even if the pt appears "stable"**

- When facing clinical scenarios that limit the ability to use target doses of all relevant therapies, a top priority should be to address the factor(s) limiting OMT:

  - **Worsenig renal function or hyperkalaemia**→discontinue aldosterone antagonist if eGFR<30mL/min or K^+>5.5mEq/dL

  - **Symptomatic hypotension**→first exclude other causes of low BP (overdiuresis, autonomic dysfunction, other vasoactive medications, …), than use best-tolerated dose of MT

  - **Scarce tolerability and side effects**→start at low doses and up-titrate according to tolerability. Pt education and frequent contact will shorten the time to achieve optimal therapy

JACC (2017) article in press

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	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
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The pathophysiology underlying HFpEF is heterogeneous, and it is associated with different phenotypes including concomitant **cardiovascular diseases** (e.g. AF, arterial hypertension, CAD, pulmonary hypertension) and **non-cardiovascular diseases** (diabetes, CKD, anaemia, iron deficiency, COPD and obesity). Unfortunately, at present, **no treatment** has yet been shown, convincingly, to **reduce morbidity or mortality in these patients**.

Eur Heart J (2016) ***37****, 2129-2200*

2003
CHARM

EF>40%, NYHA II-IV
Candesartan vs placebo
NO ↓ combined CV death +HF hospitalisation

2008
I-PRESERVE

EF at leat 45%, NYHA II-IV
Irbesrtant vs placebo
NO ↓ all cause death and H admission

2014
TOPCAT

EF ≥35%
Spironolactone vs placebo
NO ↓ combined CV death + HF hospitalisation + aborted CA

2017
EDIFY

EF≥45%, NYHA II-II, SR, HR ≥70bpm
Ivabradine vs placebo
NO ↓ E/E' o NTproBNP, no ↑ 6MWT

2019…
PARAGON-HF

EF≥45%, NYHA II-IV
ARNI vs Valsartan alone
?

Timeline of principal RCT for MT in HFpEF

BB
IVABRADINE
ACE-i/ARB
MRA
ARNI

….and SO???...

- **Symptoms improvement** remains a primary goal of treament in these pts

- Proper **treatment of comorbidities** is strongly advised

WHAT ABOUT THIS THERAPEUTIC FRUSTRATION?

For many years it was thought that HFpEF was predominantly, if not completely, driven by abnormalities in diastolic function

…but there is more…

- Chronotropic incompetence
- Abnormal oxygen extraction by peripheral skeletal musculature
- Inflammatory and cytokine effects on myocytes, cardiac interstitium and myocardial microvasculature

Circulation. 2016;133:2671-268

*Eur Heart J (2016) **37**, 2129-2200*

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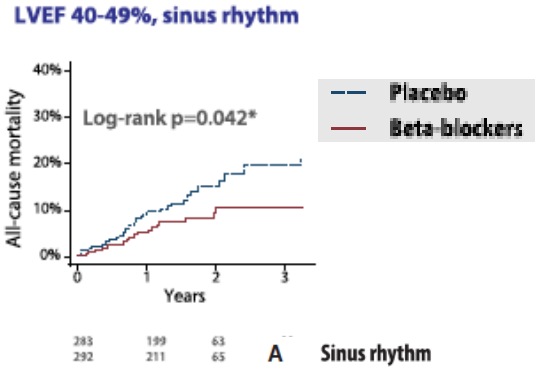
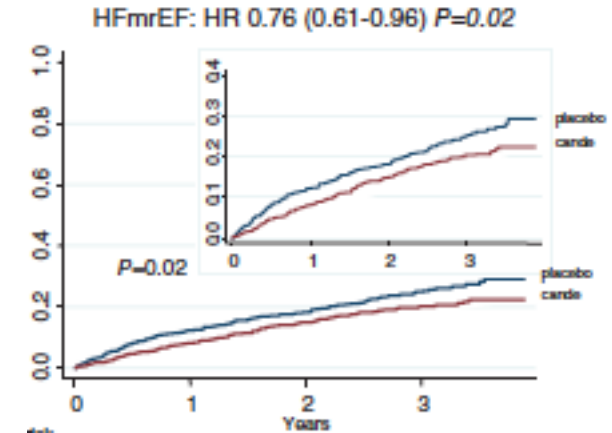
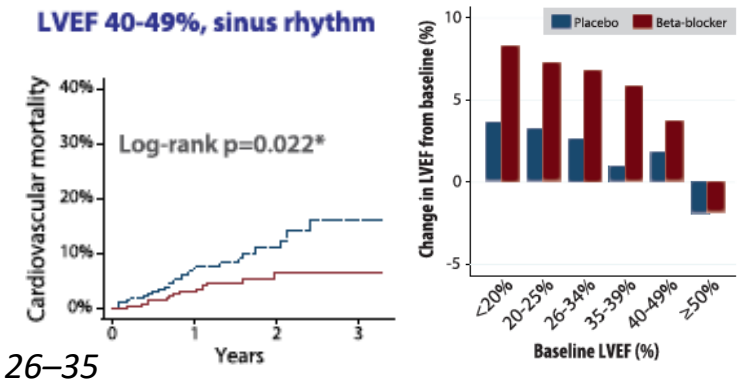
- More than 20% of pts with HF
- CHARM mid range (EJHF 2018): Candesartan ↓ composite of CV death and HF hospitalization in pts with EF 40-49%
- Metanalysis (EHJ 2018): BB ↑LVEF and prognosis in pts with EF 40-49% and SR



European Journal of Heart Failure (2018) doi:10.1002/ejhf.1149





European Heart Journal (2018) 39, 26–35

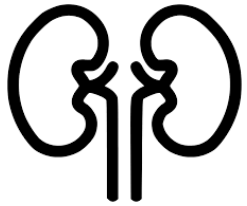
ACUTE HEART FAILURE

	CONGESTION (-)	CONGESTION (+) Pulmonary congestion, orthopnoea/paroxismal, nocturnal dyspnoea, peripheral (bilateral) oedema, jugular venous dilatation, congested hepatomegaly, gut congestion, ascites, hepatojugular reflux
HYPOPERFUSION (-)	WARM-DRY	WARM-WET
HYPOPERFUSION (+) Cold sweaty extremities, Oliguria, Mental confusion, Dizziness, Narrow pulse pressure	COLD-DRY	COLD-WET

Hypoperfusion **is not synonymous** with hypotension, but often hypoperfusion is accompanied by hypotension.

Eur J Heart Fail. 2016; 18(8):891-975

ACUTE HEART FAILURE



DIURETICS

Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of i.v. diuretics.

In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20–40 mg i.v. furosemide (or equivalent); for those on chronic diuretic therapy, initial i.v. dose should be at least equivalent to oral dose.

It is recommended to give diuretics either as intermittent boluses or as a continuous infusion, and the dose and duration should be adjusted according to patients' symptoms and clinical status.

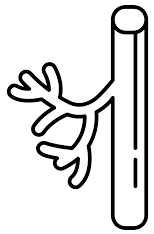
Combination of loop diuretic with either thiazide-type diuretic or spironolactone may be considered in patients with resistant oedema or insufficient symptomatic response.

- NO difference between **bolus** and **continuous infusion** (DOSE study)
- If **resistance**→sequential nephron blockade (+ thiazides or thiazide-like diuretics)
- Ultrafiltration: still debated
  - CARESS-HF study: no benefit
  - AVOID-HF trial: ↓ in HF admission

INOTROPES

	Bolus	Infusion
Dobutamine[a]	No	2–20 µg/kg/min (beta+)
Dopamine	No	3–5 µg/kg/min; inotropic (beta+)
		>5 µg/kg/min: (beta+), vasopressor (alpha+)
Milrinone[a,b]	25–75 µg/kg over 10–20 min	0.375–0.75 µg/kg/min
Enoximone[a]	0.5–1.0 mg/kg over 5–10 min	5–20 µg/kg/min
Levosimendan[a]	12 µg/kg over 10 min (optional) [c]	0.1 µg/kg/min, which can be decreased to 0.05 or increased to 0.2 µg/kg/min
Norepinephrine	No	0.2–1.0 µg/kg/min
Epinephrine	Bolus: 1 mg can be given i.v. during resuscitation, repeated every 3–5 min	0.05–0.5 µg/kg/min

- Except for digoxin (IIbB), they should be only used in pts with CS (SBP<90 mmHg)
- When inotropes are needed→STOP BB

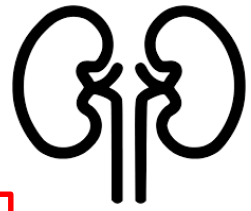


VASODILATORS

Vasodilator	Dosing
Nitroglycerine	Start with10–20 µg/min, increase up to 200 µg/min
Isosorbide dinitrate	Start with 1 mg/h, increase up to 10 mg/h
Nitroprusside	Start with 0.3 µg/kg/min and increase up to 5 µg/kg/min
Nesiritide[a]	Bolus 2 µg/kg + infusion 0.01 µg/kg/min

- Relief symptoms in pts with SBP≥ 100mmHg

Eur Heart J (2016) ***37****, 2129-2200*



2017 ATHENA-HF

AHF regardless of EF
100 mg **spironolactone** vs 25 mg placebo or for 96 hrs
I endpoint: change in NTproBNP from baseline to 96 hrs
II endpoint: clinical congestion score, dyspnea assessment, net urine output, and net weight change
NO improvement

2016 ATOMIC-AHF

Omecamtiv mecarbil 48hrs infusion vs placebo in AHF pts with EF≤40%
Increase systolic ejection time
Improve dyspnea ionly n the high-dose group

2008 HORIZON

Istaroxime infusion in AHF vs placebo
↓ PCWP, HR, ESV, EDV; ↑ IC, SBP
↓ E/E', DT E wave

2017 BLAST-HF

Phase IIb study
3 different dosage of **TRV027** vs placebo
NO improvement of clinical status at 30 days

2017 TRUE-AHF

Continuous iv infusion of **Ularitide** (natruretic peptide) vs placebo for 48 hrs did not affect CV death

Ongoing RELAX-AHF2

Serelaxin infusion in addiction to ST in pts with AHF will be able to reduce CV death at 180 days and worsening HF through day 5?

TAKE HOME MESSAGES

CHF:

- ***Neurohormonal antagonists*** are known since the dawn of time and they proved to be effective, but we have to use them well→**don't forget to titrate**!!!!
- With the publication of **PARADIGM-HF** trial we may be entering a new era of treatment for HFrEF

AHF:

- At present NO treatment for AHF has proved to increase outcome
- New molecules are currenlty under investigation; numerous studies have failed, but we hope for the future…

Thank you for your attention!